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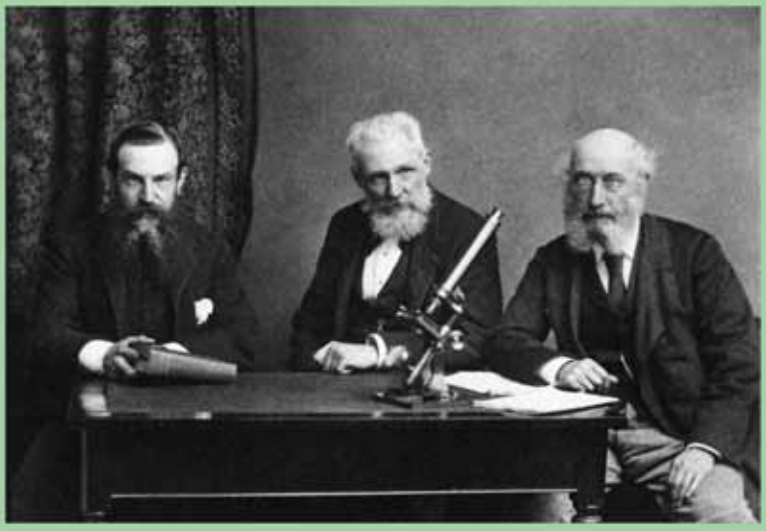
The British Pharmacopoeia, 1864 to 2014

Medicines, International Standards and the State



Anthony C. Cartwright

THE BRITISH PHARMACOPOEIA, 1864 TO 2014

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ANTHONY C. CARTWRIGHT

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Published by
Ashgate Publishing Limited
Wey Court East
Union Road
Farnham
Surrey, GU9 7PT
England

Ashgate Publishing Company
110 Cherry Street
Suite 3-1
Burlington, VT 05401-3818
USA

www.ashgate.com

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

The Library of Congress has cataloged the printed edition as follows:
Cartwright, A. C. (Anthony C.), 1940- , author.
The British pharmacopoeia, 1864 to 2014 : medicines, international standards, and the state / by Anthony C. Cartwright.
p. ; cm. -- (The history of medicine in context)
Includes bibliographical references and index.
ISBN 978-1-4724-2032-9 (hardback) -- ISBN 978-1-4724-2033-6 (eBook) -- ISBN 978-1-4724-2034-3 (ePub)
I. Title. II. Series: History of medicine in context.
[DNLM: 1. Pharmacopoeias as Topic--history--Great Britain. 2. Pharmacopoeias as Topic--standards--Great Britain. 3. History, 19th Century--Great Britain. 4. History, 20th Century--Great Britain. 5. History, 21st Century--Great Britain. 6. Publishing--history--Great Britain. QV 711 FA1]
RS141.3
615.1'141--dc23

2014039123

ISBN 9781472420329 (hbk)
ISBN 9781472420336 (ebk – PDF)
ISBN 9781472420343 (ebk – ePUB)

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About the Author

Anthony C. Cartwright is a retired pharmaceutical regulatory consultant. He graduated in pharmacy from the University of Leeds and then worked in pharmaceutical research and development in the pharmaceutical industry. A long period in government service began by working in the British Pharmacopoeia Commission's Laboratory for four years and then successively in the Medicines Division of the Department of Health and the Medicines Control Agency. He was the first chairman of the European Committee for Proprietary Medicinal Products Quality Working Party, and involved from the beginning in the development of quality guidelines in the International Conference on Harmonisation. After leaving the Medicines Control Agency he worked for Parexel, a leading Contract Research Organisation, and then in his own regulatory consultancy. He has continued to be involved with *British Pharmacopoeia* through its Expert Advisory Groups and Panels. He has written many reviews and research articles, written and co-edited three textbooks on pharmaceutical regulation and contributed chapters to four others.

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Preface

The three pillars on which drug regulation stands are quality, safety and efficacy. Since times of classical antiquity healthcare professionals have striven to apply these principles to medicinal drug substances and drug products. The first attempts were largely lists of medicinal substances and recipes for products with known efficacy – 'dispensatories' – and these were gradually codified into pharmacopoeias. The word derives from the Greek words 'φαρμακον' (*pharmakon*), a drug or remedy, and 'ποιειν' (*poia*), making or preparing.

The first official pharmacopoeias were produced by individual physicians or groups of physicians for use in their individual cities or city-states. The official guide for the apothecaries of Florence the *Antidotarium Florentinum* was published in 1498 and is often regarded as the first official pharmacopoeia. Other cities followed with Barcelona in 1535 (*Concordia Pharmacolorum Barcelonesium*) and Nuremberg in 1546 (*Dispensatorium Valerii Cordis*).

The first national pharmacopoeia was the *Pharmacopoeia Londinensis* published by the Royal College of Physicians of London in 1618. The Royal College of Physicians in Edinburgh published its first *Pharmacopoeia Collegii Regii Medicorum Edimburgensis* in 1699. The Royal College of Physicians in Dublin published its *Pharmacopoeia Collegii Regis et Reginae in Hibernia* in 1806.

The Medical Act of 1858 directed that the General Council of Medical Education and Registration of the United Kingdom publish 'a list of Medicines and Compounds, and the manner of preparing them ... to be called the British Pharmacopoeia'. The first edition of the *British Pharmacopoeia* was published in 1864 and was an attempt to harmonise the three earlier national pharmacopoeias.

This book reviews how the early development of the *British Pharmacopoeia* over its first 150 years has reflected the changes in the roles of physicians, apothecaries, chemists, druggists, pharmacists and public analysts as well as developments in chemistry and medicine. The passing of the Poor Law in 1834, and the development of infirmaries and dispensaries started to make medicines more widely available. This trend continued with National Health Insurance Act of 1911, which made medicines available to wage-earners. Prescribing of medicines increased further with the passage of the National Health Insurance Act of 1946 which brought in for the first time a comprehensive health system for all. The development of the modern pharmaceutical industry from its early

beginnings in the nineteenth century and the increasing market for its products has led to the manufacture of drug substances and the development of medicinal products for an ever-increasing range of clinical conditions, and these have been progressively included in the *Pharmacopoeia*. In the last century we have seen the transition from medicines prepared in the pharmacy from the official formulae in the *British Pharmacopoeia* and *British Pharmaceutical Codex* to increasingly sophisticated commercial medicinal products.

The function of the pharmacopoeia has evolved from merely listing suitable medicinal substances and therapeutic compositions to defining the standards for quality of medicinal substances and products. Quality of drug substances and medicinal products is now usually defined as relating to their design – development, in-process controls, Good Manufacturing Practice, validation of their process of manufacture, and finally the quality standards applied to them during development, manufacture and the shelf life. Patients often show a perverse inclination to buy imported products of unknown and often unsuitable quality on the Internet, so need to be protected by suitable publicly available standards.

Trade in medicinal substances and products has always been global, and the *British Pharmacopoeia* has worked closely with the *United States Pharmacopoeia* from the nineteenth century onwards. Early editions of the British Pharmacopoeia were also adapted to the requirements of India and the Colonies by extensive consultations with national medical and pharmaceutical bodies through the India Office and Colonial Office. In 1964 the first edition of the *European Pharmacopoeia* was published with monographs for drug substances and excipients applicable in all countries signatory to the European Pharmacopoeia Convention signed originally by eight member states of the Council of Europe. The relationship of the *British Pharmacopoeia* to the *European Pharmacopoeia* is explored. More recently the role of the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals (ICH) has led to the development of more globally acceptable monographs.

The battles against drug substance and product adulteration and counterfeiting in the nineteenth century led to the development of increasingly sophisticated analytical methods in pharmacopoeial monographs and this has continued with further improved methods for control. The *British Pharmacopoeia* continues to play an important role in the war against counterfeit products in the developed world, poor quality and counterfeit essential medicine products in the developing world. It is used in over 100 countries and remains an essential global reference tool in pharmaceutical research and development and quality control.

The evolving historic role of the pharmacopoeia should be of interest to a wide audience of students and practitioners of medicine, pharmacy and pharmaceutical analytical chemistry.

Acknowledgements

The author is indebted to many who have assisted him with the research for this book, who have contributed personal memoirs, or provided information. Particular thanks are due to the ever-helpful staff at the National Archive and the British Library. Jane Trott, the librarian at the Royal Pharmaceutical Society, assisted by finding some of the references that I needed. The Royal Pharmaceutical Society kindly made available selected minutes from the Council of the Pharmaceutical Society.

Acknowledgement is made of the kind permission of the *Pharmaceutical Journal* to use images of three former secretaries to the British Pharmacopoeia Commission – Thomas Denston, Cecil Johnson and Alan Rogers. Permission was given by the National Portrait Gallery of London to use copyright images of Professor Henry Greenish, Dr Charles Hampshire and Sir Donald MacAlister. The Museum of the Royal Pharmaceutical Society kindly gave permission to use the specially scanned image of Theophilus Redwood, John Attfield and Robert Bentley used on the cover of this book. The photographs of the three most recent secretaries and scientific directors to the British Pharmacopoeia Commission – Dr Robin Hutton, Dr M. Gerard Lee and Dr Samantha Atkinson were personally supplied to the author of this book.

Two former secretaries and scientific directors of the BP Commission Secretariat, Dr Robin Hutton and Dr M. Gerard Lee, have provided me with frank and full notes on the events and achievements during their terms of office. The current secretary and scientific director, Dr Samantha Atkinson, and her staff have been extremely helpful in providing me with access to the BP archives, giving me copies of information and advising on current policies.

Professor Derek Calam, who was chairman of the British Pharmacopoeia Commission from 1998 until 2006, has provided a note with some reflections about his long connection with the BP. Professor David Woolfson, who was chairman of the British Pharmacopoeia Commission from 2006 until 2012, has provided a note on the major changes and key events during his term of office. Dr Geoff Carr, who worked in the BP laboratory until 1984, has provided me with a note on some of the work carried out in the laboratory to introduce some new analytical techniques into the BP. Roger Trigg, who was responsible for British Approved Names at the BP Commission, has helped with information on the British Approved Names and International Nonproprietary Names. Dr Sophie Lasseur and Dr Raffaella G. Balocco Mattavelli from the World Health

Organization also helped with information on International Nonproprietary Names. Dr Susanne Keitel, the director of the European Directorate for the Quality of Medicines and Healthcare, and her staff have provided some information on the history and current practice of the *European Pharmacopoeia*.

My friends and colleagues Drs Brian Matthews and Robin Harman have very kindly read and provided editorial input into this manuscript. However any errors of fact and interpretation are all mine.

List of Acronyms and Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ACE	Angiotensin Converting Enzyme
AS	Authentic Specimen
ASMF	Active Substance Master File
BAN	British Approved Name
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMA	British Medical Association
BP	British Pharmacopoeia
BP (Vet)	British Pharmacopoeia (Veterinary)
BPC	British Pharmaceutical Codex
BPCRS	British Pharmacopoeia Chemical Reference Substance
BSE	Bovine Spongiform Encephalopathy
CD-ROM	Compact Disc Read-Only Memory
CEP	Certification Procedure of the European Directorate for the Quality of Medicines
CGS	Centimetre, Gram, Second metric system
CHM	Commission on Human Medicines (UK)
CHMP	European Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CSM	Committee on Safety of Medicines (UK)
CVMP	Committee for Medicinal Products for Veterinary Use
DHSS	Department of Health and Social Security
DNA	Deoxyribonucleic Acid
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration (United States)
FIP	Fédération Internationale Pharmaceutique (International Pharmaceutical Federation)
FTIR	Fourier Transform Infrared
GC	Gas Chromatography
GCG	Global Cooperation Group (ICH)
GLC	Gas Liquid Chromatography

GMC	General Medical Council
GMP	Good Manufacturing Practice
GPhP	Good Pharmacopoeia Practice
HMG-CoA reductase	3-hydroxy-3-methyl-glutaryl-CoA reductase
HMSO	Her Majesty's Stationery Office
HPLC	High Performance Liquid Chromatography
HSA	Singapore Health Services Authority
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
INN	International Nonproprietary Names
IR	Infrared
IUPAC	International Union for Pure and Applied Chemistry
KC	Kings Counsel
LAL	Limulus Amoebocyte Lysate – test
LC	Liquid Chromatography
LGC	Laboratory of the Government Chemist
LRCP	Licentiate of the Royal College of Physicians
M	Molar
MB BS	Bachelor of Medicine, Bachelor of Surgery
MCA	Medicines Control Agency (former UK agency)
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MRC	Medical Research Council
MRCS	Member of the Royal College of Surgeons
MS	Mass spectroscopy
N	Normal
NATO	North Atlantic Treaty Organization
NHS	National Health Service (UK)
NIBSC	National Institute for Biological Standards and Control
NIMR	National Institute for Medical Research
NMR	Nuclear Magnetic Resonance
OMCL	Official Medicines Control Laboratory
PDG	Pharmacopoeial Discussion Group
Ph. Eur	Pharmacopée Européenne (European Pharmacopoeia)

PSGB	Pharmaceutical Society of Great Britain
RHI	Regional Harmonisation Initiative
rINN	recommended International Nonproprietary Name
RPS	Royal Pharmaceutical Society
RSM	Royal Society of Medicine
SC	Supplementary Chapter of the British Pharmacopoeia
SFDA	Chinese State Food and Drugs Administration
SI	Système International d'Unités (metric) system of units
TLC	Thin layer chromatography
TSE	Transmissible Spongiform Encephalopathy
TSO	The Stationery Office
USP	United States Pharmacopeia
UV	Ultraviolet
VE	Victory in Europe (celebration of the end of World War II in Europe)
WARF	Wisconsin Alumni Research Foundation
WHO	World Health Organization

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Notes on References

Much of the detailed history of the *British Pharmacopoeia* has been obtained from the Minutes of the Pharmacopoeia Committee and the other committees of the General Medical Council from 1863 to 1970. The General Medical Council published these minutes in bound annual volumes of *Minutes of the General Medical Council* which are held by the major copyright libraries – the British Library, the University of Cambridge, the Bodleian Library of the University of Oxford, the National Library of Scotland, and the National Library of Wales. Volume I of the *Minutes of the General Medical Council* relates to 1863, and volume CVII to 1970. It is clear from the chronology in the text of each chapter which volume is being referred to.

I have also been allowed access to the archived files of the Minutes of the British Pharmacopoeia Commission from 1932. No detailed reference citations are included to them as it is again clear from the context which meeting is being referred to.

Key references to books and articles from the literature are cited for each chapter. Information and comment has also been sought from some of the key individuals involved in the recent history – particularly the secretaries and scientific directors of the British Pharmacopoeia Commission and the chairmen of the BP Commission. These are listed as personal communications.

Following conventional practice, the names of drugs when they were discovered, tested, developed or supplied in commerce are given in lower case (for example omeprazole). The titles of the official monographs for drugs and preparations in the British Pharmacopoeia are given with the first letters in upper case (for example as Omeprazole or Gastro-resistant Omeprazole Tablets).

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The views, analyses and opinions expressed in this book are mine. They do not necessarily reflect the policies or opinions of the British Pharmacopoeia Commission, the UK Medicines and Healthcare Products Regulatory Agency, or the European Directorate for Quality of Medicines and Healthcare.

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PART I:
Origins, Development and Maturity

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Chapter 1
The Earlier British National Pharmacopoeias: London, Edinburgh and Dublin

... for there the earth, the giver of grain, bears greatest store of drugs, many that are healing when mixed, and many that are baneful; there every man is a physician, wise above human kind ...

(Homer)[1]

Man has been taking medicines to treat disease since history began. The clay tablets found in the palaces in Crete, Mycenae, Pylos, Thebes and other locations from the Hellenic Bronze Age (1750–1050 BC) were written by the scribes in the Linear B script. This early Greek script was deciphered in 1952 by the architect and amateur linguist Michael Ventris (1922–1956). The deciphered tablets include the Greek word 'φαρμακου' (pharmakon), meaning medicine or drug.

Archaeologists discovered ancient Egyptian papyri in the nineteenth century which list some of the materials used in medicine at the time and these have been documented by Campbell.[2] These include the *Kahun* papyrus (ca. 1850 BC) found by Flinders Petrie at the workmen's village in the Fayoum, the *Edwin Smith* papyrus (ca. 1550 BC), the *Ebers* papyrus dating to Amenhotep I (1546–1526 BC) found in the Valley of the Kings, and the *Chester Beatty* papyrus found at Deir in Medina dating to Ramses III (1150 BC). The materia medica mentioned included plants, drugs from animals, minerals and dressings. Drugs used in ancient Egypt included linseed (*Linum usitassimum*), coriander (*Coriandrum sativum*), anise (*Anethum graveolens*), *Styrax benzoin*, *Citrullus colocynthus*, garlic (*Allium sativum*) and honey. All of these are included in the current 2014 *British Pharmacopoeia* and are in current use in conventional or alternative medicine in Britain. The medicinal preparations used at that time included linctuses, lotions, mixtures, pastes, ointments, pessaries, pills, poultices, powders, solutions and suppositories. Crocodile dung pessaries were used as a barrier contraceptive, but not surprisingly these have disappeared from modern medicine.

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[1] Homer, Book 4 of *The Odyssey*, 123, translated by A.T. Murray (1919). London: William Heinemann.

[2] Campbell, J., 2007. Pharaohs and the First Prescriptions. *Pharm. J.* 277: 735–7.

From the beginning physicians and others have collected information on which materials would be useful and which poisonous. Once written down this information could then be used to guide others as to how medicines should be prepared, their efficacy and their safety. These early lists and books on medicines have inevitably reflected the prevailing philosophy and state of scientific knowledge of medicine at the time.

The Founding Fathers of Early Medicine

The physician Hippocrates (ca. 460–ca. 370 BC), is often called the 'father of medicine'. He was born on the Greek island of Cos. Hippocrates based medicine on clinical observations and deduction, with the need to carefully record the symptoms and diagnosis. He propounded the belief that disease results from an imbalance of the four bodily humours. The four humours are black bile, yellow bile, phlegm and blood. This theory was closely associated with the theory of the four elements, earth present in black bile, fire in yellow bile, water in phlegm and all four elements in the blood.[3]

Pedanius Dioscorides (ca. 40–90 AD) was born in Anazarbus, Cilicia in Asia Minor. He probably studied medicine in Tarsus.[4] He was a surgeon in the army of the Emperor Nero and travelled widely seeking medicinal plants from all over the Greek and Roman world. Between 50 and 70 AD he wrote a five-volume book in Greek, better known by its Latin title of *De Materia Medica*. This work included 600 plants classified firstly into categories of drug and then by their physiological effect. He also described some rudimentary chemical processes such as distillation and mercury extraction from cinnabar (mercuric sulphide). The text circulated over subsequent years in various versions in Greek, Latin and Arabic. This is often referred to as the first pharmacopoeia. The word derives from the Greek 'φαρμακου' (pharmakon), a drug or remedy, and 'ποιειν' (poia), making or preparing.

Claudius Galenus (129–ca. 210/217), better known simply as Galen, was born in Pergamum on the Ionian seaboard of Asia Minor.[5] He studied philosophy and then medicine at Pergamum, Smyrna, Corinth and Alexandria. He travelled round the Eastern Mediterranean investigating local herbal and mineral remedies. Galen was the physician to the Roman Emperor Marcus

[3] Kremers, E. and Urdang, G., 1951. Ancient Prelude, 13–14. In *History of Pharmacy*, revised by Glenn Sonnedecker. Third Edition. Philadelphia: Lippincott.

[4] Petrovska, B.B., 2012. Historical Review of Medicinal Plants' Usage. *Pharmacogn. Rev.* 6(11): 1–5.

[5] Hankinson, R.J., 2008. The Man and His Work, and Vogt, S., Drugs and Pharmacology. In *The Cambridge Companion to Galen*, edited by R.J. Hankinson. Cambridge: Cambridge University Press.

Aurelius and the Imperial Family. During his life he wrote or dictated a large number of books. He attempted to systematise the known materia medica and to understand the interaction between the drug and the body. Galen developed a classification of temperaments in *De temperamentis* to explain different human behaviours. He related them to the four elements: heat, cold, moisture and dryness. The 11 books of *On the Powers of Simple Drugs* provided a catalogue of single drugs and their healing properties. They included plants and herbs, stones, and metallika pharmaka (drugs that are mined). He listed animal products including those from blood, milk, excrement, the entrails of poisonous snakes, blister-beetles and cicadas. His works on compound preparations, that is mixtures of drugs, include *On the Composition of Drugs according to Places* and *On the Composition of Drugs according to Kind*. These latter books include plasters, emollients, laxatives and painkillers. Galen also wrote about theriacs. The word 'θηριακός' (*thēriakos*) in Greek means 'pertaining to wild beasts'. Originally it meant an antidote to poisonous creatures.

According to legend, the first theriac was developed in the first century BC by King Mithridates VI of Pontus on the southern shores of the Black Sea. Mithridates was afraid of being poisoned and was reputed to have created an antidote to poisons. The antidote reportedly included over 50 ingredients all mixed into a paste with honey. This was taken daily to give immunity to poisons. When Mithridates was defeated by the Roman general Pompey in 63 BC the recipe for Mithridates's theriac or Mithridatium was taken to Rome, where it was manufactured by the city's pharmacists. By the time the Emperor Nero came to power in Rome in 54 AD other ingredients had been added to the original recipe. Nero was also concerned about being poisoned, and asked his own physician Andromachus to develop an improved theriac. This theriac contained 64 ingredients. Andromachus claimed that it would also relieve pain, weakness of the stomach, difficulty in breathing, colic, jaundice and dropsy.

Abu Ali al-Husayn ibn Allah ibn Sina (980–1037 AD) is more commonly known by the Latin name Avicenna.[6] He was born in Persia – modern Iran. He wrote over 450 books on a variety of topics. His book *The Canon of Medicine* is a medical encyclopaedia which was completed in 1025 AD. The book was based on the concept of the four humours of Hippocratic medicine, but further refines it. He also used the theory of the four temperaments – hot, cold, moist and dry – from Galen. The materia medica listed in Book 2 of the *Canon* included 700 preparations of medicine from a variety of Greek, Arabic and Indian authorities. The drugs listed included both plant and mineral substances with information on their use and efficacy. Book 5 of the *Canon* dealt with compound drugs.

[6] Kremers, E. and Urdang, G., 1951. The Arabs and the European Middle Ages, 21–23. In *History of Pharmacy*, revised by Glenn Sonnedecker. Third Edition. Philadelphia: Lippincott.

The *Canon* was translated into Latin in 1473 and became a major textbook for medical education throughout Europe.

Yuhanna ibn Masawaih was born in 777 AD in Gundishapur in Persia – modern Iran. He is known by his Latin name of Mesue or Mesue the Elder. He came to Baghdad to study medicine. He wrote in Syriac and Arabic. Many anatomical and medical writings are attributed to him. In about the thirteenth century another unknown medical writer took his name, presumably to add authority and prestige to his own writings. This later European writer is known as Mesue the Younger or Pseudo-Mesue.[7] His *Antidotarium* or *Grabadin* was very influential and many of the recipes for medicinal preparations in later books are based on those in the *Grabadin*.

Philippus Aureolus Theophrastus Bombastus von Hohenheim (1493–1541) is better known as Paracelsus.[8] He was born in the Swiss village of Einsiedeln. His father was a Swabian (German) chemist and physician. Paracelsus studied medicine at the University of Basel, then in Vienna. He gained his doctorate at the University of Ferrara in Italy. He worked as an itinerant physician in Germany, France, Spain, Hungary, the Netherlands, Sweden and Russia. He pioneered the use of minerals and chemicals in medicine. He was critical of the views of Galen and thought that sickness and health in the body were dependent on the harmony of man the microcosm and Nature the macrocosm. Paracelsus probably coined the term 'spagyric' referring to an alchemical method of processing herbal medicines. The word derives from Greek words meaning to tear apart and to collect. Spagyric medicines were made by combining an extraction process with fermentation and then extracting mineral components from the ash of the plant and adding this back to the extract.

Early Pharmacopoeias

The first official pharmacopoeias were produced by individual physicians or groups of physicians for use in their individual cities or city-states. The official guide for the apothecaries of Florence was the *Nuovo receptario composto del famotissimo Chollegio degli eximii Doctori della Arte et Medicina della inclita cipla di Firenze*, which was written by the physician Hyeronymo dal Pozzo Toscanelli in Italian and published in 1498.[9] The first section of the book dealt with the selection and preparation of individual materia medica, the second

[7] Kremers, E. and Urdang, G., 1951. The Arabs and the European Middle Ages, 25. In *History of Pharmacy*, revised by Glenn Sonnedecker. Third Edition. Philadelphia: Lippincott.

[8] Raviña, E., 2011. Antiquity, 9. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co KGaA.

[9] *Nuovo Receptario Facsimile Edition with Commentary*, 1992. Institut Medico-Farmaceutic de Catalunya, Cornet.

with compound preparations (powders, syrups, electuaries, oils, plasters, pills and so on).

The Spanish city of Barcelona followed with the publication of the *Concordia Pharmacopolarum Barcinonensium* in 1535, written by Bernardus Domenech and Ioanne Benedicto Pau for the Colleges of Medicine and Apothecaries. This was commissioned by the Archbishop of Barcelona and designated as official in the diocese. The *Concordia Aromatariorum Civitatis Cesaraugustae* was published in Saragossa.

Nuremberg followed with the publication by the physician Valerius Cordus (1515–1544) of the *Pharmacorum Omnium quae in usu Potiss., Sunt, Componendorum Ratio* – commonly known as the *Dispensatorium* – in 1546. The *Dispensatorium* included information on individual materia medica ('simples') and recipes for powders, pills, syrups, decoctions, pastilles, plasters, eye-drops, ointments and oils. It included recipes and instructions for manufacture of a number of theriacs including Mithridatum, Theriaca Andromachi and Theriaca Andromachi Senioris. It was a useful practical guide with information as to the use of the drugs and the compounded preparations – the powders, pills, syrups and so on. This book was influential and it was copied and reprinted many times. Editions were issued in Antwerp, Leyden, Lyons, Tubingen and Venice. It was translated into Italian (Venice, 1558) and Dutch (Amsterdam, 1592). One of Cordus's other achievements was the synthesis of ether in 1540 using ethyl alcohol and sulfuric acid.

Other German cities followed. The *Enchiridion sive ut vulgo vocant Dispensatorium, compositorum medicamentorum, pro Reipub. Augstburgensis Pharmacopoeis* was published in Augsburg in 1564. The *Dispensarium usuale pro pharmacopoeis inclytae Republicae Colonensis* was published in Cologne in 1565.

The first use of the word 'pharmacopoeia' in the title of a book was in 1548 with the publication by the French physician Jacques du Bois of his *Pharmacopoeae, libri tres*. In 1560 the German physician Bretschneider-Placotomas issued his formulary *Pharmacopoeia in compendium redacta* in Antwerp. In 1561 the *Pharmacopoeia medicamentorum omnium, quae hodie ad publica medentium munia Officines extant, tractionem et unum ex antiquorum Medicoru praescripto continens, Pharmacopeis omnibus, atque etiam ris qui opus factitant medicum, valde utilis et necessaria* written by Anutus Foesius in Basel was published. Many of the individual recipes in this book are credited to earlier writers such as Galen, Avicenna and Mesue the Younger. The book is dedicated to Duke Charles III of Lotharingia (Lorraine).

It rapidly became a matter of local or national pride to have a pharmacopoeia. Urdang has documented how the pharmacopoeias were dedicated to princes

and kings.[10] In 1567 the *Ricettario Fiorentino* was compiled under the order of Alexander de Medici the first Duke of Florence and dedicated to him. In 1583 the first edition of the *Antidotarum Romanum* was compiled by the Collegium Medicum in Rome and published with a dedication to Pope Gregory XIII. In 1816 the Bourbon King Louis XVIII declared the French publication then in progress to be official under Article 38 of the law of 11 April 1803. This was published in 1818 under the title *Codex Medicamentarius sive Pharmacopoea Gallica* with the French royal coat of arms and the words 'Jussu Regis Optimi' which roughly translates as meaning 'at the command of the best'.

London Pharmacopoeia

The College of Physicians of London was founded in 1518 by Henry VIII. In 1540 one of the earliest statutes to include some control of medicines was adopted – 32 Henry VIII Cap XL. This gave the physicians the right to appoint four inspectors, called 'censors' of 'apothecary wares, drugs and stuffs' and to search for any that were 'defective, corrupted, and not meet nor convenient to be ministered in any medicine for the health of man's body'. Any found defective could be 'brent [burnt] or otherwise destroy[ed]'. A further Act of Parliament of 1553 in the reign of Queen Mary – 1 Mary session secunda, Cap IX authorised wardens of the grocers to go with the physicians to 'execute their search and view' to detect 'any evil and faulty stuff'. The penalty for resisting such a search was £10.

In 1585 the Royal College of Physicians of London discussed the possibility of preparing a pharmacopoeia which would provide an official guide for the apothecaries of London but as it 'seemed a toilsome task' it was left in abeyance. On 10 October 1589 it was 'Proposed, considered and resolved that there shall be constituted one definite public and uniform dispensatory or formulary of medical prescriptions obligatory for apothecary shops'.[11] On 15 October 1589 the president of the College and 15 fellows met in committee. They appointed sub-committees of two, three or four members to deal with 10 groups of medicaments. About a third of the members of the committee had graduated abroad – in Nantes, Padua, Leyden and three in Basel. The Annals of the London College of Physicians of 10 October 1589 records their intention to include all of the old groups of remedies but also Extracts, Sales (salts), Chemica and Metallica. Thus they proposed that the contents of the new pharmacopoeia would not only

[10] Urdang, G., 1946. Pharmacopoeias as Witness of World History. *Journal of the History of Medicine and Allied Sciences* 1(1): 46–70.

[11] Clark, G., 1964. Book 1 of the *History of the Royal College of Physicians of London*, 226–9. Oxford: Clarendon Press.

be based on the prevailing orthodoxies of Hippocrates, Galen and Avicenna, but controversially would also include some of the inorganic chemicals advocated by Paracelsus. On 23 October a new committee of six was appointed to edit the text. On 13 December 1594 a further new committee was appointed, but thereafter the project seems to disappear from the College's records.

In 1614 the College started work again on the pharmacopoeia – firstly with a committee of nine working for two years, then with a new committee after the work had been found to be unsatisfactory. A further committee was then appointed and its members changed several times. Dr Fox and Dr Clement were charged with correcting the proofs. Various fellows were asked to write the preface to the book. Two physicians had a key hand in the new book – Dr Henry Atkins (1558–1635) and Sir Theodore Turquet de Mayerne (1573–1665). Atkins had received his Doctor's degree at the University of Nantes. Theodore de Mayerne began his medical career in Paris but then moved to England as a Huguenot refugee. He became the physician to King James I.

In 1607 King James I agreed to grant a charter to the Grocers' Company. At that time the apothecaries were part of the Grocers, but they wanted their independence and control of their own affairs.[12] The de Laune family came to England as Huguenot refugees in 1573. Their son Gideon practised as an apothecary and became the apothecary to Ann of Denmark, the wife of James I. He was part of the group determined to break away from the Grocers. With the help of his fellow Huguenot Theodore de Mayerne he petitioned the king.[13] Part of their petition read:

> Very many Empiricks and unskilful and ignorant men do abide in the City of London ... which are not well instructed in the Art or Mystery of Apothecaries, but do make and compound many unwholesome, hurtful, dangerous and corrupt medicines and the same do sell ... to the great peril and daily hazard of the King's subjects.

Sir Francis Bacon as the Chief Law Officer was consulted and supported the petition, which was then granted by the king. The Worshipful Society of Apothecaries of London was incorporated by royal charter on 6 December 1617.

A Proclamation was issued by James I on 26 April 1618 informing the Apothecaries what was to be expected of them. This text was included in the second edition of the *London Pharmacopoeia*:

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[12] Hunting, P., 2004. The Worshipful Society of Apothecaries of London. *Postgrad. Med. J* 80: 41–4.

[13] Copeman, W.S.C., 1967. *The Worshipful Society of Apothecaries of London. A History, 1617–1967*. Oxford: Pergamon Press.

> Apothecaries within our Realme of England or the dominions thereof ... do not compound or make any medicine, or medicinal receipt or prescription ... by any other books or Dispensatories whatsoever but after the onely manner that hereby is, or shall be directed, prescribed and set downe by the said booke and according to the weights and measures that are or shall be therein limited and not otherwise and upon paine of our high displeasure, and to incurre such penalties and punishment as may be inflicted upon offenders herein for their contempt or neglect of this our royall commandment.

After receiving the king's Proclamation the printer published the text of the *Pharmacopoeia Londinensis* on 7 May 1618 under his own responsibility. Sir William Paddy, the President of the College, was away and when he returned he found the book to be full of errors. A new definitive and official first edition was compiled and published on 7 December 1618. The epilogue to the revised edition contained the following text (in translation from the original Latin by George Urdang):[14]

> We now edit the London Pharmacopoeia in a second endeavour, with more fortunate result. We (I say) edit. For that previous unformed as well as deformed [book], may we say the hasty printer has edited it? On the contrary he hurled it into the light. As a blaze flares up from the fire and in a greedy famine deprives the stomach of its still unprepared food, so the printer snatched away from our hands this little work not yet finished off, without consulting the president yea even during a time when the latter who most thoroughly took care of corrections and polishing was out of town because of a call.

This was the first national pharmacopoeia as it was to apply not only to London but to all of England. The whole of the pharmacopoeia was in Latin. The preface to the book, which was probably written by Mayerne, was addressed to the 'Candido Lectori' – the friendly reader – and gave some of the key aims of the publication. The major objective was, again in translation by George Urdang:[15] 'to secure the most wholesome medicine'. The publication of the book had several other aims which are made clear in the preface. Firstly it was to help to define and control the work of the apothecaries. Secondly it was to prevent the use of the medicines described in the book by the 'empiricks' – the quack doctors and drug peddlers. The preface states:

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[14] Urdang, G., 1944. *Pharmacopoeia Londinensis of 1618. Reproduced in Facsimile with Historical Introduction*, 23–4. Hollister Pharmaceutical Library Number Two, Madison State Historical Society of Wisconsin.

[15] Urdang, G., 1944. *Pharmacopoeia Londinensis of 1618. Reproduced in Facsimile with Historical Introduction*, 28–32. Hollister Pharmaceutical Library Number Two, Madison State Historical Society of Wisconsin.

> ... our book will counteract, namely the very noxious fraud or deceit of people who are allowed to sell the most filthy concoctions ... for the sake of profit and instigated by sordid avarice.

and

> Finally, in most of the older, as well as the more recent antidotaria, the uses and medical attributes of each remedy have been described. From this quiver, the itinerant drug peddlers and the quacks, being as ignorant as they are unscrupulous, equip themselves for their medical practice and seizing our weapons, are responsible for the death of the sick, to the great detriment of the state. We, therefore, do not add anything about the efficacy of the medicines. We write this book only for the learned, for the disciples of Apollo and for the welfare, not the information of the common people.

The first edition contained 680 ingredients. The December 1618 revised and definitive first edition contained 1,190, so there was a considerable enlargement of its contents. Many were derived from plants: 292 from various leaves, 144 from seeds, 138 from roots and 34 from barks. One hundred and sixty-two were from animal parts or excrements, including human dung. Perhaps one of the most unusual ingredients was *Cranium hominis violenta morte extincti* – skull of a man who died a violent death. The powdered skull was used to treat epilepsy.

Another material which was included in both the first and revised editions was *Cornu unicorni* – unicorn horn. This was used to strengthen the heart, and to relieve headaches and fevers. A modern reader may wonder how material from a mythical beast came to be included in the pharmacopoeia. However unicorns were mentioned in the books of the King James Bible in Numbers, the Psalms, Isaiah and Job. In Job 39.9 God asks Job 'Will the unicorn be willing to serve thee, or abide in thy crib?'[16] The reference to a unicorn is now considered to be due to a mistranslation of the original Hebrew word 're em' by the scholars in the third century who translated it into Greek as the word 'monoceros', literally one-horn.[17] It is now thought that the material traded in commerce was probably not a horn at all, but a hollow canine tooth, the spiralled tusk of the Arctic marine mammal known as the narwhal (*Monodon monoceros*), one of the smaller members of the whale family, which is sometimes known as the sea unicorn.[18] This tusk can grow up to three metres in length. Humphreys records the Doge

[16] *The Holy Bible, King James Version*, Job 39.9.

[17] Lavers, C., 2009. Chapter 3: The Judaeo-Christian Unicorn, 44–51. In *The Natural History of Unicorns*. London: Granta Publications.

[18] Humphreys, H., 1951. The Horn of the Unicorn. *Ann. R. Coll. Surg. Engl.* 8(5): 377–383.

of Venice as having two tusks which had been looted from Constantinople, and in 1404 William of Wyckham, when he died, left one to New College, Oxford, which is still preserved. The prices for unicorn horns varied but they were a prestige item.[19] In 1553 a unicorn horn owned by the King of France was apparently valued at £20,000. The second issue of the *Pharmacopoeia* allowed the substitution of rhinoceros horn for that of the unicorn, since it was presumably much cheaper and more readily available.

The text also included minerals such as amethyst, beryl, bezoar, opal and sapphire. A bezoar is a stone found in an animal's digestive system. Bezoar stones were believed to be a universal antidote to poisons. Although the book included herbs which we can still recognise as useful such as valerian and opium, most ingredients have now disappeared from conventional medical use. The preparations included waters, wines, syrups, preserves, powders, pills, troches, lozenges, oils, ointments and plasters. Many of these derived from the works of Galen and other published dispensatories. The theriacs included Mithridate, Theriaca Andromachi (Venice Treacle) and Theriaca Londinensis (London Treacle). Theriaca Andromachi contained the flesh of vipers and the preface to the book says that the theriacs are 'especially precious'. Mayerne had succeeded in introducing several inorganic chemicals into the book, such as the mineral acids, Tartarus vitriolatus (potassium sulfate), Mercurius dulcis (calomel or mercurous chloride) and iron salts.

Nicholas Le Fèvre came to England at the request of Charles II and became the Royal Professor in Chemistry to His Majesty and also Apothecary in Ordinary to the Royal Household. His book *Traité de la Chymie* was translated into English as *A Complete Body of Chemistry* (1664, 1670). In 1671 the Society of Apothecaries was able to use this information to set up the vessels and furnaces needed to establish a manufacturing laboratory for inorganic chemicals which it could then sell through a Stock Company set up by investors in the Society.[20] Thus inorganic chemicals gradually came into general use in medicine and their number increased in the later editions of the pharmacopoeia.

Nicholas Culpeper (1616–1654) was born in Ockley on the borders of Surrey and Sussex. His grandfather was a minister and Nicholas was sent to Cambridge to study for the church. However he was more interested in studying anatomy and the works of the Greek physicians. He was involved in an illicit love affair with the daughter of a wealthy family. However she was killed in an accident as she travelled to meet Nicholas to marry him. He left Cambridge without graduating and went to London where he was apprenticed to Francis Drake, an

[19] Lavers, C., 2009. Chapter 5: Beneficent Unicorns, 94–11. In *The Natural History of Unicorns*. London: Granta Publications.

[20] Hunting, P., 1998. *A History of the Society of Apothecaries*, 155ff. London: Society of Apothecaries.

apothecary in Threadneedle Street. He studied herbal medicine and astrology. He set up practice in Red Lion Square in Spitalfields as 'a student of physick and astrology' where he wrote a number of books, including his *Complete Herbal* first published in 1653, and which is still being reprinted in new editions today. Culpeper fought on the Parliamentary side during the Civil War (1642–1649), and raised a troop of volunteers to fight at the siege of Reading.[21] During the battle he was wounded by a musket bullet and then came back to London.

From the sixteenth century onwards all publications in England had to be licensed by a censor and recorded in the Stationer's register. Enforcement was under the jurisdiction of the Star Chamber, a royal prerogative court. Offenders could be punished by fines, whipping, imprisonment, branding or even by cutting off their ears. During the English Civil War parliament dissolved Charles I's prerogative courts, thereby removing the enforcement of censorship. In 1649 Culpeper took advantage of this change to publish his English translation of the *London Pharmacopoeia* with his own notes on the uses of the drugs.[22] This constituted an assault on the privileged position of the College of Physicians since it disclosed information on drugs, their preparation and uses, and discussed them in an often highly critical way – for example he described Mithridate and Theriac Andromachus as 'terrible messes'. The enraged College of Physicians attacked him in the weekly Royalist publication *Mercurius Pragmaticus* and his translation was described as 'by two years' drunken labour hath Gallimawfried the Apothecaries' book into nonsense'. However Culpeper had opened Pandora's box, and many of the subsequent editions of the *London Pharmacopoeia* were translated or the subject of analysis and commentary in English, thus making them available to a wider readership. The effect was to make information on treatments more widely available to ordinary people. Culpeper himself published a book called *Medicaments for the Poor; or Physick for the Common People*. The Anglo-Irish chemist Robert Boyle (1627–1691) published a book called *Medicinal Experiments or a Collection of Choice and Safe Remedies for the most part useful in FAMILIES, and fitted for the SERVICE of Country People* intended for 'the use of those that live in the Country, in places where Physicians are scarce if at all to be had, especially by Poor People'.[23] In 1650 the English population was around five million, but there were only just

[21] Woolley, B., 2004. *The Herbalist. Nicholas Culpeper and the Fight for Medical Freedom.* London: Harper Perennial.

[22] Culpeper, N., 1653. *Pharmacopoeia Londinensis or the London Dispensatory Further Adorned by the Studies and Collections of the Fellows now living of the Said College*. Printed by John Allen for Nicholas Boone.

[23] Boyle, R. Esq. Fellow of the Royal Society, 1703. *Medical Experiments or a Collection of Choice and Safe Remedies for the most part useful in FAMILIES, and fitted for the SERVICE of Country People*. Printed for Sam Smith at the Prince's Arms and Jo Taylor at the Ship in St Paul's Church-yard.

over 100 Fellows, Honorary Fellows and Licentiates of the College of Physicians. Thus most ordinary people, and particularly the poor, had very limited, if any, access to a physician, instead they relied on the apothecary or their own household recipes.

The second edition of the *London Pharmacopoeia* was published again in Latin, as were all subsequent editions, in 1650 during the Commonwealth. Corrosive sublimate – mercuric chloride – was added to the list of materia medica, and some recipes were amended.

During 1665, the year of the Great Plague in London, at the special command of King Charles II, the College of Physicians issued a special pamphlet in English, entitled *Certain Necessary Directions as Well as for the Cure of the Plague and for the Prevention of Infection*. The recommended treatment of victims was stated as: 'The use of London treacle is good both to preserve from the sickness and also to cure the sick.'[24]

The third edition of the *London Pharmacopoeia* was published in 1677, dedicated to King Charles II. This text remained in force for 44 years. However although few changes were made to the original text, an important one was the addition of Peruvian bark for the treatment of fever.[25] Jesuit priests in Peru in the sixteenth century had observed the local population using the bark of the cinchona tree to reduce the shaking caused by severe chills. In 1630 Juan Lopez de Canizares, the Spanish corregidor of Loxa in Ecuador (then part of Peru) was taken ill with an intermittent fever and this was cured by the local Indians who told him about the bark and how to administer it. The Jesuits sent supplies of the bark to Spain. In 1639 a Jesuit priest (subsequently a cardinal) took the bark back to Rome. From Italy it reached the Netherlands and England. The English apothecary Robert Talbor used it to cure King Charles II. Tabor was then sent by the King to France to cure the Dauphin of an ague. It was taken up by Sir Thomas Sydenham (1624–1689), and then became a fashionable remedy.

The fourth edition of the *Pharmacopoeia* was published in 1721 under the Presidency of the College of Physicians of Sir Hans Sloane.[26] Sloane was born in 1660 in Killyleagh, County Down. He studied medicine in London from 1679 to 1683, in Paris and Montpellier and finally graduated as Doctor of Physic from the University of Orange. His expertise in botany can be seen in the improvements in the list of plant drugs and their botanical descriptions in the *Pharmacopoeia*. He is still remembered in the names of London streets: Sloane Street, Sloane Square and Hans Square. The vast Sloane collection of 71,000

[24] Griffin, J.P., 2004. Venetian Treacle and the Foundation of Medicines Regulation. *Br. J. Clin. Pharmacol.* 58(3): 317–25.

[25] Keeble, T.W., 1997. A Cure for the Ague: The Contribution of Robert Talbor. *J. Royal Soc. Med.* 90: 285–90.

[26] Clark, G., 1964. Book 2 of the *History of the Royal College of Physicians of London*, 487ff. Oxford: Clarendon Press.

objects and curiosities were bequeathed to King George III for the nation in return for a payment of £20,000 for his daughters. They were bought for the nation on his death in 1753 and helped to form the basis of the British Museum. The British Library holds a collection of books which belonged to Sloane – the Sloane Printed Books catalogue.

William Heberden was born in Southwark in 1710.[27] He studied in Cambridge, gaining his BA in 1728/1729 and subsequently his MD in 1739. He practised medicine in Cambridge until 1748 when he moved to London. Whilst at Cambridge he delivered an annual series of lectures on materia medica. The text of one of his lectures was *Antitheriaca: An essay on Mithridatum and Theriaca*. This was printed in 1745 as a pamphlet of 19 pages. Heberden suggested that the famous recipe for a theriac – antidote to poisons – found in the cabinet of King Mithridates VI of Pontus after he was conquered by Pompey was likely to have only been a simple remedy made from rue, salt and dried figs. The details of the Antidotum Mithridatium which was published in Rome was a 'pompous medicine which was pretended to have been found amongst his (Mithridates) papers: although Plutarch who gives minute detail of them says not one word of this famous medicine, which one can hardly think that he would have omitted, if he found that the tradition supported by any proper testimonies'. Heberden documented the changes made in the composition of theriacs through their history: Celsus describing it as having 38 simples, 5 were then removed before Nero's time, but 20 others were added, Andromachus took out 6 but added a further 28. The composition was in a 'state of perpetual fluctuation' over the years. His pamphlet emphasised the 'unreasonable number of ingredients, their contradictory effects even according to the Ancients themselves, the inconsiderable portion of many of them in the quantity of a dose'. Finally his pamphlet expressed the hope that 'the glory of it's first expulsion from a public Dispensatory' would be 'reserved to these times and to the English Nation'. Heberden was also known for 'Heberden's ink' or Mistura ferri aromatic devised in 1760. It contained iron, cinchona, calumba, cloves, cardamom and orange peel. It remained in the *British Pharmacopoeia* until 1890.

The fifth edition of the *Pharmacopoeia* was published in 1746. The sixth edition was published in 1788. This edition was the first to omit the theriacs such as Mithridatium and Theriaca Andromachi. This edition was the first *London Pharmacopoeia* to use the system of binomial plant nomenclature devised by the Swedish scientist Carl Linnaeus (1707–1778) and published in his book *Systemae Naturae*. The 1788 edition contains the text of a Privy Council order at the Court at St James made in the presence of King George III dated 16 January 1788. This was in response to a memorandum from Sir George Baker, the president of the Royal College of Physicians. This states that the 'said book

[27] Rolleston, H., 1933. Part 1 of Volume V of *Annals of Medical History*, 409–27.

may tend to the prevention of such deceits in the making and compounding medicines'. It directs apothecaries in England, Wales and Berwick-upon-Tweed that they 'do not compound or make any medicine or medicinal receipt or prescription, or distil any oil or waters, or make other extracts, that are or shall be in the said Pharmacopoiea Collegii Regalis Medicorum Londinensis mentioned or named, in any other manner or form than is or shall be directed, prescribed and set down, by the said book'.

The seventh *London Pharmacopoeia* edition appeared in 1809 and this incorporated some of the preparations from the Edinburgh and Dublin pharmacopoeias.

The eighth edition was published in 1824 and the ninth in 1836. The Preface of the Censors' Board in the 1836 edition recorded that there had been an attempt to create a national pharmacopoeia to include Scotland and Ireland with England. The Academies in both countries were consulted but it was found extremely difficult and impracticable, so the attempt was abandoned. Bell and Redwood have speculated that another reason for the unwillingness to start work on preparing a national pharmacopoeia was that there was a considerable stock in hand of the *Dublin Pharmacopoeia* which would have needed to be sacrificed at a considerable loss to the publisher.[28] This 1836 edition consisted of an alphabetical list of the Materia Medica and details of the preparation and properties of the Preparations and Compounds. The Preparations were listed in alphabetical order of the name of the preparations, starting with Acids – such as Acetum Destillatum – and ending with Unguenta – Ointments. This edition included some of the recently discovered alkaloids such as aconitine, morphine, quinine and strychnine. English translations of the 1836 edition were published by George Frederic Collier in 1837 and by Richard Phillips in 1839 and 1841.

Work began on the tenth (final) edition in 1841. This edition was published in 1851. Additions included chloroform and cod liver oil.

Edinburgh Pharmacopoeia

Cowen has summarised how the development of the *Edinburgh Pharmacopoeia* was influenced by the ongoing friction in the seventeenth century between the Physicians of Edinburgh and the Chirugeon-Apothecaries.[29] The physicians wished to separate these two branches of the profession and claimed the legal right to regulate the apothecaries. In 1680 Sir Robert Sibbald and Dr Andrew Balfour had begun to prepare a pharmacopoeia for Scotland. A committee of

[28] Bell, J. and Redwood, T., 1880. *Historical Sketch of the Progress of Pharmacy in Great Britain*. London: Pharmaceutical Society of Great Britain.

[29] Cowen, D.L., 1957. The Edinburgh Pharmacopoeia. *Med. Hist.* 1(2): 123–39.

the College of Physicians had taken on the work in 1862, but had not been able to produce an agreed draft text. In 1694 Sir Archibald Stevenson took over the Presidency of the College and under his chairmanship a series of committees struggled to agree a text. One of the main sticking points seems to have been whether the book should include the spagyric remedies developed by Paracelsus or only the orthodox herbal remedies. Agreement was only reached when Pitcairn, Stevenson and some of the proponents of the 'new science' were suspended from their Fellowships of the College. A version of the text was then finally adopted by the College, and first edition of the *Pharmacopoea Collegii Regii Medicorum Edinburgensis* in Latin was published in 1699.

The first few editions of the *Edinburgh Pharmacopoeia* were divided into three sections. The first was a list of simples (materia medica) divided into vegetable, animal and mineral sources. The second concerned the preparations divided into waters, powders, pills, oils, ointments, electuaries – oral pastes, etc. The third section dealt with chemical medicines made from materials of animal, vegetable and mineral origins.

In common with the first edition of the *London Pharmacopoeia*, the *Edinburgh Pharmacopoeia* of 1699 contained many human products (blood, urine, fat, milk and cranium) amongst the animal simples.

The Edinburgh College of Physicians frequently reviewed and revised their pharmacopoeia. Eleven further editions were published after the first – 1722, 1735, 1744, 1756, 1774, 1783, 1792, 1803, 1817, 1839 and 1841. The 1839 edition was published in English for the first time, perhaps as a result of the poor sales of the previous edition in Latin.

The fifth edition in 1756 started a fundamental review of the materia medica by removing all of the human body parts and reducing the list of other animal simples. The vegetable materia medica were similarly reduced. The theriacs of Mithridates and Andromachus were also removed from this edition.

Dublin Pharmacopoeia

The history of the *Dublin Pharmacopoeia* has been described by Widdes in his *History of the Royal College of Physicians of Ireland, 1654–1963*.[30] In January 1718 Dr Duncan Cumyng proposed to the Dublin College of Physicians 'the making of a Dispensatory for this City and Kingdom'. He was asked to prepare 'a rough draft of such medicines as he thinks proper for a Dispensatory'. However he died in 1724 without finishing his task. A Dispensatory Committee was established in 1728 but did not get far with the work.

[30] Widdes, J.D.H., 1963. *A History of the Royal College of Physicians of Ireland, 1654–1963*. Edinburgh: E and S. Livingstone Ltd.

In August 1745 the president and fellows of the College of Physicians of Ireland unanimously agreed to use the new *London Pharmacopoeia* for their prescriptions from 1 March 1746. A translation of the 1746 *London Pharmacopoeia* into English by Dr Henry Pemberton was published in Dublin in 1754. The Irish College was to continue to use the *London Pharmacopoeia* until 1806.

In June 1784 a committee consisting of Drs Cullen, Hill and Perceval were given the task of 'the preparation of a dispensatory under the title of *Pharmacopoeia Dublinensis*, for the general use of this Kingdom'. Their committee was enlarged and by January 1794 100 copies of a specimen pharmacopoeia were printed and circulated for comment. A new committee was then appointed to revise the specimen pharmacopoeia for publication. In 1796 the Apothecaries Corporation was asked for their assistance with the work. In 1802 Robert Perceval (Professor of chemistry at Dublin University) was involved in compiling the text. The work was finally completed in 1805, revised and published as the *Pharmacopoeia Collegii Regis et Reginae in Hibernia* in October 1806. The text was in Latin apart from a proclamation from the Lord Lieutenant in Council directing all apothecaries who compounded medicines to use the book 'unless by special direction of some learned physician'.

Work on a second edition was led by Dr Barker (Professor of chemistry in Dublin), assisted by a committee from the College. This was published in 1826, again in Latin. An English translation by Spillan was published in 1828 and another by Barker and Montgomery in 1830.

The last Dublin pharmacopoeia was published in 1850 in English, and this was reprinted in 1856. A particular innovation in this edition was a system of weights and measures where a variation of the Imperial system was adopted instead of the conventional apothecaries' weights. The new scruple and drachm weights were different to those used previously.

Conspectuses, Compendia and Dispensatories

A number of conspectuses were produced where the contents of the three national pharmacopoeias were listed and combined. Some of these are listed below:

A pocket conspectus of the new London and Edinburgh pharmacopoeias by the Royal College of Physicians of London and Robert Graves, 1799 – first edition.

The Conspectus of the London, Edinburgh and Dublin pharmacopoeias by Edward Clarke, 1811 – first edition.

A conspectus of the pharmacopoeias of the London, Edinburgh and Dublin Colleges of Physicians: being a practical compendium of materia medica and pharmacy by Anthony Todd was published in 1829 – eighth edition.

Materia medica, medicine their uses and mode of administration; including a complete conspectus of the three pharmacopoeias by J. Neligan was published in 1851 – third edition.

A Conspectus of the Pharmacopoeias of London, Edinburgh, Dublin, Paris and the United States edited by G.M. Mowbray was published in 1847.

The Conspectus of the Pharmacopoeias of the London, Edinburgh, and Dublin Colleges of Physicians by Anthony T. Thompson went through at least 15 editions between 1810 and 1843, two in the United States and one translated into German.

A dispensatory can be defined as a pharmaceutical reference text based on a pharmacopoeia or pharmacopoeias. They were a practical guide for the apothecary. The two most important were the various editions of the Edinburgh and London Dispensatories. In 1753 the first edition of the *New Dispensatory* was published. Cowen has catalogued the 35 British, 6 American and 12 foreign language editions of the *New Dispensatory* and its successor the *Edinburgh New Dispensatory*.

International Influence of the National Pharmacopoeias

Cowen has summarised the extensive international influence of the London and Edinburgh pharmacopoeias.[31, 32] He has identified over 200 reprints, translations and edited versions of these texts. British works were reprinted in the original Latin or in translation in Portugal, Spain, the Low Countries, Switzerland, Germany, France, Italy, India and Austria. There were 47 foreign editions of the *London Pharmacopoeia* and 27 of the *Edinburgh Pharmacopoeia*. The earliest was an edition of the *London Pharmacopoeia* published in 1677 in Leyden.

Versions of the *London Pharmacopoeia* were published in Dublin in 1746, 1759, 1772 and 1788. As we have seen, the *London Pharmacopoeia* was official in Ireland from 1746 until 1806.

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[31] Cowen, D.L., 1982. The Influence of the Edinburgh Pharmacopoeia and the Edinburgh Dispensatories. *Pharmaceutical Historian* 12: 1–7.

[32] Cowen, D.L., 1974. The Spread and Influence of British Pharmacopoeial and Related Literature. *Veröffentlichungen der Internationale Gesellschaft für Geschichte der Pharmazie* 41: 1–106.

United States Pharmacopeia

Nicholas Culpeper's translation and commentary on the *London Pharmacopoeia* was published in Boston in 1720, and this was the first formulary published in America. Cowen has shown that the *Edinburgh Pharmacopoeia* was the basis – with the addition of a few indigenous drugs – of the *Pharmacopoeia of the Massachusetts Medical Society*, published in Boston in 1809.[33] Since more than 90 per cent of the articles in the first *United States Pharmacopeia* (USP) published in 1820 were derived from the *Massachusetts Pharmacopoeia*, the *Edinburgh Pharmacopoeia* is thus the direct progenitor of the USP.

Indian Pharmacopoeias

Singh has reviewed the history of pharmacopoeias used in India.[34] The *London Pharmacopoeia* was used by medical students in Calcutta in the 1830s. A Hindustani edition of the *London Pharmacopoeia* was published in 1836. In 1837 the government of India appointed a committee to review the state of the East India Company's dispensaries and the possibilities of using cheaper indigenous remedies. The committee recommended the compilation of a pharmacopoeia especially for use in Bengal and Upper India. William O'Shaughnessy, Professor of Chemistry and Materia Medica in Calcutta, was asked to start work on the *Bengal Pharmacopoeia* which included both imported and indigenous remedies. The *Pharmacopoeia* was published in 1844.

In 1864 a proposal was made for an Indian pharmacopoeia by Edward Waring, an assistant surgeon in the Madras Establishment of the Indian Army. This was accepted and a committee was set up with Sir Ranald Martin as its president and Waring as the editor. The compilation was carried out in London. The *Pharmacopoeia of India* was issued under the authority of the Secretary of State for India in 1868. In addition to all of the contents of the *British Pharmacopoeia* of 1864 it included 40 materia medica indigenous to India.

Quality of Drugs and Preparations

Since the early pharmacopoeias only listed the materia medica to be used in making preparations, without any detailed specification as to what were their physical and chemical properties, there was clearly considerable scope

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[33] Cowen, D.L., 1957. The Edinburgh Pharmacopoeia. *Med. Hist.* 1(2):123–139.

[34] Singh, H., 1994. *History of Pharmacy in India and Related Aspects. Volume 1: Pharmacopoeias and Formularies*. Delhi: Vallabh Prakashan.

for creation of what would now be called both 'substandard' and 'falsified' medicines. Substandard medicines are those that do not meet a quality standard, for example because of substantial adulteration. Falsified medicines have a false representation as to their identity.

Almost from the beginning there were complaints about quality of materia medica and medicaments. In the first century Dioscorides in *Materia medica* gave 40 examples of adulteration and provided methods of identification. In other cases he gave detailed descriptions of the drugs which would have helped to identify adulterated samples. Galen also complained about the quality of drugs to be from merchants and the root-gatherers, and gave information as to how to check for optimum quality by checking appearance, taste, odour or biological effect.

In the absence of formal tests and specifications in the pharmacopoeias for the materia medica, the early apothecaries and physicians had to rely on organoleptic tests – appearance, taste, colour and so on. If the pharmacopoeia lacked a description of the crude drug reliance had to be placed on the medical botanical or zoological description in a separate reference book.

In the absence of formal standards for preparations, the system of inspection of apothecary wares by censors – inspectors – from the Royal College of Physicians was subjective and could give rise to dispute. When the censors visited Mr Hammond's apothecary shop in 1715, the records of the RCP state:[35]

> He at ye first appeared Surly and soon gave unmannerly Language. He wanted (lacked) several medicines which he was obliged to keep, particularly Diascordium and Venice Treacle, and said that Mithridate which he had would serve for both. He said ye Censors came to affont him; and when they found fault with ye Barley Cinnamon Water asked if they knew when it was good, or how it should be made. This Water being bad of its kind, they ordered it to be thrown into the Street.

The 1748 pamphlet entitled *Frauds Detected or Consideration offered to the Public*[36] stated that many materia medica were 'mixed up with straws, sticks, leaves, seeds, stone and dirt'. The anonymous author stated 'Sometimes they send from Abroad one thing for Another. Oftentimes the whole Appearance is a Cheat, a made-up Composition'. The author indicated that many drugs

[35] Dodds, C. and Payne, L.M., 1961. The Influence of the Royal College of Physicians, 39. In *The Evolution of Medical Practice in Britain, Papers read at the First British Congress on the History of Medicine and Pharmacy, London, 1960*, edited by F.N.L. Poynter. London: Pitman Medical Publishing Co.

[36] Anon, 1748. *Frauds Detected or Consideration offered to the Public Shewing the Necessity of some more effectual Provision against Deceits, Differences and Incertainties in Drugs and Compositions of Medicines occasioned by the late Reformation of the London Pharmacopoeia*. London: G. Woodfall.

were received 'in a damaged or perishing state, particularly the Rhubarb, Bark, Jalap, Cantharides'. He gave examples of adulteration, with 'chymical oils of great efficacy' being adulterated with 'various mixtures of Spirits of Wine, Oil of almonds, Oil of Turpentine'. When Black Cherry Water was substituted by an extract of Laurel-Leaves, which would have contained hydrogen cyanide, it made 'a Poison of extraordinary Violence'. The theriacs in particular were prone to 'saving Artifices' with the spices, gums and other costly ingredients being omitted.

The 1826 book *The Tricks of the Trade in the Adulteration of Food and Physic*[37] provided many further examples of both adulteration and fraud. The supply-chain from sources of the materia medica to the patient was by now quite a lengthy one, including the importing company – such as the East India Company for opium, brokers, wholesale manufacturing chemists, drug-grinders who ground the crude drugs into a powder to use for manufacture of preparations, and finally the retailing chemist. Adulteration could arise at any of these stages. Amongst the examples given of adulteration were calomel (mercurous chloride) contaminated with chalk; cod liver oil adulterated with other oils, and in some cases containing no cod liver oil at all; ipecacuanha mixed with tartar emetic (antimony potassium tartrate), chalk, wheat flour or starch; jalap mixed with sawdust or guaiacum; opium mixed with poppy capsule, wheat flour, sugar; quinine sulphate mixed with water, sugar, gum and ammoniacal salts; rhubarb mixed with flour and turmeric; and scammony (a purgative) mixed with guaiacum resin, chalk, jalap, wheat flour and occasionally sand. The main miscreants implicated in adulteration were the drug-grinders. The bulk drug was sent to the drug-grinder as a given weight and the grinder returned the same weight; but he was sometimes even asked to return more. However part of the moisture content of the vegetable drug was lost during the processing and some drug was inevitably lost in the grinding machinery. The difference in weight was made up by adding different kinds of sawdust 'in the pretence of cleaning out the mill'.

The 1836 edition of the *London Pharmacopoeia* included for the first time short notes on how to check the purity of medicines for use in the chemical remedies. These had by this date had increased in number and importance. The tests included identity tests, limit tests, solubilities and specific gravities. In 1690 the great Anglo-Irish chemist Robert Boyle (1627–1691) had published a book called *Medicina Hydrostatica or Hydrostaticks applied to the Materia Medica*, in which he described the use of specific gravity as a means of detecting drug adulteration.

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[37] Anon, 1826. *Tricks of the Trade in the Adulteration of Food and Physic with DIRECTIONS FOR THEIR DETECTION AND COUNTERACTION*. London: David Boyne, Fleet Street.

In 1855 a Parliamentary Select Committee took evidence preparatory to developing the Adulteration of Food and Drugs Act.[38] Arthur Hassall MD provided evidence of analyses he had carried out on a number of samples he had purchased from wholesale and retail chemists of some key drugs. Of 33 samples of ipecacuanha tested, 18 were adulterated with tartar emetic, chalk, wheat flour, starch and, in 12 cases, with woody fibre. Of 34 samples of powdered opium, 19 were adulterated and only four were genuine. The range of alkaloid content in the opium samples ranged from 2.3 per cent to 12.2 per cent. Of 30 samples of scammony, only one was genuine, the adulterating ingredients included chalk, wheat flour and considerable quantities of wood fibre. Dr Hassall blamed the drug-grinder for 'a very large proportion of the adulteration practised'. John Simon, the medical officer of the City of London, testified that laudanum (tincture of opium) 'varying four-fold, or six-fold or eight-fold in strength. Very great evils may arise from our having professionally no certain standards of dose'. Robert Dundas, Professor of Chemistry at St Thomas's Hospital, said that every drug which is purchased in the hospital was subject to examination, and that they rejected one-third 'either from impurity or adulteration'. Theophilus Redwood, Professor of Chemistry and Pharmacy at the Pharmaceutical Society, gave evidence on the process of drug-grinding using stone-runner mills where two large cylindrical stones are made to trundle around a central axis. He felt that the use of sawdust was a necessary material in the drug-mill. Thomas Herring, a wholesale chemist and druggist, also gave evidence of adulteration in samples he had tested. Of four samples of scammony none contained but a small amount of scammony, one contained 80–90 per cent chalk. Henry Letheby, the analyst for the Lancet Commission on food and drug quality, testified that a sample of French quinine sulphate was contaminated with 50–60 per cent quinidine sulphate, but that of 30 samples of castor oil none were contaminated.

There was a gradually increasing awareness of the need for improvements in the control of drugs and preparations, to guarantee their efficacy and safety. This marks an evolution in the role of the pharmacopoeia from formulary to a compendium where quality is of key importance. Pharmacists such as John Attfield and Theophilus Redwood were to play a key role in developing this aspect. Theophilus Redwood (1806–1892) was one of the group of chemists and druggists who formed the Pharmaceutical Society on 15 April 1841. Redwood became the sub-editor of *The Transactions of Pharmaceutical Meetings* which then renamed *The Pharmaceutical Journal* in July 1895. In 1846 Redwood

[38] Parliamentary Select Committee, 1855. *Report of the Select Committee inquiring into the Adulteration of Food, Drink and Drugs. Mr Scholefield, Chairman. Being the Evidence taken before the Parliamentary Committee. Arranged and Simplified, with a comprehensive index*. London: David Bryce.

became Professor of Chemistry and Pharmacy at the Pharmaceutical Society's School of Pharmacy.

Patterns of Disease

In some London parishes in the 1750s child mortality ranged from 80 to 90 per cent, and this was even higher for children of less than one year. This was mainly due to infection and from diarrhoea from feeding infected milk.

Clayton and Rowbotham[39] have shown that the pattern of causes of death in the mid-nineteenth century resembles that of many developing countries today. The main causes of death were infection (including tuberculosis, pneumonia, scarlet fever, smallpox, influenza, typhoid and cholera). Infant and mother mortality was again mainly due to infection. Cancers were relatively rare, although probably only diagnosed at a late stage. Heart failure was a common cause, but mainly due to damage to the heart valves caused by rheumatic fever. The effective treatment of most of these diseases would have to wait until the twenty-first century; any remedies used at the time would mostly only provide symptomatic relief.

Vaccination

Edward Jenner (1749–1823) was born in Berkeley, Gloucestershire.[40] He was apprenticed to a country surgeon, Mr Ludlow of Sodbury, and then sent to be a pupil of John Hunter in London, before returning to practice in Berkeley. In the eighteenth century smallpox was a major cause of child mortality, and there were no effective remedies. The practice of variolation – inoculation with material from the pustule or scab from a smallpox patient to try to prevent the disease – had been introduced into England but was not widely practised. Jenner was aware of the country legends associating the immunity from smallpox in milkers handling the teats of cows affected by a similar disease – cowpox. In 1796 he took off some fluid from a large vesicle on the hand of a milkmaid, Sarah Nelmes. He then inoculated the arms of an eight-year-old boy, James Phipps. Two weeks later he inoculated the boy with smallpox to demonstrate that cowpoxing had made him resistant to the disease. He then extended his experiment to several others, and published his findings in July 1798 in a book, *An Inquiry into the*

[39] Clayton, P. and Rowbotham, J., 2009. How the Mid-Victorians Worked, Ate and Died. *Int. J. Environ. Res. Public Health* 6(3): 1235–53.

[40] Creighton, C., 1889. *Jenner and Vaccination: A Strange Chapter of Medical History*. London: Swan Sonnenschein.

Causes and Effects of the Variolae Vaccinae, a Disease discovered in some of the Western Counties, especially Gloucestershire, and known by the name of Cowpox. His findings were taken up by others. Dr William Woodville was one of the most practised inoculators, and he established vaccination – the process named after *Vacca*, the Latin word for cow – on a grand scale. Woodville used inoculation which was kept up from arm to arm of applicants using an exceptionally mild form of cowpox.

In 1840 the first Vaccination Act made variolation illegal and provided free optional vaccination. The 1853 Vaccination Act made it compulsory 'that every child, whose health permits, shall be vaccinated within three, or in case of orphanage, within four months of birth'.

Access to Medicines

The rich could call in a physician, although their fees were high. However the physician sometimes also treated members of the households he visited, which might include the servants.

The gentry, merchants and professional classes comprising the middle classes tended to rely more on the apothecary to supply any medicines prescribed by the physician. They would also consult the apothecary directly. The apothecary could not charge for consultation but could make a profit from the sale of medicines he recommended.

The physicians and apothecaries were constantly jockeying for position and professional prestige. In 1697 Dr Harrel, the physician and chemist to the King William III, set up a laboratory of the College of Physicians to manufacture 'all sorts of Medicines, both Chymical and Galenical'. The purpose was so that 'medicines should be prepared at the College and given to the poor at prime Cost', because of the allegedly excessive charges made by the apothecaries. The tract in which this service was reported was described by the apothecaries as 'only a Fardle or Bundle of Lies containing scarcely one Grain of Honesty or Word of Truth in it'.

The rivalry between the physicians and apothecaries continued. The apothecary William Rose was prosecuted for not only prescribing and dispensing medicines but also for visiting a patient. He was found guilty but appealed to the House of Lords. In 1704 judgement was given in his favour, thus effectively giving legal recognition to the wider role of the apothecaries. In 1815 the Apothecaries Act designated the Society of Apothecaries as an examining body for medical students. The Licentiate of the Society of Apothecaries became a recognised medical qualification. The apothecaries are now regarded as the predecessors of today's general medical practitioners.

During the eighteenth century access to medicines by the poor improved. At the beginning of the century hospitals hardly existed, except in London. Rosen has provided an account of the founding of hospitals in Britain.[41] St Bartholomew's Hospital was originally founded in 1123 and then re-founded by Henry VIII in 1545 as a hospital for the City of London. St Thomas's was founded in the twelfth century. However the provision for the sick poor in London was inadequate, as the population grew. Westminster Hospital was founded in 1719 by a charitable society. This was followed by Guy's in 1714, St George's in 1733, the London in 1740 and the Middlesex in 1745. The first provincial hospital was Winchester in 1736, followed by Bristol in 1737, York in 1740, Exeter in 1741 and Liverpool in 1745. These hospitals provided free or cheap treatment by medical practitioners. In addition the first dispensary was opened in Holborn in 1769 by Dr George Armstrong for the treatment of the Infant Poor. By the end of the eighteenth century London had 15 dispensaries and there were 13 in the provinces. Many of the major London hospitals had their own hospital pharmacopoeias with a set of preparations which were to be used in their institution – a hospital formulary. The *Pharmacopoeia in usum nosocomii a Thoma Guy, Armigero* (Guy's Hospital Pharmacopoeia) was published in 1721, the *Pharmacopoeia nosocomii regii Edinburgensis* (Pharmacopoeia of the Edinburgh Royal Infirmary) in 1746, the *Pharmacopoeia in usum Nosocomii Londinensis Sancti Georgii* (St George's Hospital Pharmacopoeia) in 1768, and the *Pharmacopoeia quam in usum nosocomii academiae Londinensis* (University College Hospital Pharmacopoeia) in 1828. Most of the preparations were made in-house, but some, such as Theriaca Andromachus and Mithridatium, were probably purchased. These hospital formularies were partly based on the preparations in the *London Pharmacopoeia*.

The Act for the Relief of the Poor of 1601 gave parishes the legal responsibility for care of those who were unable to work because of age or infirmity. The workhouse system was created where the poor could learn to work to support themselves. The passing of the Poor Law Amendment Act in 1834 led to the creation of system where workhouses were administered by Poor Law Unions each run by a local Board of Guardians. The whole system was overseen the Poor Law Commission. The funding of each Union and its workhouse came from the poor law rate levied on property in each parish. Copies of correspondence – held in the UK National Archive at Kew – between Boards of Guardians and the Commission show that the cost of medicines was sometimes included in the salaries of medical officers appointed to serve the inmates of the workhouse, and sometimes paid for separately. Two examples will illustrate this. A letter of

[41] Rosen, G., 1993. Chapter V: Health in a Period of Enlightenment and Revolution (1750–1830), 123–5. In *A History of Public Health*. Baltimore: Johns Hopkins University Press.

May 1836 from Dr James Kay, Assistant Poor Law Commissioner for Cromer to the Poor Law Commission regarding the Mitford and Launditch Poor Law Union,[42] proposed that 'a medical officer be elected for each district at a salary of £100 per annum to include: 1. Remuneration for attending the poor in their own cottages and the workhouse. 2. Medicines. 3. Assistance in the case of midwifery. 4. Surgical operations. 5. Provision of surgical instruments. 6. Treatment of disease or accident and vaccination'. A letter of 1845 from Charles Hart, Secretary to the Liverpool Select Vestry to the Poor Law Commission, informed them that Edward Parker had been elected Surgeon to the Liverpool Industrial School and that 'Parker's salary is to be £100 per annum, the Parish funding the medicines'.[43] Special arrangements sometimes had to be made to cover the costs of expensive medicines such as quinine and cod liver oil. Several of those who gave evidence to the Parliamentary Select Committee of 1855 stated that the quality of medicines provided to the poor was lower than to those who could afford to buy the best.[44] Robert Dundas from St Thomas's Hospital asserted that 'some druggists will sell any powder you like at 36s the cwt'. One of the major challenges for the state in the next century would be to provide medicines of suitable quality to rich and poor alike.

[42] 1836. The National Archive of the UK MH 12/8474/127 Folios 260–269 Letter from Dr J.P. Kay, Assistant Poor Law Commissioner for Cromer.

[43] 1845. The National Archive of the UK MH 12/5967/87 Folio 183 Letter from Charles Hart, Secretary to the Liverpool Select Vestry to the Poor Law Commissioner.

[44] See note 38.

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Chapter 2
Early Years: 1864–1914

> *Only about seventy years ago was chemistry, like a grain of seed from a ripe fruit, separated from the other physical sciences. With Black, Cavendish and Priestley, its new era began. Medicine, pharmacy, and the useful arts, had prepared the soil upon which this seed was to germinate and to flourish.*
>
> (Justus von Liebig)[1]

As we have seen, the Royal College of Physicians in London made an unsuccessful attempt to create a national pharmacopoeia in the 1830s. However it was not until the passage of the Medical Act 1858 that the creation of a national pharmacopoeia became a legal requirement. This Act was passed after 18 years of parliamentary debate on the reform of the medical profession and abolition of unqualified practitioners. No fewer than 17 Bills had failed before the Medical Act received Royal Assent on 2 August 1858. The main purpose of the Act of 1858 was to regulate the qualifications of practitioners in medicine and surgery in the United Kingdom. It came into force on 1 October 1858. It established a General Medical Council of Medical Education and Registration of the United Kingdom to register medical practitioners and control medical education in England, Scotland and Ireland (GMC).

Section LIV of the Act stated:

> The General Council shall cause to be published under their Direction a Book containing a List of Medicines and Compounds, the Manner of preparing them, together with the true Weights and Measures by which they are to be prepared and mixed, and containing such other Matter and Things relating thereto as the General Council shall think fit, to be called "British Pharmacopoeia"; and the General Council shall cause to be altered, amended, and republished such Pharmacopoeia as often as they shall deem necessary.

However the wording of the Act did not give legal power to supersede the three existing pharmacopoeias of London, Edinburgh and Dublin. The GMC Executive Committee sought from parliament the necessary extra powers, and these were obtained with the passage of a subsequent Act, the 25th and 26th

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[1] Von Liebig, J., 1851. *Familiar Letters on Chemistry in Relation to Physiology, Dietics, Agriculture, Commerce and Political Economy*, 4–5. Third Edition. London: Walton and Maberly.

Victoria cap 91. This stated that 'the British Pharmacopoeia, when published, shall for all purposes be deemed to be substituted throughout Great Britain and Ireland for the several above-mentioned Pharmacopoeias'.

Since the purpose of the new book was to supersede the three national pharmacopoeias – the *London Pharmacopoeia*, the *Edinburgh Pharmacopoeia* and the *Dublin Pharmacopoeia* produced by the Royal Colleges of Physicians in each country, it was essential to set up and consult national committees to help with the work.[2] Three branch committees were set up in London, Edinburgh and Dublin. Each commenced their sittings in December 1858. The London Committee held 158 meetings, the Edinburgh Committee 108 meetings and the Dublin Committee 141 meetings. This made a total of 407 meetings. Two conferences of delegates were held in London and Edinburgh. The Pharmacopoeia Committee met at the offices of the GMC in Soho Square in London. Professor A.B. Garrod, then Professor of Materia Medica, Therapeutics and Medicine at University College Hospital, was the secretary to the Pharmacopoeia Committee. These extensive meetings were arranged at a cost to the GMC for expenses, payments to the secretaries and editors and for remuneration for 'Chemical Investigations'. Six hundred pounds was advanced from the GMC's Registration Fund and it was intended that this would be paid back in due course from the sales of the book.

The draft manuscript of the *Pharmacopoeia* included a proposed change in the system of weights and measures to be used. In particular the Committee proposed to abandon the existing troy grain and replace it with a new grain weight. When this became known the Royal College of Physicians of London and others raised objections. A special meeting of the GMC was held in October 1862 to discuss it. The manuscript was then altered. Printing of the volume then started with proof sheets being laid before the GMC. The GMC Registrar formally announced the publication of the book on 25 January 1864 in the *London Gazette*. The *London Gazette*, now *The Gazette*, is the official journal of record and the newspaper for the Crown. It was first published in 1665 in the reign of Charles II.

The book consisted of two parts and two appendices. The first part consisted of the materia medica, the second the preparations and compounds. The appendices consisted of articles which were used in chemical processes for the manufacture of medicines and articles used in qualitative and volumetric chemical analyses, for example the test solutions. Each of the materia medica was given a Latin name and an English name, also a chemical symbol where applicable or its botanic name or source if it was obtained from a plant. No recommended doses were given for any of the materia medica or their preparations and compounds.

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[2] 1863. Reports, &c., Presented to the Medical Council, 1863. Report of the British Pharmacopoeia Committee. *Br. Med. J* June 13: 632–9.

In view of the controversy about its abuse in the twentieth and twenty-first centuries it is interesting to note the book included a new official monograph for Cannabis Indica (Indian Hemp) which was used to make up an extract or a tincture. It was probably mainly prescribed as a hypnotic. Garrod, in one of his lectures on the first edition to the Royal College of Physicians printed in the *British Medical Journal*,[3] noted that 'In large doses it causes delirium; in smaller, it exalts the mental faculties, and for this purpose it is used in Eastern countries in the form of haaschisch'.

Perhaps unsurprisingly given the extent of changes from previous national pharmacopoeias which had been used for decades, the 1864 edition was not popular with the medical profession as they could not find in it many of the preparations they were used to prescribing, or if they were retained by name they had a different composition. It was also felt to be full of errors. The controller of the Stationery Office criticised it as being printed in too expensive a style. Sir Thomas Watson, the president of the Royal College of Physicians, denounced the book as being 'a dangerous one' and said that it should not be used. Twenty-eight thousand copies of the 1864 *Pharmacopoeia* were produced but owing to the imperfections half had to be destroyed at an overall loss of £1,206.

Dr Richard Quain moved a motion at the meeting of the GMC on 27 April 1864 recommending that a committee be established to report on the arrangements for producing the book. Dr Christison was elected as chairman and Quain acted as secretary – starting a 30-year stint on the new Pharmacopoeia Committee; he became its chairman in 1874. Work on the second edition was carried out by a committee consisting of four members of the GMC. The book was ready for press on 15 March 1867. They used the services of Mr Robert Warrington FRS, who was the chemical operator at the Society of Apothecaries, and Professor Theophilus Redwood of the Pharmaceutical Society as editors. They followed a plan drawn up by Redwood.

Theophilus Redwood (1806–1892) was born in Glamorgan, South Wales.[4] In 1820 he was apprenticed to his brother-in-law, who was a surgeon-apothecary. In 1823 he was sent to be an assistant in the pharmacy of John Bell in Oxford Street in London. In 1830 he established his own dispensing business in Crawford Street in London. Redwood was one of the founding fathers of the Pharmaceutical Society in 1841. In 1842 the Pharmaceutical Society set up its own school of pharmacy and Redwood was appointed its first Professor of Pharmacy. He was also the first librarian and from 1844 the first curator of its

[3] Garrod, A.B., 1864. Garrod's Lectures on the British Pharmacopoeia. Third Lecture. *Br. Med. J*. Feb 13 1(163): 178–81.

[4] Theophilus Redwood and the Redwood Building. http://www.cardiff.ac.uk/phrmy/aboutus/redwood building/index.html (accessed July 2014).

museum. In 1874 he was the first president of the Society of Public Analysts. He died in March 1892.

The 1867 revision incorporated many of the published researches of Redwood and Dr John Attfield. Attfield was at this time the Professor of Practical Chemistry at the School of Pharmacy at the Pharmaceutical Society, where he had succeeded Redwood.

John Attfield was born in Whetstone, Middlesex in 1835, the son of an auctioneer and surveyor. He served his apprenticeship with William Smith in Lambeth from 1849 to 1854. During his final year he attended the School of Pharmacy at the Pharmaceutical Society. He became an assistant to Dr Edward Franklin at St Bartholomew's Hospital in 1854. He studied in Tübingen to obtain his MA and then PhD. In 1862 he was appointed director of the laboratories of the School of Pharmacy of the Pharmaceutical Society. In 1863 he was one of the founders of the British Pharmaceutical Conference. He died in March 1911. A tribute by the distinguished American pharmacist Joseph Remington stated that he was 'one of the strongest men of the Victorian Era, who had given the greatest part of his life in improving the profession of pharmacy by his chemical knowledge'.

Forty thousand copies of this 1867 edition were printed. For the first time this edition introduced recommended adult doses for all of the more important medicines. This new edition was much more favourably received. The *Pharmaceutical Journal* stated that 'the work has been carefully and well prepared, and that it is, on the whole, a decided success' and an editorial in the *British Medical Journal* (BMJ) said that 'We have already expressed our belief that it will prove to be the best Pharmacopoeia yet published, and we see no reason to retract or modify that opinion. On the contrary, we already hear expressed a general agreement with that view'.[5] The sections of the *Pharmacopoeia* on materia medica and preparations were integrated in this edition. There was an increasing emphasis on pharmaceutical quality, and the preface stated that great attention had been made to 'make the description of all of the substances in the work sufficiently comprehensive and minute to afford a clear indication of what the medicines of the Pharmacopoeia are intended to be, and to enable those who are engaged in their administration to determine the identity and test the purity of such as are met with in commerce'.

The preface to the 1867 edition of the Pharmacopoeia included a discussion of the possible future use of the metric system for doses instead of grains and ounces for weights; minims, fluid drachms and ounces for liquid measures. The GMC stated that as the system is 'as yet but little used, and is to a great extent

[5] Leach, D.J., Tirard, N. and Stockman, R., 1895. The Approaching Revision of the British Pharmacopoeia. Memorandum on the British Pharmacopoeia by the Therapeutic Committee of the British Medical Association. *Br. Med. J*. June 8, 1(1797): 1276–8.

unknown in this country', it has not 'employed the metrical system'. As we will see later, this debate was to continue for nearly another century, as the 1958 *Pharmacopoeia* still included some doses in grains. However the metric system was introduced in the 1867 edition alongside the Imperial weights and measures for the volumetric analyses used in some of the monograph tests. Thus there was recognition that metric weights and measures would increasingly be used by pharmaceutical scientists and analysts even if the clinicians still clung to the ancient and familiar.

In 1874 an *Addendum* to the *British Pharmacopoeia* (BP) 1867 was prepared with Attfield as the editor, Redwood's health having by then failed. This sold 11,040 copies.

The third edition of the BP was published in 1885. It was produced by a committee consisting of eight members of the GMC chaired by Dr Quain. Professors Redwood, Attfield and Robert Bentley were the joint editors of this edition.

Robert Bentley (1821–1893) was a pharmacist, who subsequently studied medicine at King's College, London. He was a botany lecturer the London Hospital Medical School and then in 1859 he became the Professor of Botany at King's College, London. He was the joint editor of the *Pharmaceutical Journal* with Redwood.

Amongst the new drugs included in this edition were caffeine, caffeine citrate, cinchonidine sulphate, cocaine and cocaine hydrochloride, ergotine, menthol, morphine sulphate, eucalyptus oil, physostigmine, pilocarpine, salicylic acid, sodium salicylate and thymol. The first tablet was introduced into the *Pharmacopoeia* – Tabellae Nitroglycerini – Glyceryl Trinitrate Tablets. Two additional hypodermic injections were added – Hypodermic Injection of Apomorphine and Hypodermic Injection of Ergotin. Both of these injections were directed to be made up as required for use, however no mention was made of the need for their sterilisation.

An important issue which was being considered even in the nineteenth century was that of the purity of drug substances and control of their impurities. The monograph in the 1885 BP for Quinine Sulphate included gravimetric tests for the related alkaloids cinchonidine and cinchonine, quinidine and cupreine. The limit imposed was that 'Sulphate of Quinine' should not contain much more than 5 per cent of sulphates of other cinchona alkaloids. This was one of the first quantitative limit tests for impurities.

An *Addendum* to the *Pharmacopoeia* was prepared in 1889 and published in 1890. The Pharmacopoeia Committee was chaired by Quain, with Attfield again acting as editor. A sub-committee was appointed to work with the medical authorities in the Royal Colleges, universities and the Society of Apothecaries to produce a list of new medicines of well-recognised medicinal value. One hundred and forty were proposed, of which the Committee adopted 37. The

Pharmaceutical Society added a further four articles. The Committee itself added Acetanilidum, Phenacetinum and Pulvis Sodae Tartaratae Effervescens. Five thousand copies of the *Addendum* were printed.

As the preparatory work on each successive edition of the *Pharmacopoeia* was announced there was often a detailed discussion and comment in the medical journals. The Therapeutic Committee of the British Medical Association (BMA) set out its proposals for revision in June 1895 in a BMJ article.[6] The Therapeutic Committee of the BMA was chaired by Dr D.J. Leech with Dr Nestor Tirard as one of its honorary secretaries. The role of the *Pharmacopoeia* was discussed – whether or not it should be a daily reference text for medical practitioners. Some medical examination boards only required knowledge of some of the drugs in the book; other boards included all of the substances and preparations in their curriculum. The Therapeutic Committee felt that the *Pharmacopoeia* should include 'all such remedies as the existing state of medical practice requires'. To help them to ascertain which preparations should be included they conducted a survey of BMA members. Replies were received from 5,609 members (about a half of those sent the survey). The BMJ article listed the preparations in terms of frequency of use and categorised them as Often, Rarely and Never Used.

The 10 most frequently used preparations from this 1895 list are tabulated below in Table 2.1 and in Figure 2.1 in terms of the numbers of practitioners using each of the top 10 preparations 'often'.

Table 2.1 British Medical Association 1895 survey of number of practitioners using the medicines 'often' (the top 10)

Preparation		English title of preparation	Therapeutic use
1	Liquor ammonii acetatis	Solution of Ammonium Acetate	Diaphoretic (increases sweating), diuretic
2	Liquor ammonii acetatis fort	Strong Solution of Ammonium Acetate	Diaphoretic, diuretic
3	Pilula aloes barbadensis et myrrha	Pill of Aloes and Myrrh	Purgative
4	Tinctura zingiberis fortiori	Strong Ginger Tincture	Carminative, dyspepsia, flatulence
4	Ferri sulphas exsiccate	Dried Ferrous Sulphate	Anaemia, amenorrhoea and general debility
5	Tinctura aurantii recentis	Fresh Orange Tincture	Flavour

[6] 1928. Obituary: Sir Nestor Tirard. *Br. Med. J.* Nov 17 2(3541): 917.

Preparation		English title of preparation	Therapeutic use
6	Spiritus aetheris compositus	Compound Spirit of Ether	Stimulant, antispasmodic
7	Pilula ferri carbonatis	Pill of Ferrous Carbonate	Anaemia, amenorrhoea, neuralgia
8	Syrupus papaveris	Syrup of Poppies	Soothing syrup
9	Pilula hydrargyi subchloridis composita	Compound Pill of Mercurous Chloride	Purgative, diuretic, treatment for syphilis, chronic hepatitis
10	Charta sinapsis	Mustard Paper	Rubefacient used externally for pneumonia, pleurisy, rheumatism, bronchitis and colic

The fourth edition of the *British Pharmacopoeia* was published in 1898. The Pharmacopoeia Committee of the GMC which produced this edition was chaired by Sir Richard Quain, who was by then also the president of the GMC, with Dr Nestor Tirard acting as the secretary to the Committee.

Nestor Tirard (1853–1928) studied medicine at King's College Hospital, where he became a consulting physician and then professor of principles and practice of medicine. He had a research interest in renal disease. Tirard served as secretary to the Pharmacopoeia Committee until 1915 when he had to step down because of his war work in command of the Fourth London General Hospital with the rank of lieutenant-colonel. He was knighted in 1916. In 1922 he was appointed a Crown nominee to the GMC and resumed his duties as honorary secretary to the Pharmacopoeia Committee.[7]

Since the book would be official in a number of countries in the Dominions and Colonies, there had been widespread consultation of the medical and pharmaceutical authorities. Comments had been received from Canada, Hong Kong, India, Jamaica, New South Wales, Queensland, Tasmania, Victoria, the Bahamas, Barbados, Bermuda, British Honduras, the Cape of Good Hope, Ceylon, Cyprus, Malta, Natal, St Helena, Sierra Leone, South Australia, Western Australia and Zulu-land. A Committee of Reference in Pharmacy through the Pharmaceutical Society was chaired by Mr Walter Hills and gave pharmaceutical advice to the Pharmacopoeia Committee. The Pharmacy Committee included Mr William Martindale who is perhaps better known as the principal author, with Dr W. Wynn Westcott, of *The Extra Pharmacopoeia of Unofficial Drugs and Chemical and Pharmaceutical Preparations* first published in 1883. This edition of the *Pharmacopoeia* was edited by Dr John Attfield. Drugs included in this edition for the first time included cocaine, codeine phosphate, hyoscine

[7] 1928. Obituary: Sir Nestor Tirard. *Br. Med. J.* Nov 17 2(3541): 917.

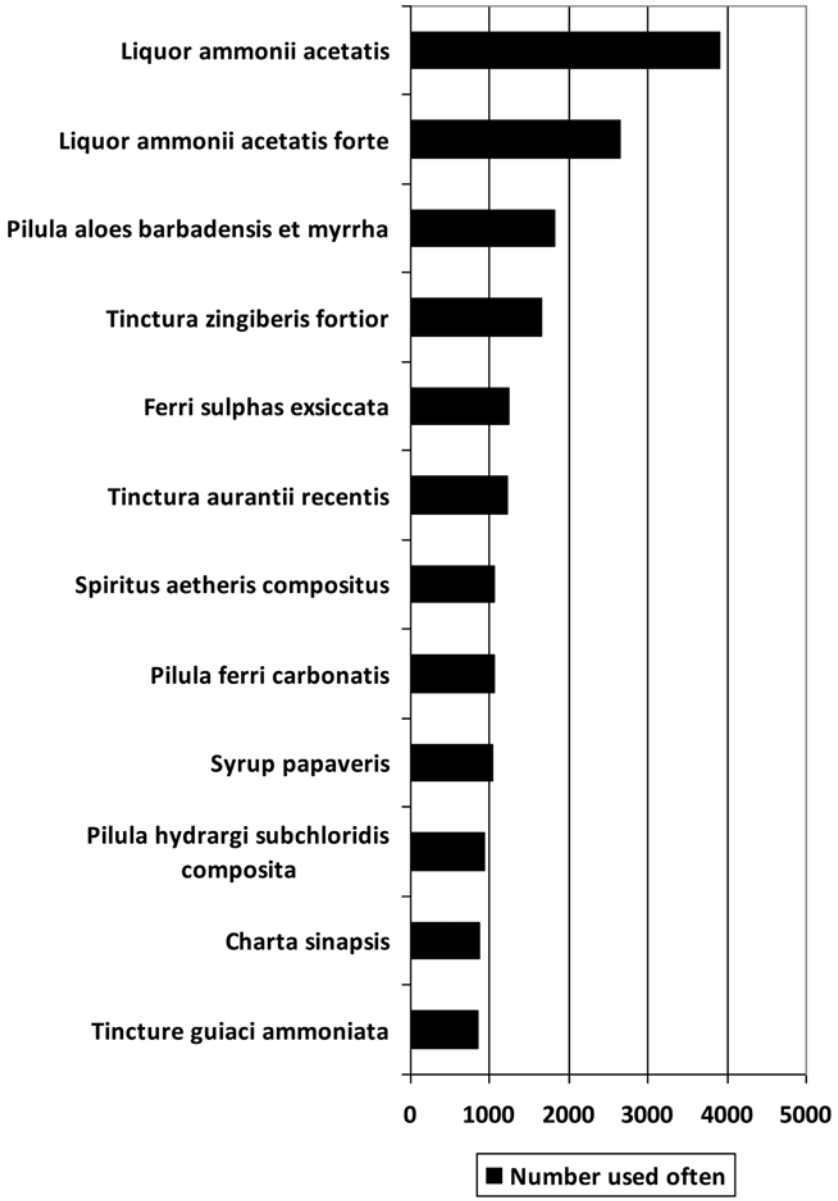

Figure 2.1 The most widely used medicines from a British Medical Association survey of prescribers for the 1896 *British Pharmacopoeia* (the number of practitioners using each medicine 'often')

Source: Produced by the author using the BMA published survey data.

hydrobromide, kaolin, lithium citrate, liquid paraffin and dried thyroid. One hundred and eighty-seven drugs and preparations from the BP 1885 and the additions of 1890 were omitted from the new edition. Thus many of the older drugs and preparations were gradually being replaced or superseded. Some of the newer dosage forms coming onto the market, such as capsules, cachets and granules, were not included in the *Pharmacopoeia*, and indeed were airily dismissed in a sentence in the preface: 'It has not been thought desirable to describe, in the Pharmacopoeia, various pharmaceutical devices which have been introduced in recent years for the more easy administration of medicines.' This edition did however include many more chemical analytical tests in both individual monographs and in the appendices, and a new section entitled 'Tests for Substances Mentioned in the Text of the Pharmacopoeia', which mainly comprised identity tests for inorganic elements and salts.

The Indian and Colonial Addendum 1900

An *Addendum* to the BP 1898 was published in December 1900. In 1893 the Earl of Kimberley, the Secretary of State for India, asked the General Medical Council to investigate how the *British Pharmacopoeia* could be better fitted to the needs of India and the Colonies. On 26 May 1893 the GMC asked its Pharmacopoeia Committee 'to enter into correspondence, through the Privy Council, with the India Office and the Colonial Office, with a view to ascertaining in what degree, if any, the *British Pharmacopoeia* can be better fitted than at present to meet Indian and Colonial requirements as regards important natural drugs and pharmaceutical preparations'. The 1898 BP had already included a two-page Appendix XI of Alternative Preparations Sanctioned for Use in India and the Colonies. This allowed, for example, the use of extra alcohol in Liquid Extracts to prevent fermentation, and the substitution of more or less White Beeswax instead of Oil of Theobroma in suppositories because the higher ambient temperatures would otherwise cause them to become too soft.

The work on the 1900 *Addendum* was supervised by a small Pharmacopoeia Committee of six members chaired by Dr MacAlister.[8] Donald MacAlister (1854–1934) was a member of the GMC for 44 years, and its president from 1904–1931. He was born in Perth and was a native speaker of Gaelic. He studied medicine in Cambridge, then at St Bartholomew's Hospital in London and Leipzig. He was the principal of Glasgow University from 1907 to 1929 and its chancellor from 1929 until his death in 1934. He was knighted in 1908 and created a baronet of Tarbert, Cantire in the County of Argyll in 1924.

[8] Crilly, A.J., 2004. MacAlister, First Baronet (1854–1934). *Oxford Dictionary of National Biography*. Oxford: Oxford University Press.

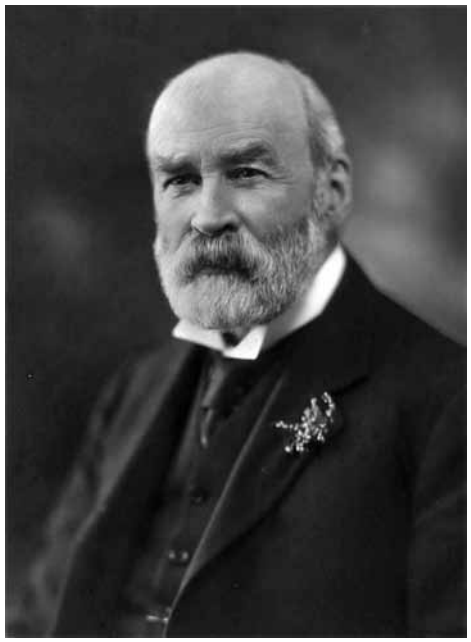

Figure 2.2 Sir Donald MacAlister, Chairman of the General Medical Council Pharmacopoeia Committee, President of the General Medical Council, 1904–1931

Source: © National Portrait Gallery, London.

Dr John Attfield again acted as the editor. The *Addendum* was designed to serve the needs of all of the Divisions of the British Empire with locally available materials. These included India, the African Colonies, the Australasian Colonies, the Eastern Colonies (Ceylon, Hong Kong, Labuan, Mauritius, Seychelle Islands and the Straits Settlements), the Mediterranean Colonies (Cyprus, Gibraltar and Malta), the North American Colonies, the West Indian Colonies and the Falkland Islands. Each of the individual materia medica and preparations are annotated with a note as to which of the colonies they were official. For example Arnica Flores (dried heads of arnica flowers) was official in the North American Colonies, and Oleum Arachis (Arachis Oil) was official in India, the African Colonies, the Eastern Colonies and the Australasian Colonies. The *Addendum* included Oleum Gynocardiae, otherwise known as chaulmoogra oil, which was used, internally and externally, for the treatment of leprosy. This was official in India and the Eastern Colonies. By December 1901 320 copies of the *Addendum* had been sent to officers administering the governments of the Colonies.

The Secretary of State for India wrote again to the GMC asking for 3,500 copies of the *Addendum*. However some further alterations were requested to the formulae. Anderson has shown[9] how the original text caused difficulties since lard was contained as a constituent in some formulae – killing pigs was against the Muslim religion and killing cows against the Hindu religion. Indurated lard from pigs was deleted and prepared suet from sheep was added. Benzoated lard from sheep suet was used instead of pigs' lard. The GMC Council sanctioned the publication of this special *Government of India, Edition 1901*. This was published in February 1902.

By the end of November 1913 45,598 copies of the 1989 *Pharmacopoeia* had been sold and 4,522 copies of the *Indian and Colonial Addendum*.

1914 *British Pharmacopoeia*

Dr Leech, the chairman of the Pharmacopoeia Committee from 1898 to 1900, had instituted the establishment of a regular Conference between the members of the Committee and the Pharmaceutical Societies of Great Britain, Ireland and Northern Ireland. After his death in 1900 Dr Donald MacAlister took over as chairman of the Committee and continued to involve the Pharmaceutical Societies. The meeting of the Conference in 1900 had recommended investigations to be carried out for the next edition. Much of this research was carried out by Professor Henry Greenish at the Pharmaceutical Society's laboratories. Studies included solubilities of official drugs, and percentage of ash in crude drugs and their powders. Two meetings of the Conference were held in 1902. The GMC made a grant of £100 towards the expenses of carrying out these investigations. A special meeting of the Committee was held in October 1903 to consider William Chattaway's *Digest of Researches and Criticisms ... of the British Pharmacopoeia, 1898*. A £50 grant was awarded to Professor Dunstan of the Imperial Institute for his studies on development of a pharmacopoeial test for arsenic. In February 1905 a Committee of Reference in Pharmacy was formed to advise the Pharmacopoeia Committee. Mr Walter Hills was chosen as its chairman, with Professor Greenish as its secretary.

The GMC had been liaising with the India Office and the Colonial Office to seek the views of the 29 Colonial governments and administrations on their needs in a new edition, which was clearly intended as a pharmacopoeia to serve the whole British Empire – an Imperial pharmacopoeia. These views were received in 1905.

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[9] Anderson, S., 2010. Pharmacy and Empire: The British Pharmacopoeia as an Instrument of Imperialism. 1864 to 1932. *Pharmacy in History* 52(3 & 4): 112–21.

In 1906 the Committee of Reference in Pharmacy made a detailed report on the published criticisms of the 1898 *Pharmacopoeia*, with recommendations for changes in the monographs or for further laboratory work which was needed. In 1907 they reported that a special assistant had been recruited to carry out investigations. This Pharmacy Committee was also obtaining prescribing statistics from a survey of pharmacists for official and non-official medicines dispensed in England, Wales and Scotland during a year to help the Pharmacopoeia Committee chose which should be included in the new edition.

In May 1907 the Pharmacopoeia Committee requested that the president of the GMC ask the Royal Colleges of London, Edinburgh and Ireland, and the other Medical Authorities for their suggestions for revision of the *Pharmacopoeia*. By May 1908 these views had been obtained together with the results of the analysis of 48,000 prescriptions dispensed by pharmacists. The results of all of the views on the suggestions for revision were tabulated by Dr Nestor Tizard, the secretary to the Committee. The Committee met for a two-day meeting in October 1909 to come to a decision on the inclusion or omission of articles in the new edition.

In May 1910 the Committee of Reference in Pharmacy presented a further report on its work on the revision to the Conference of members of the Pharmacy Committee and the Pharmaceutical Societies. It was agreed that this report should be published for wider comment. A further meeting of the Conference took place in 1911 where the third report of the Committee of Reference in Pharmacy was presented.

In November 1911 Dr Tirard and Professor Greenish were appointed as editors for the new edition, and they started classifying all of the text materials relating to the revision. By June 1912 the editors had presented to the Pharmacopoeia Committee the first drafts of some of the monographs. Two additional Committees of Reference in Botany and Chemistry were appointed to advise on the revision. By November 1912 four sections of the text had been prepared by the editors for review by the Committee. This work continued throughout 1913. The India Office was again consulted on the draft text in September 1914[10] to ask if a special edition would be needed for India. This time they noted that the book contained Ox Bile and stated that 'ox bile would offend the Hindoo as Hog's Lard would offend the Mussalman'. After much discussion the Viceroy of India cabled the Secretary of State for India to agree that they did not need a special edition.

The 1914 *Pharmacopoeia* included 44 new articles or preparations. One hundred and sixty-eight articles or preparations in the 1898 edition or the *Addendum* were deleted. Amongst the new drugs included for the first time

[10] Anderson, S., 2010. Pharmacy and Empire: The British Pharmacopoeia as an Instrument of Imperialism. 1864 to 1932. *Pharmacy in History* 52(3 & 4): 112–21.

Figure 2.3 Professor Henry Greenish, Co-Editor of the *British Pharmacopoeia*
Source: © National Portrait Gallery, London.

were acetylsalicylic acid (aspirin), adrenaline, barbitone, cresol, diamorphine hydrochloride (heroin), glucose and phenolphthalein. Seven of the plasters were deleted. *Aristolochia indica* had briefly appeared in the *Indian and Colonial Addendum*, but was now deleted – it is now known that aristolochic acid from *Aristolochia* species can cause cancers of the urinary tract and kidney damage.

The preface to the *Pharmacopoeia* stated that doses were given in both Imperial and metric systems 'in the expectation that in the near future the metric system will be generally adopted by British prescribers'.

There were a number of new appendices of analytical methods in the 1914 text. These were Reactions and Tests for Substances mentioned in the Text (such as for Acetates, Aluminium, Ammonium Salts and so on), a Quantitative Limit Test for Lead, a Quantitative Limit Test for Arsenic, and various tests on oils, fats and waxes (acid value, saponification value, iodine value, esters in volatile oils, and so on). The appendices also gave the limits for Arsenic and Lead in individual monographs. For example the limits in Acetylsalicylic Acid were 10 parts per million of Lead, and two parts per million of Arsenic.

Legal Status of the *British Pharmacopoeia*

The 1852 Act for regulating the Qualifications of Pharmaceutical Chemists – known as the Pharmacy Act, legally constituted the Pharmaceutical Society of Great Britain and gave it powers to regulate the education, training and registration of pharmacists. This Act was amended in 1868 with further provisions to regulate the sale of poisons. The Pharmacy Act 1868 for the first time made it a legal offence for pharmacists to 'compound any Medicine of the British Pharmacopoeia except in accord with the formularies of the said Pharmacopoeia'. The penalty for this offence was £5.

The Adulteration of Food and Drugs Act 1872 made it an offence to 'wilfully admix any ingredient or material with any drug to adulterate the same'. The penalty for this was a fine not exceeding £50 for a first offence, and for a second offence a period of imprisonment not exceeding six months, with hard labour. The Act required the City of London and local authorities to appoint 'persons possessing competent medical, chemical and microscopical knowledge' to carry out the analysis for the courts (public analysts). The Adulteration of Food and Drugs Act 1875 amended the 1872 Act. It incorporated the provisions of the Pharmacy Act 1868, thus making compliance with the *British Pharmacopoeia* a broader legal requirement.

The Food and Drugs (Adulteration) Act 1928 made it an offence to 'sell to the prejudice of the purchaser any article of food or any drug which is not of the nature, or not of the substance, or not the quality of the article demanded by the purchaser'. However proprietary medicines were exempt from the Act. The Act also made it an offence to 'sell ... any compounded drug which is not composed of ingredients in accordance with the demands of the purchaser'. In both cases if there was a *British Pharmacopoeia* monograph it would be implied that this should be the relevant standard.

Enforcement of Legal Standards

The Local Government Board was created in 1871. Its function was to provide a central body responsible for public health. This included the administration of the Adulteration of Food and Drugs Acts. Most sampling and testing concerned foods. Stieb[11] has summarised the results of tests of adulteration by the public analysts for a period from 1876 to 1931. In 1876 250 samples were taken across the country and 18.8 per cent were adulterated. In 1879 613 samples were taken and 27.8 per cent were adulterated. After that matters gradually improved and

[11] Stieb, E.W., 1966. *Drug Adulteration. Detection and Control in Nineteenth Century Britain*. Madison: University of Wisconsin Press.

by 1931 when 5,257 samples were taken only 4.5 per cent were adulterated. However even if adulteration had been detected it did not always result in legal action – in 1893 of the 85 samples found which were adulterated only 35 were proceeded against, and only 28 had penalties imposed. Some of the adulteration reported was very serious. For example jalap (a purgative) was reported as containing two-thirds strychnine, tincture of rhubarb as being half-strength, paregoric (camphorated tincture of opium) containing no opium, and borax containing arsenic.

British Pharmaceutical Codex

On 4 November 1903 the Council of the Pharmaceutical Society of Great Britain decided to produce its own reference book on drug substances and preparations. The first edition of the *British Pharmaceutical Codex* (BPC) was published in 1907.[12] Its full title was *The British Pharmaceutical Codex. An Imperial Dispensatory for the use of Medical Practitioners and Pharmacists*. It had a broader scope than the BP as it claimed to cover all drugs and medicines in common use throughout the British Empire, and also included the principal substances and preparations which were official in the pharmacopoeias of France, Germany and the United States, as well as those described in the BP. The format of the book was alphabetical with the names of monographs for drugs of vegetable and animal origin, chemical substances and formulae for their preparations. The work was produced by a committee of seven members chaired by Mr Michael Carteighe. The compilation and laboratory investigations were organised by a sub-committee consisting of Professor W.E. Dixon (Professor of Pharmacology, Kings College, London), Professor Greenish (from the Pharmaceutical Society), Mr Edmund White, Mr W.F. Gulliver, Mr F.W. Gamble and Mr John Humphreys (Secretary). The book included a wide range of preparations (pills, capsules, tablets, lozenges, powders, ointments, pastes, plasters, eye-drops, hypodermic injections, pastilles, sprays, suppositories, cachets, infusions, lotions, nebulae [sprays for the throat and nose], spirits, gargles, tinctures and pessaries), but also at least one dressing – Absorbent Gauze. As we can see the BPC included some of the 'various pharmaceutical devices' such as capsules, cachets and tablets that had been so summarily dismissed in the preface to the 1898 *Pharmacopoeia*.

An *Addendum* to the 1907 BPC was issued in 1911 and served as a war emergency formulary during World War I (1914–1918). Further editions were published in 1923, 1934, 1949, a *Supplement* in 1952, 1954, a *Supplement* in

[12] 1907. *The British Pharmaceutical Codex. An Imperial Dispensatory for the use of Medical Practitioner and Pharmacists*. Pharmaceutical Society. London: St Clements Press Ltd.

1957, 1959, 1963, a *Supplement* in 1966, 1968, a *Supplement* in 1971, 1973 and a final *Supplement* in 1976.

A companion book on veterinary drugs and preparations, the *British Veterinary Codex*, was first published in 1953, a *Supplement* in 1959, 1965 and a final *Supplement* in 1970.

Although the BPC was in many ways a competitor to the BP it lacked the official legal status of the BP.

Responsibility for Production of the *Pharmacopoeia*

The GMC was legally responsible under the Medical Act 1858 for the production of the *British Pharmacopoeia*. As we have seen, it delegated this function to a Pharmacopoeia Committee. The Pharmacopoeia Committee consulted a range of medical bodies such as the BMA, the Royal Colleges of Physicians and the Apothecaries Society, together with the universities concerned with medical education. From these consultations the Committee could draw up a list of the drugs and their preparations to be included in the next edition, and state the recommended adult dose of each. However, after that the major part of the work was to draw up the quality standards for the chosen drugs – the Description and the Characters and Tests – solubility, melting point, colorimetric identification test, and so on. For the preparations – the mixtures, liniments, ointments and so on, a detailed method of preparation was required for pharmacists to use, and again a specification with Characters and Tests. Most of this work was delegated to a Committee of Reference in Pharmacy Committee set up by the Pharmaceutical Society of Great Britain. Once the text had been compiled by the editor, the final text was approved by the Pharmacopoeia Committee of the General Medical Council. Pharmacists had no seat on the Pharmacopoeia Committee and an increasing dissatisfaction was felt. However the medical practitioners were clear that theirs was the legal responsibility and any change was deemed unnecessary. An article in the BMJ of 10 December 1892 sums up this point of view: 'for the presence of medical and pharmaceutical practitioners on one and the same committee would involve much waste of pharmaceutical time, and, in the present or immediately prospective relations of medical men to chemists and druggists in this country, would probably be found to be impracticable'.[13]

Dr Leech, who was a member of the Pharmacopoeia Committee since 1892 and its chairman from 1898 until his death in 1900 had instituted regular conferences between the Committee and the Pharmaceutical Societies of Great Britain and Ireland. These had produced recommendations for research

[13] 1892. The British Pharmacopoeia. *Br. Med. J.* Dec 10 2(1667): 1297.

which were then carried out under the direction of Professor Henry Greenish in the Pharmaceutical Society's laboratory. In 1902 the GMC made a grant of £100 towards the expenses of carrying out studies on the solubility of chemical substances.

The British Pharmaceutical Conference was established in 1863 on the initiative of Richard Reynolds of Leeds and H.B. Brady of Newcastle. Its objective was the advancement of pharmaceutical science. It was independent of the Pharmaceutical Society. The 47th annual meeting took place in Cambridge under the presidency of Mr Francis Ransom of Hitchin. In his presidential address on 26 July 1910 Ransom drew attention to the difference in the organisation responsible for the production of the pharmacopoeia between Britain and other national pharmacopoeias.[14] He said that 'in nearly every instance the national pharmacopoeias were revised by commissions on which the pharmacists as well as the medical men were represented'. He went on to suggest that 'a more direct recognition of pharmacists in future revisions would be found to embody more fully the results of pharmaceutical research in our national Pharmacopoeia'.

Unification of Formulae for Potent Drugs and the *International Pharmacopoeia*

In 1902 the Belgian government wrote to the UK government inviting its participation in an international conference for the unification of formulae of 'drastic' drugs. The Privy Council contacted the GMC and requested them to send a delegate to the conference. The GMC agreed and Dr MacAlister as Chairman of the Pharmacopoeia Committee attended. The International Conference for the Unification of the Pharmacopoeial Formulae of Potent Drugs and Preparations was held in Brussels from 15 to 20 of September 1902 with 19 countries involved. Lieutenant Colonel J. Reid represented the government of India. The Conference proposed the creation of an International Secretariat for unification of national pharmacopoeias based in Brussels. Each country was invited to nominate a Correspondent. The conference report included a series of recommendations for standardising potent drugs and their preparations. The GMC agreed at its meeting of 2 December 1902 to nominate a Correspondent. This was the first step in international cooperation that was eventually to lead firstly through the League of Nations and then the World Health Assembly to the publication of the first edition of the *International Pharmacopoeia* in 1950 (more details are given in Chapter 6).

[14] 1910. British Pharmaceutical Conference. Presidential Address. *Br. Med. J.* Aug 20: 475–7.

Access to Medicines

In the nineteenth century the rich and the burgeoning middle class could afford to pay a physician. The UK population had increased from 10.5 million in 1801 to 15 million in 1841. By 1901 it had reached 38.2 million. The Medical Act of 1868 established the GMC and the *Medical Register*. Nearly 15,000 names appeared in the July 1859 *Register* and this had increased to 23,000 in 1889. By 1924 there were 50,000 practitioners on the *Register*. Access to medical care for working-class families would have been via Works Clubs – Medical Aid Societies who arranged with their employer to deduct an agreed sum for themselves and their families, Provident Dispensaries – funded partly by beneficiaries and partly by charitable donations, Doctors' Clubs, where patients paid regular contributions, Friendly Societies where families paid into a common fund used to provide sick-pay in the event of illness or accident, and public medical services whose dispensaries were controlled by local doctors' groups.[15] By 1900 about 4.5 million were members of Friendly Societies – half of the adult population of Great Britain at the time. However this still left a substantial number of patients not covered for medical care or ready access to medicines. Patent medicines were very popular and sold directly to the public by pharmacies, and in addition the major role of pharmacies was to supply pharmaceutical advice and assistance directly to the public.

In 1908 David Lloyd George, the Chancellor of the Exchequer in the Herbert Asquith Liberal government, brought in a Bill which became the 1911 National Insurance Act. For the first time this gave many workers, but not their families, access to a contributory system of insurance against illness and unemployment. This also allowed them access to prescribed medicines. This increased the demand on medical practitioners for prescriptions for medicines, and for pharmacists to dispense them. Anderson[16] has shown that the number of prescriptions rose from 15 million to 50 million per year. It also created a market for the increasing number of manufacturing firms for commercial products, and a stimulus for the development of new medicines. The *Pharmacopoeia* would have to respond to the rapidly changing nature of the market.

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[15] Green, D.G., 1985. Professional Monopoly of Power. In *Working-Class Patients and the Medical Establishment*. Aldershot: Gower/Maurice Temple Smith.

[16] Anderson, S., 2006. From Bespoke to 'Off-the-Peg'. In *From Physick to Pharmacology*. Edited by Louise Curth. Aldershot: Ashgate.

Chapter 3
Middle Years: 1914–1968

Long overdue but highly controversial.

(Francis Hemming)[1]

The *British Pharmacopoeia* 1914 was published in December 1914 by Constable and Co. Ltd. The first issue was of 20,000 copies. By January 1923 50,000 copies had been issued.

World War I

On 4 August 2014 Britain declared war against Germany. Hostilities lasted until the armistice was signed on 11 November 1918. The war severely disrupted normal patterns of international trade and affected the manufacture and supply of many medicinal ingredients. Sugar was in short supply and glycerol was used in the manufacture of nitroglycerin for munitions. Soft paraffin was used in the manufacture of cordite. At Gretna the huge H.M. Factory had been built adjacent to the Solvay Firth to supply cordite to the munitions filling factories which produced ammunition for the British forces.[2] It employed 30,000 workers, mostly women. Sir Arthur Conan Doyle called the mixture of nitroglycerine, guncotton and soft paraffin – cordite – the 'devil's porridge'. At first the shells contained picric acid as the explosive with cordite as the propellant. The women munitions workers in the filling factories were sometimes called 'canaries' as a result of the yellowing of their skins from contact with picric acid. By October 1915 shells contained ammonal – ammonium nitrate, aluminium powder, trinitrotoluene and charcoal, with cordite. It is estimated that five million tons of shells were fired by the Allies during the war.[3]

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[1] Verdict of Francis Hemming, Secretary to the Committee of Civil Research Sub-committee on its findings about the reform of the Pharmacopoeia, in Bennet, A., 1978. Advising the Cabinet – the Committee of Civil Research and the Economic Advisory Council: A Brief Comparison. *Public Administration* 56(1): 57–71.

[2] 2014. Devil's Porridge: How the World's Largest Factory Helped Win the Great War. http://www.scotsman.com/news/devil-s-porridge-how-the-world-s-largest-factory-helped-win-the-Great-War-1-465872 (accessed July 2014).

[3] Cocroft, W.D., 2000. *Dangerous Energy: The Archaeology of Gunpowder and Military Explosives Manufacture*. Swindon: English Heritage.

The General Medical Council (GMC) Pharmacopoeia Committee continued to meet twice a year throughout the war. In June 1915 Dr Nestor Tizard resigned from his role as secretary to the committee as he had been appointed commanding officer of the Fourth London General Hospital. He had been the secretary for 20 years and had been involved in the production of both the 1898 and 1914 editions. He had been the senior editor for the 1914 edition. Tizard was knighted in 1916.[4]

In July 1917 the GMC withdrew many of the official preparations from the 1914 *Pharmacopoeia* as a result of the shortages of sugar and glycerol.[5] The only official mixtures left were Mistura Cretae (Chalk Mixture), Mistura Ferri Composita (Compound Mixture of Iron) and Mistura Olei Ricin (Castor Oil Mixture). Only six of the 23 official syrups remained, and only 3 of the 16 official lozenges (Trochischi). In March 1918 further amendments were made[6] withdrawing monographs for products such as Linimentum Hydrargyri (Liniment of Mercury) and allowing Arachis Oil or Sesame Oil to be used instead of Olive Oil in preparing official Liniments, Ointments, Plasters and Soaps. An inferior commercial grade of Castor Oil – 'neutralised seconds castor oil' – was allowed to be used instead of Castor Oil BP. The full text was restored on 30 April 1919.

In 1922 Sir Nestor Tirard became a member of the General Medical Council – as one of the Crown nominees – and a full member of the Pharmacopoeia Committee. At its meeting in May 1922 he volunteered to become its honorary secretary again.

Biological Products

In the course of preparation of the 1914 edition, discussion had begun on whether serums, vaccines and other biological products should be included. However it was felt impracticable to do so until a national institute had been established to carry out the tests and fix standards. In the United States the Hygienic Laboratory of the Public Health and Marine Hospital Service had assumed responsibility for biological standards under the provisions of the Biologics Act 1902. This had enabled the *United States Pharmacopeia* (USP) VIII published in 1908 to include a monograph for diphtheria antitoxin, and USP IX published in 1918 to admit anti-tetanus serum and smallpox vaccine.

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[4] 1928. Obituary: Sir Nestor Tirard. *Br. Med. J.* Nov 17 2(3541): 917.

[5] 1917. British Pharmacopoeia 1914: Alternation and Amendment. *The London Gazette* 27 July: 7678.

[6] 1918. British Pharmacopoeia 1914: Alteration and Amendment: *The London Gazette* 28 March: 3954.

In 1912 Nestor Tirard had given evidence to the Parliamentary Committee on Proprietary Medicines. Part of his evidence related to biological products.[7] He stated that the General Medical Council wished to see established a government laboratory for the standardisation of drugs which it was found difficult to standardise by the usual physical methods. There were certain tests involving vivisection which chemists could not be expected to perform. The government laboratory they asked for would be concerned with the standardisation of the various serums and vaccines produced.

Sir Donald MacAlister had approached the government in 1914 to suggest that a public national institute be set up for the purpose of testing and fixing standards for therapeutic serums, vaccines and other medicines for which the ordinary assay methods used in the *Pharmacopoeia* were inapplicable. In 1920 a Ministry of Health Committee was set up under Sir Mackenzie Chambers to consider what was needed. Sir Donald MacAlister had given evidence to the committee on behalf of the Pharmacopoeia Committee. This departmental committee reported in 1921. In 1925 the Therapeutic Substances Act was passed. The Act was brought into force by an Order-in-Council on 6 August 1927. It regulated by licence the manufacture of a limited number of products, the purity or potency of which could not be adequately controlled by chemical means. The products controlled included vaccines, sera, toxins, antigens and insulin.

The Treaty of Versailles was one of the peace treaties signed at the end of World War I by Germany and the Allied Powers. It was signed on 28 June 1919. One of the provisions of the treaty was to direct members of the League of Nations to 'take steps in matters of international concern, for the prevention and control of disease'. This led to the creation of the Health Organisation of the League of Nations. In 1921 the Health Organisation organised an international conference in London on the standardisation of immune sera and biological reagents.[8] Previously the Statens Seruminstitut in Copenhagen had established and distributed a few biological standards. The conference was attended by scientists from 11 countries, including the United Kingdom. It was agreed that there was a need for international coordination of biological standardisation. This would enable manufacturers to sell the same standardised products in a number of different countries. After the initial conference in London, subsequent conferences and technical meetings were held in Paris in 1922, Edinburgh in 1923, Geneva in 1924 and 1925, London in 1931, 1932, 1934 and 1935. In 1924 a Permanent Health Commission on Biological Standardisation was set up which held sessions in Paris in 1924, Geneva in 1926, Frankfurt in 1928,

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[7] 1912. The Parliamentary Committee on Proprietary Medicines. The 'British Pharmacopoeia'. *Br. Med. J.* June 22 1(2686): 1432–3.

[8] Dale, H.H., 1942. Wartime Arrangements for International Biological Standards and the New Standard for Pituitary (Posterior Lobe) Preparation. *Br. Med. J.* Oct 3: 381–7.

Geneva again in 1930, London in 1931 and Copenhagen in 1934. As standards were devised they were added to the editions of many of the pharmacopoeias, including the BP (see below).

In 1935 an inter-governmental conference was held in Geneva. This was attended by representatives of 24 countries. This recommended that the use of international standards adopted by the Permanent Commission on Biological Standardisation would be used by the authorities in all countries. At this time there were 12 standards for serums and antitoxins distributed by the Danish Statens Seruminstitut and 16 standards by the National Institute of Medical Research (NIMR) in Hampstead, London. The NIMR distributed standards for insulin, dry powdered leaves of *Digitalis purpurea*, sulpharsphenamine, pituitary extract, ouabain from Strophanthus, vitamins A, B, C and D, oestrus-producing hormones, androsterone and progesterone.

Brussels Second International Conference on the Formulae of Powerful Medicaments

The Belgian government had written to the British government in 1924 inviting it to send representatives to a second international conference on the formulae of powerful – potent – medicines. Sir Nestor Tirard was nominated as the representative of the GMC. The conference took place on 21–29 September 1925. In 1930 the International Agreement for the Unification of Pharmacopoeial Formulae for Potent Drugs became operative. However the British government had a reservation clause to allow it to make such modifications as it regarded as expedient or necessary.

The International Agreement was ratified by the British government in 1930 and became operative. It defined the strength of vegetable drugs and their preparations – powders, extracts, tinctures, syrups and solutions. For example Pulvis Belladonnae (Powdered Belladonna) was defined as containing not less than 0.30 per cent of total alkaloids, Tincture Belladonnae was defined as containing not less than 0.03 per cent of total alkaloids.

The introduction to the 1932 BP contained a list of all of the vegetable drugs and preparations in the International Agreement and the way in which the International Agreement had been interpreted in the text. Some of the drugs and preparations such as those of Aconite had not been included. In other cases the BP 1932 had modified the strength specified in the International Agreement, for example, Tinctures of Digitalis and Strophanthus were standardised biologically in terms of units of activity.

The International Agreement was terminated by a proposed Treaty Protocol agreed in Geneva on 20 May 1952 as a result of the development of the *International Pharmacopoeia* by the World Health Organization (WHO). In

1956 copies of volumes I and II of the *International Pharmacopoeia* were sent to the current and former British territories listed in the earlier agreements.

Preparations for a New Post-War Edition

In May 1925 the GMC Pharmacopoeia Committee started to take steps to revise the 1914 *Pharmacopoeia*. It appointed a new secretary, Dr Philip Hamill, who was at that time Lecturer on Pharmacology and Therapeutics at St Bartholomew's Hospital Medical School. It asked the medical authorities for their views on the contents of the *Pharmacopoeia* and sought the views of medical and pharmaceutical authorities throughout the Empire on suggestions for improvement. On 4 November 1925 the Council of the Pharmaceutical Society resolved that if a letter inviting its co-operation was received but without an invitation to the Society to appoint nominees to the Pharmacopoeia Committee, that this would be unsatisfactory.[9] The Council nominated a sub-committee to communicate its views to the Privy Council. A letter was received on 6 November from Sir Donald MacAlister, the president of the GMC.[10] This invited the co-operation of the Society. The letter proposed setting up two additional committees reporting to the GMC Pharmacopoeia Committee. One would be called the Pharmaceutical Advisory Committee and include three members nominated on behalf of the Pharmaceutical Society's Council. This committee would advise on all general pharmaceutical questions submitted to it. However the sting in the tail of the letter was its final paragraph which stated that GMC had the ultimate legal responsibility for the contents of the *Pharmacopoeia* and 'reserves its freedom with regard to the final adoption of the reports, proposals, advice and suggestions which may be submitted'. Mr Philip Rowsell, the president of the Council of the Pharmaceutical Society, wrote back on 2 December expressing regret that the modifications suggested were not satisfactory. He enclosed with the reply a copy of a letter of 2 December from Sir William Glyn-Jones, the secretary to the Pharmaceutical Society of Great Britain, to the Lord President of the Privy Council expressing the 'profound dissatisfaction' of the Council with the conditions governing the production of the *Pharmacopoeia*. It contended that 'the intervals between the editions are too long, that in some respects each edition is out of date when it is first published, that in the intervals between publication of the various editions the work performed in its preparation is adequate in neither quantity or quality'.[11] The

[9] 1925. *Pharmaceutical Society Council Minutes*. Meeting of 4 November.

[10] 1925. *Pharmaceutical Society Council Minutes*. Meeting of 2 December.

[11] 1925–1926. The National Archive of the UK FD1/1959. British Pharmacopoeia: Correspondence; publication; of Conference of Pharmacopoeia.

letter went on to request a 'Departmental Committee or some other means of enquiry' in order to 'secure the preparation of future editions upon a basis which will result in a pharmacopoeia satisfactory to users, medical and pharmaceutical, throughout the British Empire'.

The Pharmacopoeia Committee held a Conference on 23 February 1926 which 23 delegates from the various medical, pharmaceutical and scientific bodies attended. The meeting was chaired by Sir Donald MacAlister – then both Chairman of the Pharmacopoeia Committee and President of the GMC. Many of those invited were very critical both of the current contents of the *Pharmacopoeia* and its way of working. The Pharmaceutical Society presented to the Conference an opinion from Mr Alexander Macmorran KC questioning the GMC's legal view on the need for an all-medical committee to be responsible for the production of the *Pharmacopoeia*.[12] Having heard all of these views the Pharmacopoeia Committee concluded at its meeting on 2 June 1926 that a Committee of Inquiry should be set up to make enquiries, collect information, receive evidence and make recommendations as to whether it would be desirable to make changes to the existing law or practice relating to the preparation or publication of the *British Pharmacopoeia*, and to its adaptation to the requirements of the British Empire. The GMC minutes record the GMC as formally asking the Lord President of the Privy Council to set up such a committee. No mention was made in the official GMC minutes of the earlier request from the Pharmaceutical Society in December 1925 to the Privy Council.

Committee of Civil Research, Sub-Committee on the British Pharmacopoeia

The Committee of Civil Research was conceived as a Cabinet committee to consider the development of economic, scientific and statistical research in relation to civil policy and administration. It was set up in June 1925 under the Conservative government of Stanley Baldwin. Its sub-committees considered problems which were outside the boundaries of any one government department.

The Committee of Civil Research set up a sub-committee to consider the reform of the *Pharmacopoeia*. Its terms of reference were to receive evidence and make recommendations as to 'the law or practice relating to the preparation or publication of the *British Pharmacopoeia* and to its adaptation to the requirements of the British Empire'. The sub-committee was chaired by Hugh Pattison Macmillan (1873–1952). Macmillan was a Scottish lawyer, becoming King's Counsel in 1912. He was the Lord Advocate in Ramsay MacDonald's Labour government of 1924, when he was appointed as Privy

[12] 1926. *Pharmaceutical Society Council Minutes*. Meeting of 3 March.

Councillor. His fellow committee members were Lord Dawson of Penn (the Physician-in-Ordinary to King George V), Sir Donald MacAlister (President of the GMC), Dr Henry Dale (Director of the Department of Biochemistry and Pharmacology at the Medical Research Council), Mr Edmund White (past president of the Pharmaceutical Society), and Dr H.G. Dain from the BMA. Mr Francis Hemming, a civil servant assistant secretary to the Committee of Civil Research, was secretary to the sub-committee.

The sub-committee received written submissions from the medical, pharmaceutical and scientific interested parties, and also from governments of the Dominions.[13] The Foreign Office obtained information on the practices adopted in the preparation of national pharmacopoeias in the United States, Germany, France, Holland, Sweden, Italy, Austria, Belgium, Norway and Switzerland. The sub-committee heard oral evidence from 26 December 1925 until 8 April 1926.

Much of the written evidence submitted was a damning indictment of the existing arrangements and on the suitability of the current text of the *Pharmacopoeia*. The secretary to the Medical Research Council forwarded a memorandum from 27 teachers and investigators in pharmacology and therapeutics from medical schools and universities across Britain. This stated that the current edition of the *Pharmacopoeia* 'represents a therapeutic outlook far behind the best medical practice. The BP is much inferior to that of other countries and in particular to the Pharmacopoeia of the United States'. Professor A.J. Clark, Professor of Pharmacology at University College, London, wrote on behalf of the Royal Society of Medicine to give a long list of important drugs omitted from the *Pharmacopoeia*, a list of those where the standards were inadequate and even possibly dangerous, and a list of monographs where the standards were inadequate to provide any guarantee of therapeutic efficacy.

In 1911 the Liberal government of Herbert Asquith brought in the National Insurance Act. Part 1 of the Act provided medical benefits for insured workers, with free access to treatment for tuberculosis and access to a panel doctor for other illness. Drs James Smith and Edward Adams from the Ministry of Health provided written evidence to the Macmillan Committee on what the Ministry felt was needed to help assure the quality of medicines provided to the 13,695,000 insured population. Prices of medicines supplied by pharmacies under the scheme were controlled by the Drug Tariff for the 45 million annual prescriptions written by 13,000 GPs. Smith and Adams pointed out that a substantial proportion of these medicines were not included in the BP, so that there was no defined standard of quality. They also argued that it would be

[13] 1926–1928. The National Archive of the UK CAB 58/105. Cabinet: Committee of Civil Research. British Pharmacopoeia: Sub-committee on British Pharmacopoeia. Memoranda Nos. 1–67.

convenient if standards for quality of biological products now covered by the Therapeutic Substances Act of 1925 could be published in the *Pharmacopoeia*.

The Pharmaceutical Societies of Great Britain, Northern Ireland and Ireland summarised the role of their members in the production of the *Pharmacopoeia*, starting with the 1867 edition co-edited by Theophilus Redwood through to the 1914 edition co-edited by Professor Henry Greenish and Nestor Tirard of the GMC. The Pharmaceutical Society's laboratory had also provided practical support to develop tests to include in the monographs. They compared the Pharmacopoeia Committee with its membership comprising only medical practitioners to the composition of the committees responsible for the major foreign pharmacopoeias, which included medical, pharmaceutical and other experts. Their submission also included the legal opinion from Mr Macmorran KC which demonstrated that although the responsibility for the *Pharmacopoeia* under the 1858 Medical Act lay with the GMC there was no requirement for an all-medical membership of the Pharmacopoeia Committee.

Professor Greenish had provided separate written evidence. He argued for a permanent Pharmacopoeia Commission with experts in the various branches of knowledge. The work should be continuous, so that as soon as one issue of the *Pharmacopoeia* is published, work on its successor should be commenced. He reviewed the composition of pharmacopoeia commissions in 21 countries and gave his opinion that there should be a ratio of one medical to three non-medical on the Commission. He also recommended that the profits from the sales of the book should be used to provide financial assistance to those who carry out the work.

Sir Nestor Tirard was still the honorary secretary of the Pharmacopoeia Committee and was the first to give oral evidence.[14] Under examination by Macmillan he explained that the members of the Pharmacopoeia Committee were all selected from the GMC members. The GMC was composed of delegates from the different medical examining bodies. The Pharmacopoeia Conference – introduced by Leech – was 'an attempt to satisfy the aspirations and desires of pharmacists to have some more intimate relations with the Pharmacopoeia-Committee'. The Pharmaceutical Societies were invited to make nominations to this conference. Asked about the erratic publication of editions of the *Pharmacopoeia*, Tirard explained that a 'new edition is published when it appears to be called for'. He explained that his committee had to begin again when a new *Pharmacopoeia* is published, but that the first thing was to produce some sort of report on the criticisms. Investigations were initiated by the Pharmacopoeia Conference – the work was purely voluntary, but they

[14] 1926. The National Archive of the UK CAB 58/103. Cabinet: Committee of Civil Research: British Pharmacopoeia: Sub-committee on British Pharmacopoeia. Meeting Nos. 1–5.

could recommend a grant if expense was involved. He explained that the choice of the list of drugs for the *Pharmacopoeia* was made by the Committee after receiving recommendations from medical authorities and the BMA. They also used a list of widely-used prescriptions prepared by the Pharmaceutical Society, and information from wholesale firms. Tirard summarised the work that had gone on between 1898 and 1914 to produce the *Pharmacopoeia*, involving the Pharmacopoeia Conferences, a Committee of Reference in Pharmacy, an analysis of prescriptions, and communications with 29 colonial governments on the requirements of different parts of the Empire. Tirard reported that even before the 1914 *Pharmacopoeia* had been issued they had been told by the Pharmaceutical Society that 'under no circumstances would the same facilities be given to us, or the same personnel be allowed to be employed'. Despite this warning he and Sir Donald MacAlister had met with the chairman of the Pharmaceutical Society in 1925 to try to develop a policy of common ground. 'They gave us every reason to think we had, and then wrote to the Privy Council.'

Professor Henry Greenish, as co-editor of the 1914 *Pharmacopoeia*, was next to give evidence. He explained the process of revision of monographs by the Committee of Revision of Pharmacy which made recommendations to the GMC Pharmacopoeia Committee. However he did not 'know that there was a member of the General Medical Council that was expert in any of those subjects'. He attended the Pharmacopoeia Committee but had no vote. He stated that the method in other countries was to have a permanent commission with representatives of medicine, pharmacy, pharmacognosy, chemistry and pharmacology. For the production of the 1914 edition the Committee of Reference in Pharmacy had held 105 meetings of about three hours from 1895 to the end of 1914. Some Committee members came from Scotland, but no fees or travelling expenses were paid as the Committee had no funds. No doubt the Macmillan Committee will have contrasted this to the normal meetings of the Pharmacopoeia Committee itself, which were every about six months and lasted for about an hour.

Norman King, the registrar of the GMC, gave evidence on the finances of the *Pharmacopoeia*. The book had been profitable with a credit balance of £7,249 after paying honoraria to the editors and research grants. £3,200 had been put in a reserve account towards the cost of producing the next *Pharmacopoeia*. £4,000 had been put in the GMC's general account and was no longer earmarked for the *Pharmacopoeia*.

Drs Bone and Anderson gave evidence for the BMA. They were in favour of keeping the GMC as the body responsible for the *Pharmacopoeia*, but setting up a committee of experts for its production, with an office and a secretary. Financial resources would need to be place at the disposal of the Committee. The BMA felt that publication of a new edition should be at a maximum of 10-year intervals, with interim supplements as needed.

Sir Walter Fletcher, the secretary to the Medical Research Council (MRC), drew attention to the memorial transmitted through the MRC and signed by practically every professor and teacher of pharmacology and therapeutics in the country. This severely criticised the *Pharmacopoeia*. An example of a drug that needed to be in the *Pharmacopoeia* was insulin, where a worldwide standard had now been set up. The MRC recommended that the *Pharmacopoeia* should come out at regular intervals bridged by temporary addenda. The work should be funded by the sales of the book.

Professor A.J. Clark of the Royal Society of Medicine (RSM), in his evidence, tried to define the purpose of the *Pharmacopoeia*.[15] It is 'to provide a uniform standard for the most important drugs used in medicine throughout the British Empire'. There were two elements – the drug must be in common use and there must be such things as are susceptible of standardisation and appropriate for standardisation. The RSM felt that the current *Pharmacopoeia* failed to provide any standard for a large number of the most important drugs used in medical practice. It also felt that the standards provided for a number of important drugs were inadequate to assure their therapeutic activity and freedom from dangerous impurities. Digitalis extract could comply with the BP 1914 monograph but be devoid of activity. Examples of drugs omitted from the 1914 edition were nitrous oxide – used for anaesthesia – amyl nitrite and dextrose injections. Clark stated that there had been a complete drug revolution since 1919.

Mr E. Hinks and Mr C.A. Hill gave evidence on behalf of the Society of Public Analysts. Public analysts used the *Pharmacopoeia* as an unofficial book of standards which has been accepted by the High Court to test whether a particular drug is of the nature, substance and quality demanded. They felt that the *Pharmacopoeia* should have an absolute legal status as far as purchase of drugs is concerned.

Sir Robert Robinson, the chief government chemist, criticised the existing pharmacopoeial standards, he felt that there should be greater precision, as the Americans had done, which would make it easier to discriminate between one supplier and another. He felt that an analytical chemist should be a member of the Pharmacopoeia Committee.

Dr Andrew Balfour, the director of the London School of Hygiene and Tropical Medicine, reported that the *Pharmacopoeia* was used very little in other parts of the Empire. He felt that the treatment of tropical diseases had undergone a remarkable change and a great many new medicaments had been introduced. But 'if you look in the Pharmacopoeia you will not find it'.

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[15] 1927–1928. The National Archive of the UK CAB 58/104. Cabinet: Committee of Civil Research: British Pharmacopoeia: Sub-committee on British Pharmacopoeia. Meetings Nos. 6–14.

Hugh Linstead, the secretary and registrar of the Pharmaceutical Society of Great Britain, gave evidence. There were 20,000 pharmacists on the register; the membership of the Pharmaceutical Society was just under 13,000. The Society had laboratories for Pharmacy, Pharmaceutical Chemistry and Pharmacognosy in Bloomsbury Square. In 1925 it had set up a Pharmacological Laboratory to do biological tests and training under the Therapeutic Substances Act. The Society had played a large part in the preparation of successive *Pharmacopoeias* through its Committee of Reference. In answer to a question from Macmillan he agreed that the Pharmaceutical Societies of Great Britain, Ireland and Northern Ireland wanted to be participators in the responsibility for the production of the *Pharmacopoeia*, not merely advisers or assistants in the work. The Societies supported more regular publication and publication of addenda. He was questioned on the production of the *British Pharmaceutical Codex* published by the Society which was organised via a Research Committee composed of pharmacists, chemists and medical men, with a permanent paid secretary and an assistant. Problems were dealt with in the laboratory and reported to the committee. The profits from sales of the *Codex* paid for its production.

Professor Fullerton Cook, the chairman of the Committee of Revision of the *United States Pharmacopeia* (USP) gave evidence on its history and organisation. The 1820 USP had been published by a group of physicians, but in 1840 the Philadelphia College of Pharmacy were dissatisfied with the preceding edition and undertook to revise the text and present it to the Medical Committee. The pharmacists were then invited to become part of the 1850 Convention and then to join the Committee of Revision. USP had a rented office with secretaries to support its work. Chairmen and members of committees were given an honorarium and travelling expenses.

Several of the medical witnesses were asked about the usefulness of the *Pharmacopoeia* in their medical practice or for teaching students. Their response was to say that they consulted the text to define the list of officially recognised drugs to teach their students, but that they did not use the book themselves. One commented that he mainly used Martindale's *Extra Pharmacopoeia* or Squire's *Companion to the British Pharmacopoeia* for reference.

The Macmillan Sub-Committee formally reported its analysis and recommendations on 12 March 1928 and these were published by HMSO when they were presented to parliament by the financial secretary to the Treasury in May.[16] They did not recommend any change in the law in Britain, the sub-committee felt that the Medical Act of 1868 gave the GMC the widest discretion – they were not themselves required to produce the *Pharmacopoeia*, they were to cause it to be prepared under their direction. Its purpose was

[16] 1928. *Committee of Civil Research. Sub-Committee of the British Pharmacopoeia. Report.* Cmd. 3101. London: His Majesty's Stationery Office.

to give authoritative recognition to, and ensure the purity and conformity to, standards of medicaments in general use throughout the Empire. They recommended the appointment of a Standing Selection Committee composed of members nominated by the GMC, the three pharmaceutical societies and the Medical Research Council. This Selection Committee would appoint the Pharmacopoeia Commission itself, which would be a small body of not more than 10–12 members qualified by their ability and experience to represent the various departments of knowledge concerned. They recommended that the new commission should have a permanent organisation and a secretariat, with an office and staff. A permanent secretary should be appointed by the GMC on the recommendation of the Pharmacopoeia Commission, and should be paid by the GMC. They recommended that the *Pharmacopoeia* should include biological substances controlled under the Therapeutic Substances Act. The interval between issues of the publication should be 10 years, with supplements to introduce monographs for new substances of value and importance in the interim.

These recommendations were broadly accepted by the Pharmacopoeia Committee of the GMC and then by the GMC itself on 22 May 1928. MacAlister, as President of the GMC Council, and a member of the Macmillan Sub-Committee, stated 'I shall have no hesitation in commending to you as worthy for adoption, the proposals for readjustment of our practice'. A Selection Committee was set up to appoint the new Pharmacopoeia Commission. The Selection Committee had four members from the GMC, two from the MRC, and three nominated by the three pharmaceutical societies.

The new British Pharmacopoeia Commission was appointed and started meeting in late 1928. It was chaired by Dr Arthur Philip Beddard, a retired consulting physician from Guy's Hospital. Beddard had studied science at Trinity College, Cambridge and then decided to take up medicine at Guy's Hospital, graduating in 1897. He lectured in pharmacology at Guy's and it was this interest which led him to accept the chairmanship of the Pharmacopoeia Commission after his retirement from hospital practice in 1927. He died in November 1939.

The first members of the Commission were Mr R.R. Bennett (a pharmacist), Dr J.H. Burn (Director of the Pharmacological Laboratory of the Pharmaceutical Society), Professor F.R. Fraser (Professor of Medicine in the University of London), Professor H.G. Greenish (Professor of Pharmaceutics in the University of London), Professor J.A. Gunn (Professor of Pharmacology in the University of London), and Mr T. Tickle (Public Analyst to the County of Devon). Tickle was qualified as a pharmacist.

At the first meeting of the new BP Commission on 7 December 1928, Sir Donald MacAlister defined its role and suggested some of the sub-committees it might wish to consider – Clinical, Pharmacological, Therapeutic Substances,

Pharmacognosy, Pharmacy and Analysis and Tests. The price of the book would be determined by the Treasury. Dr Beddard then took the chair. One of their first tasks was to appoint a full-time secretary. Several possible candidates were mentioned. They felt that it was highly desirable for the secretary to have medical qualifications, that it was essential that he should have chemical and pharmaceutical qualifications, and that a knowledge of a foreign language was highly desirable. Several candidates were mentioned, including Dr Charles Hampshire. On 1 February 1929 a Selection Committee from the Commission members interviewed candidates for the role of secretary. On 15 February the whole Commission interviewed two short-listed candidates – Dr H. Burton and Mr Boyes. Dr Hampshire was then summoned by telephone to attend. He agreed to accept the post with a pensionable salary of £750 providing that he was allowed to retain his examinership and editorship of the *Quarterly Journal of Pharmacy*. His appointment was ratified by the Executive Committee of the GMC on 25 February.

Figure 3.1 Dr Charles Hampshire, Secretary to the British Pharmacopoeia Commission, 1929–1950

Source: © National Portrait Gallery, London.

Dr Charles Herbert Hampshire attended his first meeting of the Commission on 7 March and would attend meetings until he was able to take up full-time duties on 1 June 1929. Dr Hampshire had passed the Pharmaceutical Chemist qualification at the Pharmaceutical Society's school in London. He then joined the teaching staff. Whilst teaching he studied at London University to gain a first class honours degree in chemistry. In 1914 he became chief pharmacist at University College Hospital. At the hospital he studied medicine at London University, gaining the conjoint diploma MRCS, LRCP in 1925 and the MB BS degree in 1927. He was an astute choice as secretary since he was qualified in pharmacy, chemistry and medicine, and thus able to bridge all of the major disciplines involved in the *Pharmacopoeia*.

The BP Commission set up six sub-committees to assist it, each chaired by a Commission member. These were a Clinical Sub-Committee, a Pharmacology Sub-Committee, a Biological Standards Sub-Committee, a Pharmacognosy Sub-Committee, a Pharmacy Sub-Committee and a Pharmaceutical Chemistry Sub-Committee. Experts were appointed to each of the sub-committees and in some cases subsidiary committees were set up. The Commission was to meet approximately fortnightly until the new edition had been published.

British Pharmacopoeia 1932

The new BP Commission reported twice yearly to the GMC Pharmacopoeia Committee. Dr Hamill still served as secretary to the Pharmacopoeia Committee, and was also invited to attend meetings of the Pharmacopoeia Commission. By the time of its first report in May 1929 the Commission had been meeting weekly and had held 13 meetings. It had already drawn up lists of proposed omissions and additions to the *Pharmacopoeia* which was to be circulated to the various bodies in the UK, the Dominions and Colonies for criticism. It had already received a list of proposed omissions and additions from the Canadian Committee on Pharmaceutical Standards. The Commission had been in touch with the Advisory Committee appointed under the Therapeutic Substances Act to consider standards for substances covered by the Act. It planned to get into touch with the Pharmaceutical Society on the subject of the *Codex*, to bring about an understanding that the *Codex* would be 'truly supplementary to the Pharmacopoeia' and would contain an authoritative description of drugs and preparations which either have, or have ceased to be, in the *Pharmacopoeia*.

On 6 June 1929 representatives of the Pharmaceutical Society's Council met with the BP Commission.[17] The Pharmaceutical Society intended to set up

[17] 1929. *Pharmaceutical Society Council Minutes*. Meetings of 5 June and 10 July.

a laboratory for work on the revision of the *Codex*. It offered the use of these facilities to the Commission for any work on the *Pharmacopoeia*.

By the time of its second report to the Pharmacopoeia Committee in November 1929, the BP Commission had held a further 15 meetings. It had accepted an offer made by the Pharmaceutical Society for Miss E.M. Smelt to be appointed as its first research assistant to carry out laboratory work. She commenced work in the Codex Research Laboratory of the Pharmaceutical Society on 11 November. The Commission had been in regular correspondence with the chairman of the Committee of Revision of the USP, and had set up a close link with the USP which continues to this day. The Commission had been in communication with the MRC on the subject of providing standards for biological testing of Digitalis, Strophanthus and Ergot.

By May 1930, the Commission had held a further 22 meetings. It had largely completed the work of reviewing the large number of communications on the proposed additions and deletions to the *Pharmacopoeia*. Its guiding principles were that the *Pharmacopoeia* should 'contain only those standard articles which were in general use throughout the Empire'. In the case of local drugs or substitutes these could be covered by local supplements or addenda. In the case of groups of substances containing the same or similar active principles, the number of drugs described would be reduced. Substances which were little used, or of doubtful therapeutic value, would be omitted. During this period the work of the Commission and its sub-committees was mainly concerned with writing and revising monographs. The sub-committee dealing with biological testing of Ergot, Digitalis, Sera and Pituitary Extract had made substantial progress.

In November 1930 the Commission reported on its good progress with revising and editing the draft monographs for the new edition. The Pharmaceutical Society had started work on a new edition of the *Pharmaceutical Codex*, so a meeting was held to reach an understanding on the division of subjects between the two books and the way in which the *Codex* would deal with articles described in the *Pharmacopoeia*. The new edition of the *Pharmacopoeia* would include monographs for insulin and irradiated Ergosterol, even though their manufacture was the subject of patents, as it was felt that there should be official biological tests for potency particularly for those parts of the Empire not governed by the Therapeutic Substances Act or similar control.

By November 1931 the Commission reported that the draft of the *British Pharmacopoeia* and its appendices was complete and the first proofs had been reviewed by the various sub-committees. Once finalised the completed draft would be sent to the GMC Pharmacopoeia Committee to adopt as the *British Pharmacopoeia* 1932. Official notice of the publication would be given in the official *Gazettes* of London, Edinburgh and Dublin. The Irish Free State had provided a copy of an Act allowing it to adopt the text as its own official pharmacopoeia. The State of Victoria in Australia had given notice of a similar

Act. The High Commission for South Africa had sent a copy of the Food and Drugs Act 1929 making the *British Pharmacopoeia* its official text.

In May 1932 the GMC Pharmacopoeia Committee had approved the text. It recommended that 30,000 copies be printed and 20,000 bound. The new *Pharmacopoeia* included 127 new monographs for substances and preparations which had not been included in the 1914 edition. Standardised powdered drugs were introduced: digitalis pulverata, belladonna pulverata, ergot praeparata, ipecacuanha pulverata and nux-vomica pulverata. The new monographs included Nitrous Oxide, Oxygen, Insulin, three Antitoxins, three Toxins and two Vaccines, 357 monographs for substances and preparations which had been included in the 1914 book had been omitted. Twenty-one appendices were included in the new edition (compared to 17 in the 1914 edition) with information on reagents, test methods, weights and measures and so on. Biological assays were included for Digitalis and Strophanthin as well as for Vitamin D, Anti-dysentery Serum, Diphtheria Antitoxin, Gas Gangrene Antitoxin, Tetanus Antitoxin, Insulin and Pituitary Extract. The Standard Preparations for the assays were kept in sealed vials by the National Institute of Medical Research at Hampstead. The assay for Digitalis was carried out by injecting groups of frogs, cats or guinea pigs with dilutions of extracts of the Standard Preparation and the sample and comparing the percentage mortality in the test animals. The 1914 edition had included five Hypodermic Injections but without specifying any method of sterilising them. The 1932 edition now included three methods of sterilisation for aqueous injections – Heating in an Autoclave, Tyndallisation and Filtration. Tyndallisation was devised by the Irish physicist John Tyndall (1820–1893) and was described as a process of heating the final sealed containers at 80°C for one hour on three successive days. In his address as the chairman to the British Pharmaceutical Conference held in July 1933 in London Dr Hampshire drew attention to some of the key changes.[18] He said 'The most striking change is the reduction in the number of vegetable products and as drugs. This is reflected in the *British Pharmacopoeia* 1932 from which no fewer than 60 of the crude drugs contained in the *British Pharmacopoeia* 1914 have been excluded'. He identified the discovery of the curative effect of liver in pernicious anaemia as 'an outstanding discovery of medical science, ranking almost as high as the treatment of diabetes with insulin'. Extractum Hepatis Siccum (Dry Extract of Liver) and Extractum Hepatis Liquidum (Liquid Extract of Liver), were included for the first time in this edition.

The monographs for drug substances in the 1914 BP had been fairly simple. The title of the 1914 monograph was in Latin with the English subtitle. The first statement was one which was a definition of the drug with its molecular

[18] 1933. The Drugs are Dying Out. Report of address by Dr C.H. Hampshire. *The [Gloucester] Citizen* 26 July: 4.

formula, for a chemical drug. For example the monograph for Cocaine Hydrochloride had the statement 'Cocaine Hydrochloride, $C_{17}H_{21}NO_4$, HCl is the hydrochloride of the alkaloid cocaine'. After that was a large section entitled 'Characters and Tests' which contained nearly all other information. It included a description of the crystals or powder, its odour and taste, solubility in various solvents, melting point, a series of colorimetric and other identification tests, loss on drying and an ash content. The dose range was given in both the metric and Imperial systems. A few of the monographs had an assay. For example the monograph for Lithium Carbonate had a titrimetric assay using a solution of sulphuric acid to determine the carbonate content. Many of the inorganic salts had limit tests for lead (in the range of 5 to 20 parts per million) and arsenic (in the range of 1.4 to 10 parts per million).

The monographs for drug products in the 1914 BP were formulations designed for dispensing by pharmacists and consisted of lists of the ingredients and then details of the method of manufacture. None of them contained an assay for the active ingredient(s).

The tremendous effort that had gone into the reform and revision in the 1932 BP were evident in the drug substance monographs which were much more complete. As in the 1914 BP the monograph title was in Latin with an English subtitle. The first statement for a chemical drug was the molecular formula but there was often now a minimum percentage purity. For example the monograph for Acetylsalicylic Acid had a minimum content of not less than 99.5 per cent of $C_9H_8O_4$. The large 'Characters and Tests' section in the 1914 edition was now replaced with headings entitled 'Characters' containing a description of the drug, its odour, taste, colour and solubility in a range of solvents. The next heading was the 'Tests for Identity' which typically contained colorimetric tests. The section on 'Tests for Purity' included a limit test for any major impurity – salicylic acid in the case of Acetylsalicylic Acid, and also limits for arsenic and lead. The final heading was the Assay included for many drug substance monographs, typically by volumetric titration. Again the dose range was given in both metric and Imperial systems.

The 1932 BP demonstrated the same improvements in the monographs for finished preparations. The composition and methods of manufacture were still described for the dispensing pharmacist to make up, but now often included information under the headings of Characters, Tests for Identity and Assay. They also included recommendations for storage since the pharmacist would often make up larger amounts of frequently prescribed medicinal products. The improvements in the specification would enable the public analysts to test samples of the product obtained by test prescription or test purchase.

One popular preparation omitted from the 1932 edition was Vinum Quininae (Orange Quinine Wine). This was a very popular product introduced to the *Pharmacopoeia* in 1874 and which was widely advertised in the popular

press as a 'preventive' for influenza. Despite its official removal it was still being advertised late into the 1930s as being 'prepared in strict accordance with the requirements of the British Pharmacopoeia'.[19]

The text became official on the day of publication – 8 October 1932. In view of the extent of the changes the book was made available for prior viewing at the GMC offices in London, Edinburgh and Dublin. Even so the Pharmaceutical Society made an official complaint regarding the inconvenience and difficulty for pharmacists of the text becoming official on the day of publication. There was considerable public interest in the new book and articles appeared in a number of local and national newspapers. The *Bath Chronicle and Herald* for Saturday 8 October 1932 had a headline of 'New Issue of Chemists' Bible'.[20] The article mentioned that the 23,000 chemists would have to spend the weekend in a process of 'instantaneous assimilation'.

By 19 November 1932 22,584 copies of the book had been sold. The first appointed Pharmacopoeia Commission had completed its work. It met on five further occasions to deal with queries and to prepare a list of corrigenda to be sent to the medical and pharmaceutical press. In its final report to the GMC Pharmacopoeia Committee in April 1933 the Commission proposed that addenda to the *Pharmacopoeia* be issued between publications of new editions. They also recommended the organisation of a suitable secretariat with office accommodation, a research assistant and a laboratory equipped for chemical and pharmaceutical work. In early 1933 the Pharmaceutical Society notified the GMC that the laboratory which it had loaned to the Pharmacopoeia Commission would no longer be available as it was needed for another purpose. The GMC found that the Dental Board had two unoccupied rooms in its part of the GMC Hallam Street premises. The research assistant could work there under the supervision of Dr Hampshire. Estimates were obtained for the alterations and equipment.

In May 1933 the Pharmacopoeia Committee recommended that the GMC approach the Privy Council with a view to introducing a Bill into parliament to fix a date subsequent to publication when a new book could become official.

The term of office of the BP Commission had expired on 30 September 1933. The Selection Committee had met and a new Commission was appointed with effect from 1 October 1933. Dr Beddard was reappointed as its chairman.

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[19] 1937. Advertisement for Orange Quinine Wine from Devon and Somerset Stores Ltd., Exeter. *The Western Times* 11 January.

[20] 1932. New Issue of Chemists' 'Bible' – Revised Pharmacopoeia Becomes Law. *The Bath Chronicle* 8 October.

Addenda to the *British Pharmacopoeia* 1932

Work on the first *Addendum* started in 1932. By May 1934 committees to deal with special subjects had been appointed and 63 members of the medical, chemical and pharmaceutical professions had agreed to serve on them. It was planned to publish the *Addendum* in 1936. Two topics of particular importance were standards for vitamin products and biological standards. Two international meetings were held during the year under the auspices of the Permanent Committee on Biological Standardisation of the Health Organisation of the League of Nations.

The BP Commission raised with the GMC Pharmacopoeia Committee in May 1934 the question of inclusion in the *Pharmacopoeia* of substances which are the subject of patents or trademarks. The Pharmacopoeia Committee felt that these substances should still be excluded except where multiple licences to manufacture had been granted or where the patent would expire shortly after the publication of a new edition or an *Addendum*. This topic was to continue to be discussed over the next few years.

By May 1935 the BP Commission was able to report good progress with monographs for Vitamins A, B_1, C and D_2 and their preparations. Monographs on Gas Gangrene Antitoxin, Staphylococcus Antitoxin and Anti-pneumococcus serum had been produced. The Commission continued to work closely with the USP Committee of Revision.

In May 1936 the Commission reported that the draft text of the *Addendum* had been circulated and comments received from committees in India and certain of the Dominions. The GMC Pharmacopoeia Committee held a special meeting on 15 July 1936 to consider and adopt the text of the *Addendum*, to make arrangements for publication and for authorising notices of the issue of the book in the official *Gazettes* for London, Edinburgh and Dublin.

The term of office of the Commission came to an end in September 1936. Members were nominated to the Selection Committee of the GMC, MRC and Pharmaceutical Societies. They met in February 1936 to appoint the new Pharmacopoeia Commission with a term of office of two years. Professor A.P. Beddard was reappointed as chairman. The new Commission took up office. In its report to the GMC Pharmacopoeia Committee in November it said that it would be desirable to alternate at five-year intervals with the USP. Since this had been published in 1936, they would aim to publish the next full edition of the *Pharmacopoeia* in 1941. Work on the revision was started by appointment of the expert committees and sub-committees.

In May 1937 the Commission had started its review of the scope of the next *Pharmacopoeia* by surveying the monographs and compiling a list of drugs in the 1932 *Pharmacopoeia* of decreased use or doubtful therapeutic value. List of proposed omissions and additions were sent to government departments and

medical bodies, to the governments of India and of the Dominions and to officers of the Colonial Medical Service. The Commission noted the plans of the USP Committee of Revision for the revision by means of annual supplements. By November 1937 comments had been received on the proposed scope of the new edition, and work was continuing both in the laboratory and the committees on the monographs.

In May 1937 the GMC Pharmacopoeia Committee agreed a further relaxation of the rules excluding substances from the *Pharmacopoeia* for which the only practical method of preparation was protected by patent.

By May 1938 work had been completed on a total of 522 monographs. However the term of office of the Commission was coming to an end. Members of a new Selection Committee were nominated and met in February 1938. A new Commission was appointed with Dr Beddard again as its chairman. In the final report of the old Commission it recommended that the *Pharmacopoeia* should include a larger number of preparations that were frequently prescribed in general practice. The draft *Pharmacopoeia* would include emulsions, liniments, nebulae, pills, compressed tablets, ointments and suppositories. They also intended including more synthetic drugs which were off-patent such as Sulphanilamide, Benzedrine and Theophylline with Ethylene Diamine. Additional antitoxins and vaccines would also be included.

In November 1938 the new Commission made its first report to the GMC Pharmacopoeia Committee. Work had started on the preparation of draft monographs. New committees had been formed to deal with Compressed Tablets – being included in the *Pharmacopoeia* for the first time, and alkaloidal assays.

The Pharmacopoeia Commission reported in May 1939. On 1 September 1939 World War II had started and the November report included the Commission's proposals to deal with problems arising from the state of war. Professor Beddard had died on 8 November, so the report was made by Professor James Andrew Gunn, the former Nuffield Professor of Therapeutics at the University of Oxford, acting as the emergency chairman. In a tribute to Beddard, Dr Hampshire stated that:

> Dr Beddard's charm of manner and qualities of leadership made him the ideal chairman in these early years. In the chair he always displayed great patience, preferring to allow difficult problems to solve themselves in friendly discussion rather than to force an issue. In private he gave unsparingly of his time and thought to the details of the work.[21]

[21] 1939. Obituary: A.P. Beddard. *Br. Med. J.* Nov 18: 1022–3.

His successor Professor Gunn had qualified in medicine at Edinburgh University.[22] He was appointed Professor of Pharmacology at Oxford in 1917 and held this post for 20 years before being appointed Professor of Therapeutics. He was responsible for six addenda to the 1932 Pharmacopoeia and the 1948 edition. The cost of the *Pharmacopoeia* in 1939 was £2,883, mainly due to the salaries of the staff. Sales of the 1932 edition and the 1936 *Addendum* brought in just £1,500.

In May 1940 Professor Gunn reported to the GMC Pharmacopoeia Committee that work had continued actively on the preparation of the *Second Addendum* despite many of its members being engaged in special wartime activities. The text had been finalised and it was now in press. It was published on 14 June 1940. It contained Cod Liver Oil Emulsion, and a number of vitamin A and D preparations. To deal with wartime shortages some amendments were made to the BP 1932 authorising the use of arachis oil, cottonseed oil or sesame oil in place of olive oil in making some liniments and ointments, and the use of simple ointment in place of the prescribed fatty basis in making ointment of tannic acid and ointment of capsicum.

In November 1940 Professor Gunn reported that the *Third Addendum* was now ready for press. New monographs were also being developed for drug substances and preparations which had been imported and which were now being made or likely to be made by British manufacturers. The *Third Addendum* was published on 1 January 1941.

A memorandum had been prepared by the Therapeutic Requirements Committee of the Medical Research Council entitled 'Economy in the Use of Drugs in Wartime'.[23] This provisional 1940 list classified medicines into three main groups:

a. essential drugs;
b. drugs which are essential for certain purposes but the use of which should be restricted; and
c. drugs which are not essential and do not justify importation or manufacture in wartime.

Using this memorandum as the basis for its work, a Ministry of Health committee produced a *National War Formulary*.[24] The Pharmacopoeia Commission worked to develop standards for the preparations in the *Formulary*. Professor Gunn was a member of both of these committees, and Dr Hampshire was the secretary

[22] 1959. James Andrew Gunn. *Br. J. Pharmacol*. 14: 4–5.

[23] 1940. Economy in the Use of Drugs. The Medicine Cupboard in Wartime. *Br. Med. J.* Oct 12: 499.

[24] 1941. A National War Formulary. *Br. Med. J.* Nov 8: 656–7.

of the Therapeutic Requirements Committee and a member of the Ministry of Health committee.

The MRC had worked with the Association of British Chemical Manufacturers to ensure that important synthetic drugs which had formerly been imported would continue to be available. New Approved Names were given by the Commission to a number of these drugs.[25] Examples of proprietary drugs formerly supplied by the German company Bayer which were given new Approved Names included Bayer 205 used for trypanomiasis, Atebrin originally used as an antimalarial, Evipan which was used to induce anaesthesia and Plasmoquin used as an antimalarial. These were given the names of Suramin, Mepacrine, Hexobarbitone and Pamaquin.

In some cases the British manufactured substances could be adequately tested for identity and purity by chemical tests to show equivalence to the products previously manufactured overseas. In other cases the MRC thought it necessary to arrange for comparative clinical trials in suitable clinical centres of products made using drug substances of British manufacture versus the corresponding proprietary products in order to show that they were equivalent in all respects. Products tested in this way included:

Proprietary name	Pharmacopoeial name
Avertin	Bromethol
Atebrin	Mepacrine hydrochloride
Evipan sodium	Soluble hexobarbitone
Uroselectan	Iodoxyl

Medical practitioners were also exhorted to use economy in their prescribing.[26] In rather poetic language a BMJ editorial in February 1940 exhorted 'When Aesculapius is deserted for Mars and the shadow of autarky [self-sufficiency] falls on the garden of physic the prudent physician must learn to husband his resources'. An example of economy was to use the BP 1932 standardised powdered extracts of drugs such as digitalis and belladonna rather than extracts or tinctures, thus saving alcohol and reducing costs.

In its November 1940 report to the GMC Pharmacopoeia Committee the Commission reported on the work to adapt official formulae to meet the wartime shortages of glycerine, sugar and other substances. A special committee had been set up to study substitutes, and the *Pharmacopoeia* laboratory was carrying out practical work. By February 1941 emergency action became necessary to conserve stocks of certain materials and amendments were made to

[25] 1940. New Names for Drugs. *Br. Med. J*. May 18: 824.
[26] 1940. War-Time Prescribing. *Br. Med. J*. Feb 3: 177.

the *Pharmacopoeia* by means of official notices in the London, Edinburgh and Dublin *Gazettes*. A further list of six Approved Names for formerly imported drugs was issued in May 1941.[27] This included Dithranol which had previously been known by the proprietary name of Cignolin.

In November 1941 the Commission reported that its offices and laboratory had been damaged during the war by bombs and they had to move first to temporary accommodation at the Pharmaceutical Society and then to University College Hospital Medical School. Broken apparatus in the laboratory had to be repaired or replaced. They were to stay there until 1945.

The *Fourth Addendum* had been published on 1 October 1941. Sterilisation by Tyndallisation had been found to be unreliable in dealing with spores and a new method of sterilization was added – heating at 98–100°C in the presence of a bactericide such as chlorocresol or phenylmercuric nitrate. Morphine sulphate was added to the other morphine salts – hydrochloride and tartrate. Benzyl benzoate was added to treat scabies which had increased in wartime Britain. Bismuth subgallate which was used as an antiseptic dusting powder was also added. Potable water was now allowed in place of distilled water in many preparations such as aromatic waters and infusions. This saved the cost of transporting large volumes of distilled water around the country.

Work had been carried out in the laboratory to modify certain of the formulae to reduce the use of alcohol. The Commission had also started considering monographs on the control of compressed tablets, and revising the monographs on ointments to include some of the newer ointment bases.

The *Fifth Addendum* was published on 15 May 1942. This included 18 new formulae which provided concentrated preparations to make savings on the use of alcohol. Examples included Tinctura Cinchonae Composita Concentrata and Tinctura Opii Camphorata Concentrata. The use of these preparations was authorised by a Scarce Substances Order made under Regulation 60(H) of the Defence (General) Regulations 1939.

In November 1942 Professor Gunn continued to report to the GMC Pharmacopoeia Committee on the changes to the *Pharmacopoeia* to meet wartime conditions. Quinine had been removed from Easton's Syrup – Syrup of Ferrous Phosphate with Quinine and Strychnine. Changes to the formulae of ointments were being investigated to economise in the use of some oils and fats. Other investigations were being carried out on Dithranol, tablet disintegration, synthetic menthols and ergot.

By November 1942 the Commission had issued five lists of Approved Names for substances formerly imported in proprietary products. These new Approved Names could be used freely by any manufacturer. They had now appointed a Committee on Nomenclature.

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[27] 1941. British Pharmacopoeia: Nomenclature. *Br. Med. J.* May 10: 724.

By May 1942 Professor Gunn was able to report that new formulae had been devised for some ointments using an emulsion base so that a considerable proportion of the fat and paraffins was replaced with water. The *Sixth Addendum* containing these formulae was published on 1 August 1943. It contained 17 new monographs and amendments to 31 monographs. New monographs included Alcoholia Lanae (Wool Alcohols), Chloroxyenol, Dithranol, Nicotinamide, Riboflavine and Stilboestrol.

The dialogue with the USP Committee of Revision had continued throughout the war. Copies of USP XII were received in 1942. The Pharmacopoeia Commission discussed the change in the view of the USP in that products covered by patent or a trademark could now be included, 'the question of therapeutic value only being considered'. The Commission's view was that the principles concerning the choice of products for the *Pharmacopoeia* might also need to be reviewed. USP XII included monographs on 47 tablet formulations including the first official compressed tablets, capsules and 19 official injections – including digitalis, dextrose and epinephrine. The Pharmacopoeia Commission now set up a new sub-committee to consider standards for capsules.

In May 1943 the GMC Pharmacopoeia Committee set up a sub-committee to consider the question of whether drugs subject to patent should be included in the *Pharmacopoeia*. The sub-committee recommended that in selecting the drugs for inclusion in the *Pharmacopoeia* the Commission need not consider its choice limited by actual or potential rights in manufacture. This recommendation was accepted by the GMC Council.

By the time of the November 1943 report by the Commission work had started on sulphonamide drugs. The Sub-committee on Tablets had produced a general monograph, with a number of monographs for individual tablets. The Sub-committee on Capsules had begun its work. The Commission had also published another short list of Approved Names.

In May 1944 the Commission reported that work on a *Seventh Addendum* was approaching completion. This would include a monograph on Compressed Tablets, further revisions of formulae for ointments and a revision of the requirements for certain biological products such as Insulin and Liquid Extract of Pituitary. The Commission was now concentrating on the next edition of the *Pharmacopoeia* and had started consulting the Overseas Committees on the lists of proposed additions and amendments. Some replies had already been received.

By November 1944 the *Seventh Addendum* was in press, and this was published on 1 February 1945. It contained a new general monograph on tablets with a standard for uniformity of weight and a disintegration test. Thirty-four individual tablets were included. Improvements in supply now that the war was coming to an end meant that it was possible to include a scheme of ointment bases and ointments which would meet clinical requirements until the next edition of the *Pharmacopoeia*. New monographs included Amphetamine,

Cyclopropane, Progesterone, Sulphacetamide, Sulphadiazine, Sulphaguanidine, Sulphapyridine and Sulphathiazole. A leaflet with a consolidated list of Approved Names was enclosed with the copies of the *Seventh Addendum*.

The increasing numbers of tablets used in medicine meant that standards for this dosage form were very important. Of particular importance was the new disintegration test. The poor disintegration of pills and tablets had been a concern for many years. Liverseege in his 1932 survey on analysis of food and drugs suggested a simple test where two tablets or pills were put in a 4 oz round bottle half full of cold water, lying the bottle on its side and giving it an occasional shake.[28] The sugar coating of an iron pill would be removed in five minutes, black and white pearl coating in an hour, and gelatin-coated pills would swell in two hours. Denston summarised the development of the disintegration test in a 1954 article.[29] The 1926 *Brazilian Pharmacopoeia* was the first to have a formal requirement. In 1930 the *Belgian Pharmacopoeia* had a statement that tablets must dissolve or disintegrate within a short time when shaken with tepid water. The 1934 *Swiss Pharmacopoeia V* used a 100 mL Erlenmeyer flask filled with water at 37°C, shaken gently from time to time. A tablet should dissolve in 15 minutes or less. As part of the preparation of the *Pharmacopoeia* monograph Berry carried out a series of investigations from 1939 to 1944. The method he proposed in 1944 was adopted in the 1948 edition. The test was carried out on five tablets. Each was placed in a stoppered test tube 6 in. in length and 1 in. internal diameter filled with sufficient water heated to 37°C to fill the tube apart from about half-an-inch of airspace. The tubes were placed in a water bath and repeatedly inverted at such a speed that the tablet travelled through the water without striking the end of the tube. The time taken for the tablet to disintegrate or dissolve was specified as not more than 15 minutes. A test was badly needed. A 1939 report from the College of the Pharmaceutical Society gave an example of the application of a disintegration test to samples of commercial tablets of the hypnotic drug sulphonal, where the rate of disintegration varied from seven seconds to seven days. The report in the *British Medical Journal*[30] indicated that this variability could explain why sulphonal has the reputation of being highly uncertain in its action. The *Addendum* to the 1953 BP included a disintegration test based on a method developed by Prance, Stephenson and Taylor using five tablets in glass tubes fitted with a Number 10 sieve mesh gauze and suspended in water at 37°C. The tubes are raised and lowered 30 times a minute. The tablet should disintegrate and particles fall through the mesh in not more than 15

[28] Liverseege, J.F., 1932. *Adulteration and Analysis of Food and Drugs. Birmingham Methods and Analysis of Samples*. London: J. and A. Churchill.

[29] Denston, T.C., 1954. The Standardisation of Tablets. *Journal of Pharmacy and Pharmacology* VI: 1067–80.

[30] 1940. Compresssed Tablets. *Br. Med. J*. June 29: 1064.

minutes. If the tablets failed the test could be repeated using a guided plastic disc in the tube.

In November 1944 the authorities in University College Hospital Medical School notified the Commission that due to the return of some departments they would need the accommodation which the Commission was temporarily occupying. Arrangements were made to return to the GMC Council premises at 44 Hallam Street. However under wartime conditions it was not possible to restore the laboratory and a bench was found for the research assistant in Professor Linnell's Research Laboratory in the Pharmaceutical Society building.

In October 1944 Professor Sir Francis Fraser, who had been chairman of the clinical committee, had resigned due to pressure of other duties. The Pharmacopoeia Selection Committee was convened and recommended the appointment of two new members to the Commission – Professor H. Berry and Professor D.M. Dunlop. Berry was appointed to the Committee on Sterile Solutions, and Professor Dunlop to the Committee on Doses.

On 8 May 1945 Victory in Europe Day – VE Day – was celebrated in Britain as the date when the Allies accepted the surrender of the German armed forces. On 5 July 1945 a general election was held in which the Labour Party was elected on a platform of full employment and the creation of a tax-funded National Health Service.

British Pharmacopoeia 1948

The BP Commission's report of 11 May 1945 detailed the activities it now intended to pursue to produce the first post-war edition of the *Pharmacopoeia*. After consulting with the authorities in India and the Dominions the Commission had drawn up a list of proposed additions and deletions. This list had been sent out for comments. The personnel in the various committees had been reviewed and a number of new members had been appointed. The Commission had approved a new clearer format for presenting monographs. However the revision of existing monographs would involve considerable work. Mr B.L. Reynolds had been recruited for this task.

By November 1945 Professor Gunn was able to report to the GMC Pharmacopoeia Committee that a final list of proposed contents had been agreed. Five hundred and eighty monographs had already been submitted by the committees and reviewed by the commission. They felt that it was highly desirable to publish the new edition at the earliest possible date. In May 1946 proofs had been reviewed by the Expert Committees and sent to the committees in the Dominions, to the USP Committee of Revision and the Revisions Committee of the British Pharmaceutical Codex. The Codex Committee had provided copies of typical monographs in the BPC showing how official

Pharmacopoeial materials were to be used, and the Commission had agreed these proposals.

In November 1946 the Commission reported that the text of the *Pharmacopoeia* had been sent to the printers. This included a section on Antitoxins and Vaccines, and the appendices on tests, assays and so on. However due to the difficult situation in the post-war printing industry – shortage of paper – there was as yet no idea of a date for printing and for the new *Pharmacopoeia* to become official. The *Pharmacopoeia* was eventually published and became official on 1 September 1948. A leaflet listing the Approved Names was enclosed with the book.

The format and content of the drug substance monographs in the 1948 BP had again increased in complexity. The title was still in Latin, with an English subtitle. However for organic drugs a structural formula was now included as well as the molecular formula and molecular weight. The main headings for a drug substance were Description, Solubility, Identification, Melting Point, Reaction to litmus, Arsenic, Lead, Impurity Tests, Ash and Assay. The dose ranges were again given in both metric and Imperial systems. However not all drug substance monographs contained an assay. It seems strange now to compare the monographs for Diamorphine Hydrochloride (heroin) and Morphine Sulphate and to see that the Diamorphine Hydrochloride monograph does not include an assay for the content of diamorphine.

The drug product monographs in the BP 1948 now generally contained a description, assay and so on. All of the tablets, which were commercially manufactured, had an identification test, disintegration test and an assay. But many clinically important products such as Ointment of Penicillin still lacked an assay.

The Pharmacopoeia Selection Committee met in November 1947 to appoint the new British Pharmacopoeia Commission. They placed on record their recognition of members of the outgoing Commission, and particularly of Professor Gunn as chairman during the difficult war years. During these years much of the work of the Commission had to be done by correspondence because of the difficulty of travel, and Gunn had to make many decisions personally in conjunction with Dr Hampshire as secretary.

The new BP Commission chairman was Professor Derrick Melville Dunlop (1902–1980). He was educated at Oxford and Edinburgh universities. At the age of 34 he was appointed Christison Professor of Therapeutics and Clinical Medicine in Edinburgh, in which post he remained until his retirement. He was knighted in 1960. From 1964 to 1968 he was chairman of the Committee on Safety of Drugs. Following the Medicines Act 1968 he became the first chairman of the Medicines Commission and served until 1971.

The other Commission members were Professor H. Cohen (Clinical Medicine), Dr R. Greene (Clinical Medicine), Professor A.D. Macdonald (Pharmacology),

Dr A.A. Miles (Biological Products and Assays), Professor H. Berry (Pharmacy), Mr J.C. Hanbury (Pharmacy), Professor W.H. Linnell (Pharmaceutical Chemistry), Dr R.P. Linstead (General Chemistry) and Dr J.R. Nicholls (Analytical Chemistry).

In November 1948 the Commission reported to the GMC Pharmacopoeia Committee that it had started planning the work on the next edition, and was setting up the new expert committees. A large number of topics needed experimental work and the Commission felt that it was essential to reconstruct the Pharmacopoeia Laboratory as quickly as possible. By May 1949 the Commission was able to report that 10 main committees had been established, each chaired by a member of the BP Commission. One hundred and twenty-two experts had agreed to serve on the various committees and sub-committees. Lists had been prepared of proposed additions and deletions, and these had been submitted to medical and pharmaceutical authorities throughout the British Commonwealth. Relations with pharmacopoeial committees in Canada and Australia had been re-established, and also with the authorities in South Africa, New Zealand and India. Correspondence with the Committee of Revision of USP had continued, with exchange of information with a view to keeping the two pharmacopoeias in as close an agreement as possible. The commission was being kept in close touch with the work of the WHO, Dr Miles was a member of the Expert Committee on Biological Standardisation and Dr Hampshire was the chairman of the Expert Committee on the Unification of Pharmacopoeias. The Commission planned to produce a new *Addendum* and then a new edition in 1953.

In 1950 Dr Hampshire retired from the British Pharmacopoeia Commission. He continued working with the WHO on the *International Pharmacopoeia*, and was editor of the *Journal of Pharmacy and Pharmacology* until his death in January 1955. Mr Thomas C. Denston, his successor as secretary, said of him 'No pharmacist can have had a greater influence on the growth of a national pharmacopoeia than did Dr Hampshire'. Professor Gunn, his BP Commission chairman said, 'To his natural urbanity he added a streak of obstinacy, occasionally even of pugnacity, but it was only because of the sincerity of his conviction. His life was full of varied and distinguished accomplishment to which the pharmaceutical and medical professions are deeply indebted'.[31]

Mr Thomas C. Denston, a pharmacist, was appointed secretary to the BP Commission in 1950 and was to serve until 31 March 1967. He registered as a pharmacist in 1925 and then worked in community pharmacy before being involved in manufacturing with John Bell and Croydon. He then became a lecturer in pharmacognosy, first at Bradford School of Pharmacy and then at Chelsea College. He was seconded to the War Office in 1940 and then joined the

[31] 1955. Dr C.H. Hampshire (obituary). *Chemist and Druggist* 29 January: 111.

Figure 3.2 Mr Thomas Denston, Secretary to the British Pharmacopoeia Commission, 1950–1967
Source: Pharmaceutical Journal.

Ministry of Supply's Directorate of Medical Supplies. He was appointed editor of the *British Pharmaceutical Codex* in 1946. He died on 21 December 1982.

By May 1950 the contents of the *Addendum* 1950 had been decided. This would include a number of new antibiotics – Benzylpenicillin salts and Procaine Benzylpenicillin, Streptomycin salts, Dihydrostreptomycin and Sulphadimidine – together with a number of new synthetic drugs, implantation tablets of Deoxycortone Acetate and Testosterone, human blood and preparations of it and some new tablets. The Commission had been informed of the WHO's intention to publish an *International Pharmacopoeia*. This would be issued to member state governments with the recommendation that the provisions be included in national pharmacopoeias.

By the end of November 1950 work had been essentially completed on the monographs and the appendices. Proofs had been circulated to pharmaceutical and medical bodies in Australia, New Zealand, Canada and South Africa. The use of Latin titles for the monographs in the forthcoming 1953 *Pharmacopoeia* had been reviewed. It was agreed that the main title would be in English with the Latin as a synonym. The sequence of monographs would also be changed so

that preparations such as tablets, capsules, tinctures and so on would be sited immediately after the parent drug substance. A meeting had been held with representatives of the Pharmaceutical Society's Codex Revision Committee to review the relationship between the *Pharmacopoeia* and the *Codex*. It was agreed that the style of monographs in the Codex was satisfactory. Proofs of the two books would continue to be exchanged.

On 1 December 1950 Mr George R. Kitteringham, a pharmacist, started work as assistant secretary to the Commission, reporting to Mr Denston. He was promoted to secretary in 1966 and retired in 1976.

The work on the *Addendum* was completed in December 1950 and it was published on 19 April 1951. A pamphlet of Approved Names was circulated with the book.

British Pharmacopoeia 1953

The Medical Act of 1950 enlarged the scope of the *Pharmacopoeia* to 'medicines, preparations, materials, and articles used in the practice of medicine, surgery and midwifery'. The Commission was therefore able to consider monographs for blood preparations and surgical catgut. In November 1951 Professor Dunlop reported to the GMC Pharmacopoeia Committee on progress of the 1953 *Pharmacopoeia*. New monographs would include Adrenaline Acid Tartrate, Amidone Hydrochloride, BCG vaccine, Folic Acid and a number of new tablets. Cyanocobalamin and Injection of Cyanocobalamin – vitamin B_{12} – now replaced the previous Liver Extracts for the treatment of pernicious anaemia. Blood preparations such as Human Fibrin Foam, Human Fibrinogen, Dried Human Plasma and Human Thrombin were added. In the new edition doses would be expressed only in the metric system except for those drug substances still prescribed mainly in the Imperial system. Arrangements had been made with the American Medical Association's Council on Pharmacy and Chemistry for interchange of information on Approved Names, to try to ensure adoption of identical names. By May 1952 further monographs were added on Sterilised Surgical Catgut, Tablets of Cascara Sagrada, Tablets of Penicillin and Tablets of Phenytoin Sodium. The limits on the content of medicament in tablets were being gradually tightened with each successive edition of the *Pharmacopoeia*. The assay limits for acetomenapthone in Acetomenaphthone Tablets were tightened from 89.0 to 110.0 per cent in the 1948 BP to 92.5 to 107.5 per cent in the 1953 edition. For the first time the main title of the monographs was in English not in Latin. The prevailing medical and pharmaceutical opinion was now that prescriptions should be written in English. By November 1952 work had been completed on the book

and it was published on 2 March 1953 to come into effect on 1 September 1953. A leaflet on Approved Names was included in each copy.

In 1956 all of the governments in former and current British territories were asked for the agreement to the Treaty Protocol for termination of the Brussels International Agreement on Unification of Pharmacopoeial Formulae for Potent Drugs, since it was being superseded by the WHO *International Pharmacopoeia*. Nearly all accepted the Protocol for their territories. They were also asked about their acceptance of the BP in their territories and whether there was any statutory provision regarding the BP standards. It is interesting to see their answers as they illustrate the worldwide use and acceptance of the BP in the 1950s even though the BP 1932 had abandoned the concept of a British Imperial pharmacopoeia.[32]

Aden: No official pharmacopoeia in the Colony.

Bahamas: No comment.

Bermuda: Section 9 of the Poisons Act exempts the BP and BPC from certain provisions in regard to labelling which apply to other poisons.

British Guiana: Statutory provision in Section 44 of the Pharmacy and Poisons Ordinance No. 36 of 1956. This states that the BP is the official pharmacopoeia in force in British Guiana as the standard of quality or composition for all drugs and for the method of preparation of all drugs and compounding mixtures thereof.

British Honduras: BP standards generally accepted.

Brunei: No statutory provision, but medical authorities follow the BP.

Cyprus: Statutory provision in Section 32 of the Pharmacy and Poisons Law, Cap 132, stating "No person shall sell any drug which does not conform to the standards laid down in the BP or BPC".

Dominica: No statutory provision, but BP accepted.

Falkland Islands: All drugs imported to the BP standard.

Fiji: Statutory provision regarding the standards of the BP under Section 46 of the Pharmacy and Poisons Ordinance.

[32] 1957. The National Archive of the UK CO859/1323. Protocol for the Termination of the British Agreements for the Unification of Pharmacopoeial Formulae for Potent Drugs.

Gambia: Follows the BP. Maintenance is controlled by the Governor-in-Council acting on the advice of the Director of Medical Services.

Gibraltar: Statutory provision.

Grenada: No statutory provision but the BP is applied.

Hong Kong: The Medical Council of Hong Kong in exercise of powers under Section 2 of the Pharmacopoeia Ordinance 1958 has approved the adoption of the BP in the Colony.

Jamaica: No statutory provision.

Kenya: The Pharmacy and Poisons Law requires that any drug, medicine or medicinal appliance must, unless otherwise agreed at the time of demand, conform to the standards of the BP or BPC, or as the case might be the BVetC.
Leeward Islands: No statutory provision. BP generally followed in Antigua.

Malta: Statutory provision in Section 31(1) of the Medical and Kindred Professions Ordinance, which states that 'every apothecary shall in the preparation of medicinal substances be guided by the British Pharmacopoeia'.

Mauritius: The colony follows the standards of the BP, BPC and French Codex under Section 25 of the Pharmacy and Poisons Ordinance 1955.

New Hebrides: No national legislation.

North Borneo: No statutory provision, but advised that the BP standards would be generally accepted in the Courts.

Sarawak: No comment.

Sierra Leone: No statutory provision but encouragement under Customs Tariff Ordinance for the duty-free import of BP and BPC drugs.

Singapore: Statutory provision exists in regulations published under the Food and Drugs Ordinance for the maintenance of the standards of the BP and BPC.
Somaliland Protectorate: No statutory provision except that medicines which do not disclose their composition or active ingredients in specific terms or by reference to the BP or BPC or the USP are prohibited imports under Customs Ordinance No. 5 of 1952.

St Helens: No statutory provision.

St Vincent: No statutory provision.

Tonga: The BP is used but there is no statutory provision.

Trinidad: BP generally followed but Chapter 12 No. 5 Food and Drug Ordinance allows acceptance of standards laid down in any recognised pharmacopoeia.

Uganda: Statutory provision in the Pharmacy and Poisons Ordinance.

Virgin Islands: No statutory provision but both BP and USP used.

Zanzibar: No comment.

British Pharmacopoeia 1958

The term of office of the Commission had expired in 1953, so the Selection Committee met and appointed a new Commission with effect from 1 October. The number of members increased from 9 to 11. New members included Professor S. Alstead and Dr E.F. Scowen (Clinical Medicine), Dr Frank Hartley (Pharmaceutical Chemistry), and Dr W.L. Perry (Biological Products). Its first meeting was held in October 1953 when it decided on its programme of work and made arrangements to appoint advisory committees. Twenty-one committees were appointed, each chaired by a Commission member. There was now only one wholly medical committee – Clinical Medicines and Doses chaired by Professor Dunlop. There was a Nomenclature Committee and three concerned with Biologicals – the Serological Products Committee, one on the Accuracy and Precision of Biological Assays and one on Biological Assays. All of the other committees were concerned wholly with pharmaceutical and chemical standards for drugs and preparations. Professor H. Berry chaired the Tablets and Capsules Committee and Dr Hartley the Assay of Tablets and Capsules Committee. Professor Berry also chaired the Ointments Committee and the Sterile Products Committee. By May 1954 the new Commission had met five times and its committees had held 25 meetings. They had started consultation of organisations at home and abroad on retention or deletion of existing monographs. The Clinical Medicines and Doses Committee drew up a provisional list of contents for the 1958 edition.

The November 1954 Commission report to the GMC Pharmacopoeia Committee detailed a number of new monographs being prepared for publication in the 1955 *Addendum*. These included Cortisone Acetate, Chloroquine

Phosphate, Ferrous Gluconate, Insulin Zinc Suspension, Isoniazid, Lignocaine Hydrochloride, Oxytetracycline, Phenylbutazone and Suxamethonium Chloride. New tablet monographs included amphetamine sulphate, hyoscine hydrobromide, morphine sulphate, quinidine sulphate and soluble acetylsalicylic acid – aspirin – tablets. By May 1955 the GMC Pharmacopoeia Committee had approved the draft of the 1955 *Addendum* to come into force on 1 March 1956. It was published on 3 October 1955.

In November 1955 the Commission reported on its discussions on colouring of tablets. The general monograph on tablets in the 1945 *Addendum* stated that the addition of colouring matter was not official. Views were now invited. Despite recommendations from both the Association of the British Pharmaceutical Industry and the Ministry of Health to accept coloured tablets in some circumstances the Commission was unmoved and the pharmacopoeial requirement was not changed.

In May 1956 Professor Dunlop reported that the Commission had invited a large number of medical and pharmaceutical organisations to express views on the scope of the book. It now had lists of proposed additions and deletions. The Commission continued to issue lists of Approved Names several times a year.

By November 1957 work on the new edition had been completed, and the GMC Pharmacopoeia Committee had considered and adopted the text. The 1958 edition was published on 3 March 1958 and became official from 1 September 1958. During its production the Commission had met 42 times and there had been nearly 200 meetings of its 22 committees. By June 1958 the 1953 *Pharmacopoeia* had sold 42,472 copies and the 1955 *Addendum* 13,174 copies.

The drug substance monographs in the BP 1958 were similar in format and content to those in the BP 1948, but additional tests were now often included for Specific Optical Rotation, Loss on Drying and Sulphated Ash. The use of ultraviolet spectrophotometry was being used both for identification tests and also for assays, which meant that many more drug substance monographs now included an assay with limits for minimum content.

British Pharmacopoeia 1963

The Selection Committee met and appointed a new Pharmacopoeia Commission in 1958 to produce the next edition. Ten Commission members were appointed, three experts in Therapeutics and Clinical Medicine, Dr Perry to deal with Pharmacology, and the others to deal with Biological Products, Pharmaceutical Chemistry, Pharmacy and General Chemistry. Professor Dunlop stepped down as he was unable to undertake a further term of office. Professor Edward Johnson Wayne was appointed as the new chairman.

Professor Wayne (1902–1990) was born in Leeds, studied chemistry at the University of Leeds and graduated with a first. He obtained a PhD in Manchester for work on the intermediary metabolism of fatty acids. He then returned to Leeds to study medicine, graduating in 1929. He worked at University College Hospital, London and was then appointed Professor of Pharmacology and Therapeutics at the University of Sheffield. He was Regius Professor of Practice of Medicine at the University of Glasgow from 1953 to 1967. He was knighted in 1964.

By November 1958 the new Commission had held two meetings and had proposed a programme for a new edition in 1963 and an *Addendum* in the autumn of 1960. In May 1959 the commission presented its second report to the GMC Pharmacopoeia Committee. Twenty-one committees had been set up to advise it. Professor Wayne chaired the Medicines and Doses Committee. Other committees were Nomenclature, Immunological Products, Blood Products, Antibiotics, Crude Drugs, Galenicals, Inorganic Chemicals, Organic Chemicals, Alkaloids, Fixed and Volatile Oils, Synthetic Drugs, Tablets and Capsules, Assay of Tablets and Capsules, Reagents, Sterile Materials, Assay of Injections, Hormones and Vitamins and General Tests. The Commission reported that the *Addendum* would contain 57 new monographs. These included Amylobarbitone, Amylobarbitone Sodium Injection and Tablets, Chlorothiazide, Halothane, Iron-Dextran Injection, Poliomyelitis Vaccine, Probenicid and Probenicid Tablets, Tolbutamide and Tolbutamide Tablets, Typhoid-paratyphoid A and B and Cholera Vaccine. The Commission continued to publish supplementary lists of Approved Names. By May 1960 work on the 1960 *Addendum* was completed. It was published on 3 October 1960 and would become official on 1 March 1961.

During 1960 work continued on the preparation of the next edition of the *Pharmacopoeia*. In 1961 the Commission invited views from medical and pharmaceutical experts in the UK and Commonwealth on the scope of the 1963 *Pharmacopoeia*. Lists had been prepared of the proposed deletions and additions. By May 1962 Professor Wayne was able to report to the GMC Pharmacopoeia Committee that proofs of the monographs and appendices of the 1963 *Pharmacopoeia* were being examined by members of the Commission and the committees. By November 1962 the text of the book was in the final stages.

Further lists of Approved Names were issued in August and October 1962, and the Commission noted that the work on nonproprietary names continued to expand and recorded benefits that accrued due to the close collaboration with the World Health Organization (WHO) and some of the other national authorities active in the field.

At their meeting on 27 November 1962 the GMC Pharmacopoeia Committee approved the draft of the 1963 *Pharmacopoeia* for publication in 1963. It also agreed to increase the scientific staff of the Commission – by a senior

scientific assistant and a scientific assistant – to enable the work to be carried on efficiently. It agreed that more frequent addenda should be published and also that provisional monographs be published outside the normal framework. This would provide standards for new drugs at the earliest possible date after they were introduced into medical practice.

The BP 1963 was published on 1 July 1963. It contained almost 1,000 monographs, 200 of which appeared for the first time. It became official on 1 January 1964 – 100 years since the first edition of the *Pharmacopoeia*. It was the centenary edition.

British Pharmacopoeia 1968

The 1958–1963 Pharmacopoeia Commission met for the last time in May 1963 and Professor Wayne reported to the GMC Pharmacopoeia Committee. The equipment in the laboratory had been extended and modernised at a cost of over £7,000. The purchase of the laboratory's first infrared spectrophotometer at a cost of £9,000 was being considered. The idea of establishing a collection of chemical reference substances which could be used in connection with the monographs was also under discussion.

The Ministry of Health had been contacted about the possibility of establishing a common pharmacopoeia to serve the needs of a number of European countries. The commission commented on this proposal. This was part of the preliminary discussion that was to lead to the founding of the *European Pharmacopoeia* in 1964.

In 1963 the Selection Committee met and appointed a new Commission. Professor Wayne had retired and his role as chairman was taken by Professor Eric Frank Scowen (1910–2002). Eric Scowen was educated at the City of London School and then studied medicine at St Bartholomew's, graduating in 1931. He did some research on endocrinology at Columbia University, New York for a year starting in 1937. He returned as Reader in Medicine. During the war he continued to work at Bart's and was one of Churchill's physicians. He was Professor of Medicine at the University of London from 1961 to 1975. He took over the chairmanship of the Committee on the Safety of Drugs from Sir Derrick Dunlop in 1967. He was the first chairman of the Committee on the Review of Medicines. He was knighted in 1973 for his work on the control of medicines.[33]

The other commissioners were Professor D.V. Hubble (Therapeutics and Clinical Medicine), Professor G.M. Wilson (Pharmacology and Therapeutics), Professor W.L.M. Perry (Pharmacology), Dr D. Bangham (Biological Products),

[33] 2002. Sir Eric Scowen. *Telegraph* 28 January.

Mr J.C. Hanbury (Pharmacy), Professor J.B. Stenlake (Pharmaceutical Chemistry), Dr D.C. Garratt (Analytical Chemistry), Dr F. Hartley (General Chemistry) and Professor W.G. Overend (General Chemistry). Dr Hartley was the vice-chairman of the Commission. By November 1963 the committees had all been appointed and a programme agreed for the preparation of the first *Addendum* to the 1963 *Pharmacopoeia*.

In 1963 Mr Cecil Alfred Johnson was appointed to the *Pharmacopoeia* staff as senior scientific assistant. He had graduated with a BPharm from Chelsea College and registered as a pharmacist in 1947. He had worked in the laboratories of Harrison and Self – a firm of consulting analysts – until 1952, then joined the Pharmaceutical Society laboratory working on the monographs of the *British Pharmaceutical Codex* and the *British Veterinary Codex*.[34]

By May 1964 Professor Scowen was able to report that the laboratory was now equipped to carry out ultraviolet and infrared spectrophotometry, and a variety of chromatographic procedures – paper, thin layer and gas.

The first meeting of the Committee on British Reference Substances had been held with participation by the Pharmaceutical Society. Panels of experts had been appointed to carry out the laboratory work necessary to establish the reference substances.

By November 1964 Professor Scowen was able to report that work on the 1964 *Addendum* was complete. It contained 60 new monographs including some antibiotics, chloral hydrate derivatives, measles vaccine, antioxidants and sweetening agents. Work had already started on a second *Addendum* to be published in early 1966. Scowen reported to the Pharmacopoeia Committee in May 1965 that the *Addendum* 1964 had been published on 1 December 1964 and would become official on 1 June 1965. The Commission had considered the question of the rapid identification of dispensed medicines – medicines in this era were usually labelled as 'The Tablets' or 'The Mixture'. They recommended that it should become normal practice from both the medical and pharmaceutical sides for the name of the preparation to be stated on the label of the container.

The Joint Committee on Reference Substances had made arrangements for the release of the first two substances, packaged in vials. These were Digoxin (used in the testing of Digoxin, Digoxin Injection and Digoxin Tablets) and 2-t-Butyl-4-methoxyphenol (used in the testing of the antioxidant Butylated Hydroxyanisole).

A revised edition of the booklet of Approved Names was published in December 1964, and this contained 865 names. Further supplementary lists were issued in February and April 1965 with a further 33 names.

By November 1965 the work had been completed on the 1966 *Second Addendum* which established 72 further monographs and updated some of the

[34] 1988. C.A. Johnson. *Pharm. J.* 7 May 240: 604.

other requirements. It was published on 15 March 1966 and became official on 1 September 1966.

In May 1966 the Pharmacopoeia Commission reported that work had been started on the new edition of the *Pharmacopoeia* for 1968. Its Medicines and Doses Committee had selected the proposed new monographs and recommended the deletions. Approval was given for the issue of Reference Substances for Ergometrine Maleate, Benzylpenicillin Sodium, Phenoxymethylpenicillin Sodium and Phenoxymethylpenicillin Potassium.

In May 1966 the Pharmacopoeia Committee reported that the Pharmacopoeia Commission staff and laboratory would move from the cramped GMC premises in Hallam Street to 8–10 Bulstrode Street, London W1. This would give twice the floor area. However work was needed before the laboratory could be transferred. The new home for the Commission was a terraced house with a housekeeper and her family occupying the top floor apartment. The move was eventually made in August 1967.

Mr Thomas Denston, who had been the secretary to the Commission since 1950, retired on 31 March 1967. At the GMC General Council meeting of 23 May 1967 the president stated that Denston had served under four separate commissioners and three successive chairmen. During his term of office three completely new editions of the *Pharmacopoeia* had been published – the 1953, 1958 and 1963 editions. Lord Cohen, the GMC president, paid the following tribute to him 'the maintenance of harmonious relationships between the Council and the Commission (which were not always evident in earlier days) owed much to Mr Denston's personal charm and sweet reasonableness'. The Commission recommended the appointment of Mr G.R. Kitteringham as secretary to the Commission. He had been assistant secretary since 1950. Mr C.A. Johnson was appointed to the newly created post of scientific director to the Commission.

In November 1966 Professor Scowen reported that the Commission had been heavily engaged with the revision of monographs and the preparation of new monographs for the 1968 edition. It now proposed to allow the addition of colour to capsules and tablets provided that the colouring agents are innocuous and did not influence therapeutic efficacy or the assay. By May 1967 Professor Scowen reported that the manuscript of the new edition was being despatched to the printers and galley proofs circulated to the committees. By May 1968 the text had gone through final proofing and arrangements were made to publish on 4 September 1968. The new 1968 edition contained 1,149 monographs, 150 of which were new. The new monographs included a wide range of synthetic drugs, antibiotics and biologicals. They included cephaloridine, biphasic and neutral insulins, betamethasone valerate and triamcinolone acetonide. Emphasis was

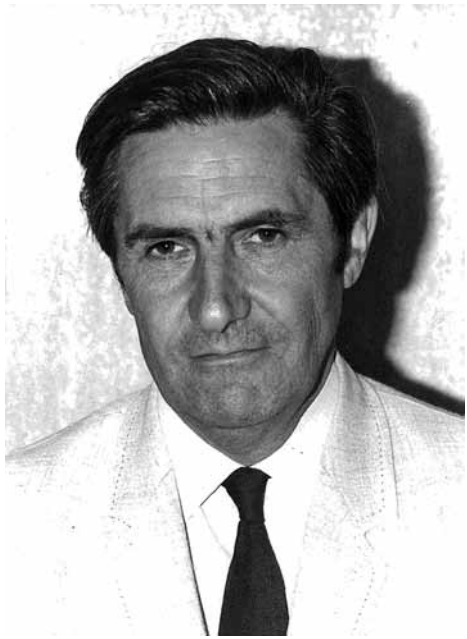

Figure 3.3 Mr Cecil Johnson, Scientific Director then Secretary and Scientific Director to the British Pharmacopoeia Commission, 1967–1988

Source: Pharmaceutical Journal.

placed in the new edition on detection and control of impurities and degradation products – for example a test for foreign steroids in the corticosteroids and a more stringent limit for 4-chloroacetanilide in phenacetin.

The Pharmacopoeia Selection Committee met on 27 February 1968 to select the membership of the new Commission with effect from September 1968. Professor Scowen was reappointed as the chairman, and two additional members were added – one as an expert on analytical chemistry and the other on immunological products. There were now 14 members of the Commission.

At the Commission meeting on 17 July 1968 the Commission discussed the future of the British Chemical Reference Substance collection. This had been set up to cover the needs of both the *British Pharmacopoeia* and the *Codex*. It was decided that in future the Commission would take responsibility for storing and distribution. Arrangements would be made with the Pharmaceutical Society to take over the stocks.

Changing from the Apothecaries' System of Weights and Measures to the Metric System

Discussions on what should be the appropriate system of weights and measures for medicines had started even before the publication of the 1864 edition of the *Pharmacopoeia*. In 1862 Dr Stiff published a paper in the *British Medical Journal* on the Metrical System of Weights and Measures. Dr E.A. Parker wrote a letter to the BMJ on 8 November 1862 stating that 'the metrical system is not merely the common language of chemists; it is rapidly coming into use among physiologists of all countries'. He asked 'are we to cling to a system becoming obsolete, and to place ourselves in a state of scientific isolation in this matter?' He proposed that if 'the Pharmacopoeia Committee will introduce it by the side of the English system, leaving it permissive for a prescriber or chemist to use which plan he prefers, the value of the Pharmacopoeia will be greatly increased'. As we have seen the 1864 *Pharmacopoeia* did not accept this forward-thinking proposal and all of the doses and the volumetric solutions used the Apothecaries' system. The 1885 *Pharmacopoeia* had moved to accept either system for volumetric solutions for analysis, and it included tables showing amounts in the both the British and metric systems. By 1898 the composition of all of the volumetric solutions was shown using only the metric system. By 1914 the metric system was used for most of the formulae for preparations and the doses were given in both systems. The preface stated that 'The metric system has also been employed in the specification of doses in the expectation that in the near future the system will be generally adopted by British practitioners'. In July 1917 the Annual Representative Meeting of the BMA passed a resolution that the general use of the metric system in the teaching of dispensing, prescribing and treatment would be beneficial to the scientific interests of the medical profession. The Pharmacopoeia Committee at its November 1917 meeting agreed. Nevertheless the dual system for doses continued in the 1932 and 1948 *Pharmacopoeias*.

In 1951 the Committee on Weights and Measures Legislation appointed by the Board of Trade recommended that the Apothecaries' system of weights and measures should be abolished after five years, and that the trades and professions should adopt the metric system. The Board of Trade consulted the GMC Council, who 'did not disagree'. The Pharmacopoeia Commission also considered the proposal. It felt that reasonable notice should be given and that it would be premature to make the change in 1958. The change would be made in the 1963 edition.

An Interdepartmental Working Party on Legislation met in 1960 and the Commission was invited to present evidence to it. It prepared a memorandum setting out its views. In September 1960 a statement was issued to the medical and pharmaceutical press outlining the proposals to abandon the Apothecaries' system of weights and measures. This was supported by the BMA and the

Pharmaceutical Society. They hoped that this would be enabled in the Weights and Measures Bill which had been introduced in the House of Lords on 1 November 1960. Lord Cohen of Birkenhead was the chairman of the GMC Pharmacopoeia Committee. He reported in May 1961 that he was prepared to move an amendment to the Bill in the Lords. However the Conservative government indicated that it hoped to introduce proposals during the passage of the Bill through the Commons. Unfortunately the Bill was not enacted during that session of parliament, and was not mentioned in the Queen's Speech in 1961. This caused concern in regard to the timetable for making the change in the 1963 *Pharmacopoeia*. The GMC Pharmacopoeia Committee started to explore other legal possibilities with the Ministry of Health.

By May 1962 with the proofs of the 1963 *Pharmacopoeia* now being prepared, the commission consulted the industry and the pharmaceutical and medical professions on a further proposal for transition from the Apothecaries' system to the metric system. It proposed that the strengths of preparations to be dispensed in the absence of directions will be in metric units, but there would be authority to dispense preparations for which the change to the metric system had been made in the corresponding Apothecaries' strengths for a limited period, and when pharmacopoeial tablets, capsules or injections were prescribed in Apothecaries' units, preparations in metric units should be dispensed. After the consultation and following legal advice a note was agreed for the 1963 *Pharmacopoeia* on Metric and Imperial Strengths. This set out the general provision that when a pharmacopoeial tablet, capsule or injection was demanded in a grain or fraction of a grain, preparations in the corresponding metric strength should be supplied. However during a transition period it would be allowable to supply products whose strengths were expressed in either grains or milligrams.

On 31 October 1962 a new Weights and Measures Bill was introduced. This would empower the Secretary of State of the Ministry of Health to issue regulations. In 1963 the Pharmacopoeia Committee issued an Amendment to the 1963 *Pharmacopoeia* extending the transition period. The Ministry of Health and the Secretary of State for Scotland issued regulations to give statutory effect to the policy. A change which had been discussed for over a century had at last been made.

Enforcement of the Standards of the *Pharmacopoeia*

The Food and Drugs (Adulteration) Act 1928 consolidated various of the earlier Sale of Food and Drugs Acts. The Act contained a General Provision that 'No person shall mix, stain, or powder, or order any other person to mix, colour, stain or powder ... any drug with any ingredient or material so as to injuriously affect the quality or potency of the of the drug', and another Provision that 'No person

shall sell to the purchaser any article of food or any drug which is not of the nature, or not of the substance, or not of the quality demanded by the purchaser'. The enforcement of this provision was the responsibility of the public analyst appointed by the local authorities.

Successive Food and Drugs Acts up to the Food and Drugs Act 1955 placed this responsibility on the local authorities to employ public analysts to assess the suitability of food and drug products under the legislation. Samples were taken from community pharmacies of medicines which could then be tested. Sometimes these were obtained in the form of a test prescription. The Food and Drug Act 1955 again required that 'if a person sells to the prejudice of the purchaser any food or drug which is not of the nature, or of the substance, or not of the quality, of the food or drug demanded by the purchaser, he shall be ... guilty of an offence'. The Courts had held that the sale on demand of a pharmacopoeial drug which did not comply with the requirements laid down in the BP provides at least *prima facie* evidence that the sample was not of the nature, substance and quality demanded. The Ministry of Health Regulations also required that a drug must conform to the standards specified when supplied by pharmacists for the National Health Service.

Inspection of manufacturers was instituted by the Medicines Division of the Department of Health as we shall see in the next chapter, and this included testing of samples of products. This was under the powers under the 1968 Medicines Act. The more recent Food Acts of 1984 and 1990 do not include reference to analysis of drugs. The modern public analysts do little if any analysis of medicines.

European Pharmacopoeia

In May 1964 Lord Cohen of Birkenhead, the chairman of the Pharmacopoeia Committee and President of the GMC reported that the GMC had agreed that representatives from the British Pharmacopoeia Commission, comprising a delegation from the United Kingdom, could attend a meeting of a European Pharmacopoeia Commission. This had been established under the auspices of the Public Health Committee of the Council of Europe. The new Commission comprised representatives from Belgium, France, West Germany, Italy, Luxembourg, the Netherlands and the United Kingdom. A legal basis for the new Commission was being developed by the Public Health Committee in the form of a draft Convention. The draft Convention envisaged 'specifications for medicinal substances'. The function of the new Commission was defined in the draft as:

to consider and decide all questions concerning:

a) The general principles applicable to the elaboration of a European Pharmacopoeia;
b) Methods of analysis for that purpose;
c) The preparation of monographs to be included in the European Pharmacopoeia
d) The fixing of time limits within which its decisions of a technical character relating to the European Pharmacopoeia shall be implemented within the territories of the contracting parties.

The Convention was signed by all parties on 22 July 1964, bringing the *European Pharmacopoeia* into official existence. The historical role of the *European Pharmacopoeia* will be considered in more detail in Chapter 5.

Indian Pharmacopoeia

The 1868 *Pharmacopoeia of India* was used until the 1885 edition of the *British Pharmacopoeia* was published and became official in India. An *Appendix to the British Pharmacopoeia* 1898 included some additional substances and local formulae for India and the other British colonies. The *Indian and Colonial Addendum* was published in 1900. The 1914 BP was provided to serve the needs of Britain and its empire. However the 1932 *Pharmacopoeia* omitted substances of local interest. An *Indian Pharmacopoeial List* of 1946 served as a supplement to the 1932 BP.

The India Independence Act 1947 granted independence to India and Pakistan on 15 August 1947. On 23 November 1948 an Indian Pharmacopoeia Committee was constituted. The new edition of the *Pharmacopoeia of India* was published in 1955.

Medicines Legislation

The GMC Council was invited in May 1960 to give evidence to an Interdepartmental Working Party which had been established by the Ministry of Health in consultation with the Home Secretary and the Secretary of State for Scotland. Its terms of reference were 'to review the legislative provisions which relate to the control of medicinal substances and to recommend what changes should be made to rationalise and simplify the law'. Separate Memoranda of Evidence were submitted by the GMC Pharmacopoeia Committee and the Pharmacopoeia Commission.

In 1956 the West German pharmaceutical company Chemie Grünenthal marketed a combination product called Grippex containing the drug thalidomide. In 1957 it sold thalidomide tablets under the name Contergan. The product was promoted as a safe sedative. The company Distillers Company Ltd obtained the marketing rights in the United Kingdom and sold them as Distaval. From 1959 adverse drug reactions of peripheral neuropathy were reported in West Germany, and in 1960 researchers reported infants with a new gross deformation – phocomelia or sealed limbs. The product was withdrawn in Germany and the United Kingdom on 27 November 1961 as a result of this teratogenicity – congenital malformation in children.[35]

In August 1962 the government's Standing Medical Advisory Committee set up a joint sub-committee on the safety of drugs, chaired by Lord Cohen. In March 1963 the Cohen Report published its final recommendations, including one suggesting that all new drugs and preparations should be submitted to a Committee on the Safety of Drugs. A voluntary arrangement was set up by health ministers to scrutinise the safety of new products. This was the Committee on Safety of Drugs chaired by Professor Derrick Dunlop.

The thalidomide disaster was clearly a failure to regulate the marketing of pharmaceutical products and to scrutinise their safety, quality and efficacy. The voluntary arrangements were a stop-gap measure. In 1964 the GMC and the Pharmacopoeia Commission were invited to comment on proposals for legislation which had been prepared by the Ministry of Health. The new legislative proposals were designed to carry out on a co-ordinated basis the functions now performed by means of the *British Pharmacopoeia*, the *British Pharmaceutical Codex*, the lists of Approved Names, the Therapeutic Substances Act, the Dangerous Drugs Act, the Poisons Board and the Committee on Safety of Drugs. Amongst the proposals was to transfer responsibility for the *Pharmacopoeia* and the Approved Names to a new organisation. The GMC's Executive Committee and Pharmacopoeia Committee did not object to this provided that the constitution, organisation and powers of the new body appeared satisfactory.

In September 1967 a Government White Paper (Cmnd 3395) was published entitled *Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines*. Paragraph 68 of the White Paper envisaged that the responsibility for the publication of the *Pharmacopoeia* would be transferred from the GMC to health ministers. The work of the British Pharmacopoeia Commission would be carried out by the new Medicines Commission or by an expert committee set up on their advice. The Queen's Speech at the opening

[35] Cartwright, A.C., 1991. Introduction and History of Pharmaceutical Regulation. In *Pharmaceutical Product Licensing – Requirements for Europe*. Edited by A.C. Cartwright and B.R. Matthews. London: Ellis Horwood.

of parliament on 31 October 1967 contained the following sentence: 'A Bill will be introduced to provide comprehensive new arrangements in Great Britain for ensuring the safety and quality of medicines, whether for human or animal use.' The White Paper proposals were considered by both the Commission and the GMC Pharmacopoeia Committee. Reservations were expressed about some aspects and further representations were made to the Ministry of Health.

The Medicines Bill was introduced into the House of Commons on 2 February 1968. As foreseen it provided that future editions of the *Pharmacopoeia* would be prepared by the Medicines Commission or by an appropriate committee under its direction. Ministers were required to publish such editions on the recommendation of the Medicines Commission. The Bill also empowered the Medicines Commission to prepare other compendia giving standards or other information, and also to publish lists of Approved Names. The GMC Council was concerned about the practical arrangements for the transfer and these would have to be negotiated with the Ministry of Health and the Treasury. The copyright for the *Pharmacopoeia* would have to be transferred from the GMC to the Crown.

The GMC Pharmacopoeia Commission considered the White Paper on medicines legislation at its meeting on 21 February 1968. It raised a number of issues with the GMC which were then passed to the Department of Health. It was concerned that not only the monographs but also the general requirements, General Notices, the Appendices and the general monographs for dosage forms were all given legal recognition. Section 56(4a) of the draft Bill allowed standards for superseded monographs to be invoked by specifying the name of the compendium and its year of issue. The Commission objected to previous monographs being accepted as valid standards. This issue was not resolved at the time and indeed still remains a problem in 2014, so that even for drugs removed on safety grounds from the market the previous published monograph standard remains official.

The Medicines Act 1968 received the Royal Assent on 25 October 1968. Section 98 of the Act dealt with the transfer of copyright from the GMC to the Crown. The actual transfer was to be effected by means of an instrument executed on behalf of the GMC Council under Section 98. Staff of the Commission were accepted and established in the Civil Service. Arrangements were made regarding preserved superannuation rights for their years of service with the GMC Council. The lease of 8–10 Bulstrode Street was assigned to the Ministry of Public Buildings and Works.

In November 1968 the GMC Council authorised its president and registrar to execute an instrument under Section 98 of the Medicines Act 1968 assigning to Her Majesty the copyright of the *British Pharmacopoeia*. The council decided that its Pharmacopoeia Committee no longer served any useful purpose and so it demitted office. In November 1969 the GMC president reported that

the Medicines Commission had now been appointed but that the transfer of responsibility for the *Pharmacopoeia* would not take place until 1970. The instrument assigning copyright to Her Majesty was executed on 3 February 1970.

In June 1970 the GMC Executive Committee considered a letter from the Department of Health and Social Security inviting comments on the proposals for the future of the *Pharmacopoeia*. A list of proposed Commission members was included in the proposals. The Executive Committee did not offer any observations.

The transfer of responsibility for the publication of the *Pharmacopoeia* from the GMC to the Medicines Commission and the transfer of the Commission staff to the Department of Health marked the end of a century during which the *Pharmacopoeia* had evolved from a formulary for pharmacists to a book which now played a vital role providing analytical standards for commercially manufactured medicines. No longer was it a repository of obsolete and obsolescent drugs, it reflected fully the therapeutic armamentarium available to physicians. Despite the earlier tensions between the professions of medicine and pharmacy during its history, they had worked together to develop a compendium which served the United Kingdom, its Dominions and Colonies, and in the post-war era gave it a world-leading role in regulating the quality of medicines in the UK and beyond. But how would it fit in with the other newly created regulatory bodies?

Chapter 4
Later Years: 1968–2014

I find the great thing in this world is not so much where we stand as in what direction we are moving.

(Oliver Wendell Holmes Senior)[1]

European Legislation

In the wake of the thalidomide disaster most European countries enacted measures to regulate the safety, quality and efficacy of medicines. In 1965 the European Community consisted of six member states – France, the Federal Republic of Germany, Italy, Belgium, the Netherlands and Luxembourg. The first of the European pharmaceutical directives – 65/65/EEC – was drawn up and adopted by the Council of Ministers on 26 January 1965, with 18 months allowed for its implementation.[2] This first directive defined a medicinal product – Article 1, and defined the need for documents and particulars to accompany an application for marketing authorisation – Article 4. Article 4(7) defined the 'documents and particulars' which need to accompany a marketing authorisation application as including 'a description of the control methods' of the constituents and the finished product. It laid an obligation on the authorities to refuse an application for a product if it is 'harmful in its normal conditions of use' or lacking in therapeutic efficacy; if the efficacy is insufficiently shown; or if its qualitative or quantitative composition is not as declared – Article 5.

In 1973 the UK, Denmark and Ireland joined the European Community. A second directive, 75/318/EC, was adopted on 20 May 1975.[3] The legal requirements for starting materials (drugs and excipients) were defined in the annex to the directive in terms of a pecking order of pharmacopoeias – if there was a *European Pharmacopoeia* monograph this should be used, if not then a monograph from a national pharmacopoeia of a European country, such as the *British Pharmacopoeia*, could be used. If neither existed then a pharmacopoeia from a third country – such as the USP – could be used.

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[1] Holmes, O.W., 1958. *The Autocrat of the Breakfast-Table*, Chapter IV. Boston: Phillips, Sampson and Co.

[2] 1965. Council Directive of 26 January 1965. *Official Journal of the European Communities* No. 22.

[3] 1975. Council Directive of 20 May 1975. *Official Journal of the European Communities* No. L147/1.

This legal requirement has now been replaced by the requirements of the updated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 as amended.[4] Annex 1, Parts 3.2.(5) and 3.2.(6) describes the legal requirements in relation to the *European Pharmacopoeia* and national pharmacopoeia monographs. However these still remain basically the same as in the earlier directives.

Medicines Act 1968 and Regulations

The Medicines Act came into force in the United Kingdom in September 1971.[5] Section 2 of the Act established the Medicines Commission to advise the licensing authority and to make recommendations with regard to committees. Section 4 mentioned that 'a committee may be established under this section for the purpose of performing any function under Part VII of this Act in relation to the *British Pharmacopoeia*'. Part VII of the Act related to the *British Pharmacopoeia* and other publications and laid down in Section 99 a legal duty to prepare new editions of the *Pharmacopoeia* containing relevant information on 'substances and articles which are or may be used in the practice of medicine, surgery, dentistry or midwifery, and substances and articles used in the manufacture of substances or articles falling within the preceding paragraph'. Section 65 of the Act made it an offence to sell or supply on prescription a medicinal product which does not comply with the standard in the official BP monograph. The Act also gave official recognition to the monographs of the *European Pharmacopoeia*.

A number of other official committees were created using the powers under Section 4 of the Act. These included the Committee on Safety of Medicines – which replaced the earlier voluntary Committee on Safety of Drugs, the Committee on the Review of Medicines – which dealt with the review of medicines which were already in existence on the UK market, and the Committee on Dental and Surgical Materials. In the work of all of these committees the standards of the *Pharmacopoeia* were used to define what was acceptable in terms of quality for drug substances, excipients and the finished product.

On 19 August 1970 the secretaries of state concerned with health in England together with the ministers responsible in Wales, Scotland and Northern Ireland were advised by the Medicines Commission to issue an Order under the Medicines Act. This was the Medicines (British Pharmacopoeia Commission)

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[4] 2001. Directive 20011/83/EC of the European Parliament and of the Council of 6 November. *Official Journal of the European Communities* L311:67.

[5] 1968. Medicines Act 1968. Chapter 67.

Order 1970.[6] This came into effect on 7 September 1970. It established the British Pharmacopoeia Commission whose function was to prepare any new edition of the BP and to publish lists of Approved Names under Section 102(2) of the Act.

In 2005 the Medicines Act was amended by the Medicines (Advisory Bodies) Regulations 2005[7] to create the Commission on Human Medicines (CHM). This took over the functions of both the Medicines Commission and the Committee on Safety of Medicines. The Commission came into being on 30 October 2005.

In 2009 the Medicines and Healthcare Products Regulatory Agency (MHRA) undertook a consultation on the reform and consolidation of the provisions of the Medicines Act. In August 2010 it published a working draft of the consolidated regulations. Further informal consultations took place in 2010 and 2011. The Human Medicines Regulations 2012 were laid before parliament on 24 July 2012 and came into force on 14 August 2012.[8] Regulation 11 of the Human Medicines Regulations states that there continues to be a committee to be appointed by health ministers called the British Pharmacopoeia Commission which is charged with the preparation of editions of the *British Pharmacopoeia* and the preparation of lists of names to be used as headings for monographs. Regulation 317 makes the BP Commission responsible for production of editions of the BP for:

> (a) substances, combinations of substances and articles (whether medicinal products or not) which are or may be used in the practice of medicine or surgery, dentistry or midwifery, and (b) substances, combinations of substances and articles used in the manufacture of anything falling within paragraph (a).

Regulation 317(4) states that 'Ministers must arrange for the publication of anything prepared or caused to be prepared under this regulation'.

Addendum 1971 to *British Pharmacopoeia* 1968

The first meeting of the new BP Commission established by health ministers on the recommendation of the Medicines Commission was held on 18 March 1970. In 1970 Sir Eric Scowen, the chairman of the BP Commission, had said that he did not wish to continue in office in view of his other commitments, and

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[6] 1970. The Medicines (British Pharmacopoeia Committee) Order 1970. SI 1970 No. 1256.

[7] 2005. The Medicines (Advisory Bodies) Regulations 2005.

[8] 2012. The Human Medicines Regulations 2012. SI 2012 No. 1916.

in particular his chairmanship of the Committee on Safety of Medicines. His vice-chairman, Dr Frank Hartley, was invited to become the new chairman and accepted; he was to serve in this office until 1980. This broke the tradition of the previous 42 years of having a chairman who was medically qualified. It was a further recognition that the *Pharmacopoeia* was now more concerned with quality standards than providing therapeutic advice to doctors.

Frank Hartley (1911–1997) was the son of a Lancashire plumber, whose father died when he was five.[9] He did a three-year apprenticeship in a Nelson pharmacy and then studied for his pharmaceutical chemistry diploma at the School of Pharmacy in London, qualifying in 1932. He then studied for a degree in chemistry at Birkbeck College, University of London. He obtained his PhD in 1941. He became the chief chemist at the UK subsidiary of Organon Laboratories. After the war he joined British Drug Houses as its director of research. In 1964 he returned to the School of Pharmacy and served as its dean until 1976 when he was made vice-chancellor of London University. He was knighted in 1977. Herbert Grainger, the head of the Technical Secretariat of the European Pharmacopoeia Commission from 1965 to 1980, knew him well from the years when Hartley was head of the UK delegation to the European Pharmacopoeia Commission. He said of him that he 'nearly always spoke at length, deploying it seemed, three or four strands of reasoning simultaneously, finally plaiting them into a rope on which he hoisted his now fatigued opponents'.

At this first meeting, the secretary, Mr G. Kitteringham, described the responsibilities of the Commission and outlined the programme for preparation of a second *Addendum* to the 1968 edition and the new 1973 edition. Some modifications were agreed to the committees and panels. Mr S.C. Jolley, the editor of the *British Pharmaceutical Codex*, was appointed as a corresponding member of the relevant committees. Mr Arthur Fishburn, chair of the Topical Preparations Committee, raised the question of how to ensure the efficacy of potent topical preparations where the monograph only controlled identity and content. Dr Hartley said that he hoped that the full implementation of the Medicines Act 1968 would overcome this deficiency. He envisaged the licensing procedures to be introduced under the Act as the means of ensuring the efficacy of all preparations before they were allowed to be marketed. When this had been established it would be the function of the *Pharmacopoeia* to publish specifications by which the continued suitability of the preparations could be judged.

[9] 1997. Obituary. Sir Frank Hartley by A.T. Florence. *The Independent* 19 February.

British Pharmacopoeia 1973

In 1971 work was proceeding on the preparation of the 1973 BP. Two lists of Approved Names were published, in May and October 1971. At the Pharmacopoeia Commission meeting of 14 June 1971 consideration was given to the legal situation regarding the *Pharmacopoeia*. Part VII of the Medicines Act envisaged a single authority for the issue of standards but in 1971 the Pharmaceutical Society was still responsible for the *British Pharmaceutical Codex* and the BP Commission for the BP. The BP Commission reviewed the contents of the *British Pharmaceutical Codex* and felt that nearly all of the contents of the *Codex* fell within the scope of the *Pharmacopoeia*. It also felt that there would be no obstacle to extending its remit to veterinary medicines. At its July 1971 meeting a document on the future developments in the preparation of standards was agreed for the Department of Health to send to the Medicines Commission. In 1972 the Medicines Commission decided that in future there should be only one official compendium of standards – the *British Pharmacopoeia*. This would contain standards for formulated preparations including any mentioned in the current and future editions of the *British National Formulary*. In 1939 the Minister of Health had appointed a small committee to prepare a formulary for wartime use. This was the *National War Formulary*. After the war ended the Pharmaceutical Society and the British Medical Association wanted to continue publication, and produced the first edition of the *British National Formulary* in 1949. In 1975 the Medicines Commission became concerned about the influence of the pharmaceutical industry on prescribing and suggested to the Department of Health that a more comprehensive national formulary was needed. A new Joint Formulary Committee was appointed in 1978 and a new edition of the *British National Formulary* was published every six months from 1981 until the present time.[10]

The twelfth edition of the BP was brought to proof stage, published and then became official on 1 December 1973. This edition was the first in an A4 format. It contained 1,277 monographs, an increase of 128 over the previous edition. Amongst the new monographs were the antibiotics Cephalexin and Lymecycline, Carbenoxolone Sodium used for treatment of gastric ulcer, Clomiphene Citrate for the treatment of infertility, the antitubercular substance Ethambutol Hydrochloride, the beta-blocker Practolol – which was later withdrawn from the market in 1976 due to adverse events involving dry eyes, conjunctivitis and blindness, and Vincristine Sulphate for treatment of cancer. Sodium Cromoglycate in an inhaler system for asthma necessitated the creation of the name of 'Cartridges' for the new dosage form. This edition

[10] Wade, O., 1993. British National Formulary: Its Birth, Death and Rebirth. *Br. Med. J.* 306: 1051–4.

of the *Pharmacopoeia* also included for the first time the monographs from volumes I and II of the *European Pharmacopoeia*, but with additional titles, and information on storage, labelling, dose and action and use.

Addenda to the *British Pharmacopoeia* 1973 and *British Pharmacopoeia* 1978

At the July 1970 BP Commission meeting discussion started on the need for a solution rate test for tablets which measured the release of drug. In February 1972 the discussion in the BP Commission on the need for solution rate tests for tablets continued. Some commissioners were against the early adoption of the test for a range of tablets as the only available test – published in the USP – was apparently being revised. There was also little experience of the test from UK manufacturers. Both the chairman and Mr Adamson (a retired industry chief analyst) stressed the importance of a test to reduce batch to batch variation and eliminate poor quality tablets. Work began on a new edition of the *Pharmacopoeia* for 1978 and an *Addendum* to be published in 1975.

The programme for the new BP was planned to include addition of standards for all of the articles currently in the *British Pharmaceutical Codex*, although this proved to be over-ambitious. The new Commission had 20 advisory committees and a number of panels.

There had been adverse drug reaction reports of nephropathy (kidney damage) for the analgesic phenacetin since the 1960s, and concerns expressed about the extent of its use.[11] The BP Commission therefore started work in 1970 on alternate preparations omitting phenacetin and using paracetamol instead – such as replacements for Aspirin, Phenacetin and Codeine Tablets and Soluble Aspirin, Phenacetin and Codeine Tablets. In 1974 the Committee on Safety of Medicines recommended that the long-term use of the drug be discouraged. In 1978 the Committee on the Review of Medicines recommended that, on grounds of safety, phenacetin had no place in analgesic, anti-inflammatory or anti-pyretic therapy. The Secretary of State then issued an order under Section 62 of the Medicines Act banning the sale and supply of products containing phenacetin.

Work was proceeding in 1974 on the 1975 *Addendum*. This included new monographs for Amoxycillin Trihydrate, Candidicin, the antihistamine Diphenhydramine, the analgesic Ibuprofen, the oral hypoglycaemic Glibenclamide, Glucagon and Streptokinase. As a result of the restriction in use of phenacetin, new monographs for Aspirin and Codeine Tablets, Soluble Aspirin and Codeine Tablets and Aspirin and Caffeine Tablets were introduced. The text included the new solution rate test for Digoxin Tablets, which the

[11] Stewart, J.H., 1978. Analgesic Abuse and Kidney Failure in Australia. *Kidney International* 13: 72–8.

introduction suggested would be a general procedure and the precursor to the extension of the method to other tablets and capsules. The book was published at the beginning of April 1975.

On 8 June 1975 the Commission's laboratory and its associated offices moved from Bulstrode Street to Canons Park, to one of a series of single-storey buildings used by various government departments in a site on Honeypot Lane, near to Canons Park Underground station. The new laboratories had been specially designed for them by the Head of Laboratory Mrs Sylvia Richens.

At the October 1975 Commission meeting Professor Paul Turner, Professor of Clinical Pharmacology at the University of London, raised the issue of bioavailability of a newly approved generic formulation of methyldopa tablets, for which he asserted that there was no bioavailability data in comparison to the originator's product. This raised the question of revision of the pharmacopoeial monograph when any supporting data for the generic product was regarded as confidential but had only been considered by the assessors in the Licensing Section of the Medicines Division. The relationship between Licensing and the *Pharmacopoeia* was to be an ongoing issue.

At the same meeting Mr C.A. Johnson reported on the development of the use of infrared spectra for identification. Many of the monographs for drug substances included an infrared test using an Authentic Specimen (AS). The publication of spectra would enable the test to be carried out without the need for the AS, thus saving the Pharmacopoeia Commission Laboratory the need to maintain and distribute AS samples. At the November Commission meeting there was a discussion on identification tests for drugs. The monographs in the 1973 BP usually contained a series of tests such as colorimetric tests for functional groups on the drug molecule as well as an infrared identification test. It was felt that the non-instrumental methods were still useful to enable the identification to be carried out by pharmacists – in hospital quality assurance departments for example.

At the April 1976 meeting of the Commission Mr George Kitteringham retired as the secretary. Dr Hartley as chairman proposed a resolution that members express their profound admiration of his services, and wished him a long and happy retirement. From 1 July Mr Cecil 'Johnny' Johnson was to take over as the first secretary and scientific director combining both roles. Efforts were being made to recruit more staff – however there was a complete embargo on recruitment to the Department of Health.

Kitteringham did not lose his association with the BP – he volunteered to help with editorial work when staff recruitment difficulties caused problems with the publishing programmes, and he was appointed to the BP Nomenclature Committee, where he served for many years. He died in 2000.

At the September 1976 meeting of the Commission the difficulties in recruitment of both professional and clerical staff were mentioned, and this was

having an effect on the preparation of monographs and the timetable for the production of the addenda. There were also staffing difficulties in the rest of the Medicines Division and these were to continue until the reorganisation of the division in 1989. Cuts in meetings were necessary and this would slow down the work.

At the November meeting of the Commission the text of the second *Addendum* to the BP 1973 was reviewed. New monographs included the antiemetic Metoclopramide Hydrochloride, Methysergide Maleate for migraine, the antibacterial Furazolidone, and Fentanyl Citrate which was a narcotic analgesic. Cholecalciferol (vitamin D_3) was introduced to replace calciferol (vitamin D_2). Many of the requirements of the *European Pharmacopoeia* general dosage form monographs were introduced, such as the Test for Uniformity of Weight being applied to tablets, capsules, suppositories and powders for injection. The *Second Addendum* to the BP 1973 was published in 1977. It became official on 1 December 1977. The first edition of the *British Pharmacopoeia Veterinary* was published simultaneously with the 1977 *Addendum*. It was a companion volume to the BP and contained standards and substances used in veterinary medicine in the UK.

The April 1977 Commission meeting discussed the future publication programme for the BP. It was agreed that the situation was unsatisfactory in that the reader of the BP was referred to the *European Pharmacopoeia* for many standards. There would shortly be a total of eight volumes to be consulted for standards applicable in the UK. It was agreed that a unified edition of the BP should be prepared which would include specifications from the *European Pharmacopoeia*, suitably edited. Mr Johnson would discuss with HMSO the possibility of issuing annual and cumulative addenda.

At the June 1977 meeting Mr Johnson drew the Commission's attention to the legal position of obsolete monographs published in old editions of the BP. There was no legal means of abrogating responsibility for them, and the old specification could still continue to be used in perpetuity. This is an issue that was raised by the GMC during the consultation on the Medicines Bill in 1968 and which still continues to dog the *Pharmacopoeia* over 40 years later; subsequent amendments to the Medicines Act have failed to deal with this problem. The monographs for drug substances and products that have long since been removed from the market remain official because of their inclusion in old editions of the *Pharmacopoeia*.

Another issue raised at the June 1977 Commission meeting was the recommendation from the Committee on Safety of Medicines to delete chloroform from medicines as a result of the March 1976 report from the US National Cancer Institute that this substance produced malignant kidney

tumours in rats and hepatocellular carcinoma in mice.[12] Chloroform was used in many pharmaceutical preparations included in the *Pharmacopoeia*; the reformulation work would be lengthy and likely to take several years. At the Commission meeting in July a list of 24 formulated preparations was agreed as having priority for reformulation. These included many widely prescribed formulations for use as laxatives, cough suppressants, expectorants, antacids and urine alkalising preparations.

The June 1977 Commission meeting included a long discussion on impurities in drug substances. The pharmaceutical reviewers in the Licensing Section of the Medicines Division who assessed generic products were asking for information on the impurities in the drug substances used. These drug substances were often imported and different sources which were manufactured using different synthetic routes or different manufacturing conditions could contain different impurities. Thus the Licensing Section could approve a different company specification to that in the *Pharmacopoeia*. However the Licensing Section did not have ready access to a laboratory to be able to check new analytical methods. It was agreed that the confidentiality restrictions on pharmacopoeial access to licensing information needed to be revisited, and further that the Licensing Section should not introduce into a product license any specification in conflict with the relevant pharmacopoeial monograph. The Commission felt that much closer liaison with the Licensing Section was essential.

On 28 July 1977 three members of the Commission – Mr Holbrook, Professor Overend and Dr Wills – had visited the BP Commission Laboratory at Canons Park to look at the supply of British Pharmacopoeia Chemical Reference Substances. They had been surprised at the scale of the operations involved – the catalogue contained 360 items. They recommended that the use of infrared spectra for identification be extended from the 60 then current, and that the use of alternative analytical methods not using reference substances be considered. Mr Johnson indicated that the USP made the supply of reference substances a profitable business, but felt that this was not feasible for the BP at the present time. It is interesting as the author of this book to speculate, with the benefit of hindsight, that this was a commercial opportunity which was being missed, and which could have given a greater contribution to the Commission's revenues.

The October 1977 meeting of the Commission came back to the vexed question of new generic sources of drug substances reviewed by the Licensing Section. It had been agreed that in future applicants for product licences would be asked if they agreed to disclose to the British Pharmacopoeia Commission information on the pharmaceutical standards applicable to the product or its active ingredient. At the Commission meeting in November 1977 the first

[12] Weisburger, E.K., 1977. Carcinogenicity Studies on Halogenated Hydrocarbons. *Environmental Health Perspectives* 21: 7–16.

responses by companies to this initiative were discussed. Most had been negative, so this had not been a successful tactic. The differences between the needs and expectations of Licensing and the BP Commission were thus to continue.

New monographs in the third 1978 *Addendum* were Alclofencac and Alclofenac Capsules – which had been requested by the Committee on Review of Medicines, Disulfiram Tablets, Naproxen, Naproxen Tablets and Rifampicin. The control of toxic impurities was a subject that was always of concern for monographs. In this *Addendum* mention was made of the teratogenic impurity 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Hexachlorophene, which was used as a disinfectant. It was proposed to control it at 15 parts per thousand million, but the analytical method had not been finalised. Other changes were made as a result of the publication of volume III of the *European Pharmacopoeia*.

At the November 1977 meeting the Commission discussed the decision to include *European Pharmacopoeia* monographs in the 1980 BP. Some preliminary work had been done to estimate the time needed to edit the European monographs into the BP style. This was quite considerable. There was also an issue of the timing of the publication of European monographs in the BP so that they did not ignore European monographs which had been revised but were not yet official. At the February 1978 meeting of the Commission it was agreed that for legal reasons two versions of some European monographs would need to be included in the BP 1980 – the current and the revised versions. The time taken to translate the European monographs into the BP style was estimated at 20 per cent of the time of the six staff in the BP's editorial staff, and this was felt to be acceptable.

British Pharmacopoeia 1980

Work started on the text of this edition in 1978. One issue discussed at the November 1978 Commission meeting was the appropriate limit for impurities and degradation products in monographs. It was agreed to allow a limit of 5 per cent for the hydrolysis product in sugar-coated Chlordiazepoxide Tablets, as the hydrolysis product had no toxicity problems. However, for Isoniazid injection there needed to be a much more stringent control on the levels of hydrazine as an impurity. Concern was expressed about a commercial sample investigated by the BP laboratory which contained 400 ppm hydrazine, an impurity which had been reported as being mutagenic.

However the 1978 and 1979 annual reports both mentioned the difficulties with staff recruitment and limited resources. The Commission felt that its efforts to fulfil its legal function under the Medicines Act and to maintain a satisfactory liaison with the *European Pharmacopoeia* were jeopardised. The secretariat was only able to meet the publishing schedule by devoting many hours of voluntary

overtime. The continuing need for the BP was emphasised by the comparison with the *European Pharmacopoeia* which only had 350 monographs compared to the 1,900 in the BP 1980. Thirty-six new Reference Substances had been established during 1979.

At the April 1979 Commission meeting the future of its Medicines and Doses Committee was discussed. Dr Harman, its chairman, felt that its functions of selecting medicines for inclusion in the book were being superseded by the Committee on Safety of Medicines, the Committee on the Review of Medicines and the *British National Formulary*. The two committees decided which products should be approved for sale and the BNF decided which were the more clinically important products. The dosage statements in the BP were not used by doctors and the Committee was not sure that they were useful to pharmacists. However the Commission felt that some assistance was still needed with information on action and uses in the *Approved Names* booklet. It was agreed that some advice would be needed for the *Addendum* to the BP 1980.

At the October 1979 Commission meeting a report was received from the Pharmaceutical Society's Pharmaceutical Quality Assurance Committee on the possibility of replacing rabbits used in the pyrogen test with a test using an extract of blood cells (amoebocytes) from the horseshoe crab *Limulus polyphemus*. This Limulus Amoebocyte Lysate (LAL) test had first been approved by FDA in 1970 and was already used in some tests in the USP. It was agreed to refer it to the appropriate European Pharmacopoeia Group of Experts. This would be an important step in starting to minimise the use of laboratory animals in the tests in the *Pharmacopoeia*.

The book was published in June 1980 and came into force on 1 December 1980. It was printed using Monotype Lasercomp laser typesetting equipment. It included 411 monographs not included in the previous edition or the addenda. One hundred and twenty-eight monographs from previous editions were omitted. The format was different to earlier editions in that the first section of the book comprised monographs on medicinal and pharmaceutical substances and then sections on specialised groups of products. The book was in two volumes. It included for the first time monographs on surgical dressings and sutures. The section of infrared spectra for identification purposes introduced in 1977 was considerably extended. The first group of infrared spectra was published separately in the *Addendum* to the BP 1980. Agreement had been reached between the Pharmaceutical Society and the Medicines Commission that all published standards for medicinal substances and preparations would be in the BP, and about 800 monographs from the *British Pharmaceutical Codex* were included. The 1978 *Annual Report* recorded that there were 396 Reference Substances and about 345 samples were issued each month, 70 per cent of them were being sent overseas.

At the end of 1979 Sir Frank Hartley retired as chairman of the British Pharmacopoeia Commission and was replaced in 1980 by Professor John Bedford Stenlake.[13] Stenlake was appointed in 1952 as a senior lecturer in pharmaceutical chemistry at the School of Pharmacy in the Royal Technical College in Glasgow. He was promoted to professor and head of department and he led the transition from the Royal College to the University of Strathclyde. His research efforts led to the discovery and development of the short-acting muscle relaxant atracurium, which became used routinely in surgical operations. He died in April 2006. Professor Frank Fish paid tribute to him in the obituary in the *Pharmaceutical Journal* by recalling 'John's vast knowledge and skill in chairing important committees so calmly and efficiently'.

In August 1980 the BP Commission Secretariat moved from the terraced house in Bulstrode Street to offices on the seventeenth floor in Market Towers. This was a tower block on Nine Elms Lane near the Thames in Vauxhall, near the Nine Elms fruit, vegetable and flower markets. They joined the other staff of the Medicines Division, but would function as a self-contained unit. This allowed a closer liaison with Licensing staff on matters of mutual concern. The *Annual Report* for 1980[14] again mentioned the shortages of staff. Economies had been made by reducing the membership of committees and their frequency of meetings. The BP Commission met bi-monthly instead of monthly.

The *Annual Report* for 1981[15] mentioned the same issues of restrictions on staff recruitment and limitation of resources. These made it difficult to proceed with the development of the BP. The work of the laboratory had also suffered. The report expressed concerns about the inordinate delays in preparing and revising European monographs. A supplement to the volume of infrared spectra had been published in 1981 containing 56 spectra, and a further supplement was in course of preparation. The 1981 *Addendum* to the BP published during the year contained 35 new monographs, including the analgesics Fenoprofen and Ketoprofen, the cytotoxic drug Cytarabine and the dopa-decarboxylase inhibitor Carbidopa – used in the treatment of Parkinson's disease. The introduction to the *Addendum* mentioned the ongoing consideration into setting appropriate limits for the toxic impurity hydrazine.

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[13] 2006. Obituaries and Tribute. Frank Fish tribute to Professor John Stenlake. *Pharm. J.* 276: 550.

[14] 1980. British Pharmacopoeia Commission Annual Report in *Annual Report for 1980 of the Medicines Commission, the Committee on Safety of Medicines, the Veterinary Products Committee, the British Pharmacopoeia Commission, the Committee on Review of Medicines, the Committee on Radiation from Radioactive Medicinal Products*, HMSO.

[15] 1981. British Pharmacopoeia Commission Annual Report in *Annual Report for 1981 of the Medicines Commission, the Committee on Safety of Medicines, the Veterinary Products Committee, the British Pharmacopoeia Commission, the Committee on Review of Medicines, the Committee on Radiation from Radioactive Medicinal Products*, HMSO.

The *Addendum* 1982 was published. It had been agreed that future addenda would be additive and would not include material included in earlier addenda. This included the anti-inflammatory drug Diflunisal, the hypnotic Chlormethiazole and the anti-oestrogen Tamoxifen Citrate – used in treatment of breast cancer. One issue mentioned was the relatively high level of impurities in the new monograph for clofazimine, used for treatment of leprosy. The quality of this drug was however felt to be appropriate in view of the indication. Quality is not an absolute criterion; it has to be considered in relation to the indication for use of the product. The text on Efficacy of Antimicrobial Preservatives which had first been published in 1980 was reviewed and amended. It was noted that certain biological products, such as the insulin injections, would not meet the strict criteria of the test. This was a non-mandatory test but one which was also to prove very useful to the industry and the Licensing Section of the Medicines Division in reviewing new product license applications for products containing preservatives.

The activity of the BP Commission was again curtailed in 1983 due to staffing problems. Two very senior members of the staff retired during the year – Irene Ladden after 31 years, and Cherry King after almost 20 years.

One issue which was discussed during the year was the fixed formulae for products which were included in the book. Most of these were no longer made up by community pharmacists for their own patients, but were manufactured and then sold in bulk to pharmacies. It was agreed that the formulae would be written in a flexible way to allow modifications to secure chemical and microbiological stability. The 1983 *Addendum* was published and became official on 1 June 1984. It contained new monographs for the hypnotic Flurazepam Monohydrochloride, the sedatives Oxazepam and Lorazepam, the anti-inflammatory drug Benorylate, Dihydroergotamine Mesylate for migraine, Fluorouracil as a cytotoxic drug, the antifungal Econazole nitrate and Lactulose as a laxative. The section on methods of sterilisation had been reviewed and new text was included reflecting the recent changes in the *European Pharmacopoeia*. Sterilisation by Heating with a Bactericide was less effective than autoclaving and its continued use was under review.

At the July 1984 meeting of the BP Commission meeting the Antimicrobial Preservative Efficacy test was reviewed again and a modified text agreed. This would be published as a separate document by the Medicines Division. Formulated products in the BP would now be referred to as having 'a suitable antimicrobial preservative'. The technology used to produce the next BP was debated at length at this meeting. The Norsk computer terminal, printer and hard discs for computer input of the text had been ordered but not yet delivered. It had been agreed that a word-processor operator would be appointed, but only at the expense of an existing clerical post. In addition HMSO had expressed reservations about the use of this advanced technology for the production of

such a major work as the BP. However if the old technology had to be used it would necessitate re-keying the entire work – comprising 15 million keystrokes, and this would take 18 months. It was suggested that another *Addendum* could be published using the new technology, and this might allay the HMSO concerns. It was agreed to delay production of the next edition of the BP to utilise the new technology.

In September 1984 changes to the management of the BP laboratory took place. Dr Geoffrey Carr, the head of the laboratory, had resigned to take a post in the pharmaceutical industry. Dr Amirul Islam had been appointed as the new head. A Laboratory Management Group was formed with the Medicines Division to integrate the work of the BP laboratory and other laboratory work. Regular liaison meetings were also set up between principal pharmacists responsible for pharmaceutical assessment in the Medicines Division and the BP Secretariat to review progress and priorities and help to advise on the policy of the Commission. The introduction of new computer technology for input of the text of the BP was discussed again. The Norsk equipment was in the country but not yet installed. It was agreed to produce an intermediate *Addendum* in late 1985 or early 1986 before the next full edition to test the new technology.

At the November 1984 meeting of the BP Commission Mr Johnson reported that the Norsk equipment had been installed. HMSO had agreed to accept the programme for future publications of the BP and addenda. A word-processor operator was being recruited.

In 1985 work continued on the *Addendum* 1986 to the BP 1980 using the new computer technology. A computer database was also set up to facilitate retrieval of information. Work also commenced on the production of the new full edition of the BP. The next BP edition would for the first time be in two volumes. The new edition would contain over 400 infrared spectra to be used for identification of drug substances.

The 1986 *Addendum* to the BP 1980 was published in June 1986 and became effective on 1 December. As with the *Addendum* 1983 the volume was additive, and the page numbering was consecutive with the earlier *Addenda*. It included 56 new monographs for substances and preparations. New substances included the oral hypoglycaemic Acetohexamide, the antifungal Clotrimazole, the anxiolytic Medazepam and the anticonvulsant Phenytoin. The reference to the process of Heating with a Bactericide was removed from all specific monographs in the BP as it was no longer regarded as an acceptable sterilisation process.

In 1986 at the March regular meeting of the BP Commission/HMSO Steering Group the pattern of sales of the BP 1980 and the *Addenda* was discussed. The sales of the BP 1980 were 22,584 whereas the *Addendum* 1983 had only sold 8,624 copies. Mr Johnson said that he felt that this was due to the fact that pharmacy students only purchased the main volume, but not the addenda or the infrared supplements. At the October 1986 meeting of the

Steering Group the major markets for the book were reviewed. Mr Johnson said that he saw the major markets as being the pharmaceutical industry, hospital pharmacies, academic institutions and reference libraries. He foresaw few sales to students, the medical sector or retail pharmacies.

In 1987 the major activity was the editing of material for the next edition of the BP. This was to contain over 2,000 monographs, over 400 infrared spectra and the customary appendices. For the first time the contribution of material from the *European Pharmacopoeia* would approach 25 per cent. The material was being edited at computer terminals and sent to the printer as magnetic tapes.

The 1987 *Annual Report*[16] of the BP Commission noted the increasing sales of reference substances. There were many new customers and there was an increasing interest in the BP in the UK and overseas. Many of the sales were to US customers.

The BP 1988 was published in June 1988.

The 1987 Evans Cunliffe Study on the Control of Medicines

In the 1980s the pharmaceutical industry became dissatisfied with the increasing delays in processing their applications for product licences which were eroding the remaining patent lives of commercially important new drugs. In 1987 the average time taken to approve a new drug was 18 months. The response of the Conservative government was to set up an enquiry into the processing of product licence applications and also to consider all of the work undertaken by the Medicines Division of the Department of Health. The enquiry was conducted by Dr N.J.B. Evans and Mr Peter Cunliffe. The remit of their enquiry was 'to examine the issues for the Department of Health and Social Security arising from the continued increase in licence applications and other work under the Medicines Act and to recommend ways of dealing expeditiously with this work, while maintaining adequate standards for the safety, efficacy and quality of medicines in the United Kingdom'. One of the areas covered by their enquiry was in relation to the British Pharmacopoeia Commission. They began their work in April 1987 and their report entitled *Study on the Control of Medicines* was published in December 1987.[17] In April 1988 the Minister of State for Health announced his decision on the implementation of the report.

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[16] 1987. British Pharmacopoeia Commission Annual Report in *Annual Report for 1987 of the Medicines Commission, the Committee on Safety of Medicines, the Veterinary Products Committee, the British Pharmacopoeia Commission, the Committee on Review of Medicines, the Committee on Radiation from Radioactive Medicinal Products*, HMSO.

[17] 1987. Study of the Control of Medicines. Report by Dr N.J.B. Evans CB and P.W. Cunliffe CBE. Department of Health and Social Security.

The major problem identified by Evans and Cunliffe was that there had been approximately a 5 per cent increase in licensing work each year between 1976 and 1987. During this time there had been no increase in the nearly 300 staff within the Medicines Division – the Conservative government under Margaret Thatcher had imposed a reduction of 20 per cent in the Civil Service generally during the 1980s. Salaries in the Medicines Division had become uncompetitive making it difficult to recruit senior experienced professionals. However the industry trade association, the Association of the British Pharmaceutical Industry, had told the enquiry team that it was prepared to pay higher fees if it led to the appointment of more senior staff. In 1987 the cost of the Medicines Division was £8.875 million, but the income from fees was only £5.728 million, giving a shortfall of £3.466 million. The report recommended that the Medicines Division be reorganised into functional teams – called 'businesses', each with a team leader responsible for the quality and quantity of its work. It recommended that the post of the new director be advertised.

As part of their investigation Evans and Cunliffe interviewed Professor Stenlake as chairman of the BP Commission, Dr Brian Wills, the chief pharmacist in the Department of Health, Mr Johnson the BP secretary and scientific director and also Dr Alan Rogers of the BP staff. In 1987 the BP's costs totalled £964,000 but the income from sales of the book and the British Pharmacopoeia Chemical Reference Substances was only £438,000. There was a shortfall of £526,000. Their recommendations showed little understanding of the unique role of the *Pharmacopoeia*. Their first recommendation stated that 'Despite its distinguished history, we felt that the BP is in some respects an anachronism. Sooner or later it is due to be replaced by the *European Pharmacopoeia*'. This completely ignored the role of the BP in setting standards for specific dosage forms, which the *European Pharmacopoeia* did not and still does not currently do, with only a few exceptions such as for some biological products. Their second recommendation was that the BP 'does not greatly benefit from its apparent closeness to the licensing operation' and that 'the DHSS should consider transferring the responsibility for the BP to the Pharmaceutical Society of Great Britain'. It was certainly true that the BP did not have ready access to commercially confidential licensing information, but the conclusion ignored the constant use made by the pharmaceutical industry and the pharmaceutical assessors in the Medicines Division of the official BP standards – facilitating and speeding up the assessment process. It was also unclear why the Pharmaceutical Society would be interested in taking over a loss-making part of the Medicines Division, and when they were contacted they were unsurprisingly not in favour of doing so. This part of the Evans Cunliffe report was not accepted or implemented, but its flawed analysis and the lack of any useful suggestions for improving its finances was to cast a cloud over the BP for the next few years. In the interim period before the decision was made

about the future of the BP Commission, discussions were held with HMSO alerting it to the fact that it might not be the publisher for future editions of the book if the Pharmaceutical Society took it over. Arrangements were made for to have preliminary discussions with the Pharmaceutical Society, which owns the Pharmaceutical Press. At the regular meeting between the BP Commission and HMSO on 7 December 1988 they were told that publication would remain with HMSO for the immediate future.[18] At the meeting on 15 February 1990 HMSO was advised that the BP Commission would remain part of the new Medicines Control Agency (MCA).[19] The funding of the BP would still be via the Exchequer, whereas the rest of the work of the MCA would be funded from fees paid by the pharmaceutical industry. At this same meeting HMSO gave a demonstration of equipment for producing CD-ROMs. The first CD-ROM was made available in 1993 and then updated at regular intervals.

In January 1990 Professor David Ganderton took over from Professor Stenlake as chairman of the BP Commission. Ganderton was the Professor of Pharmaceutics in the University of London. He expressed his 'pride and delight in his appointment to the chair' but felt that 'it was important that the Commission should examine its role, in particular in relation to other national and European regulatory authorities'.

The reorganisation of the Medicines Division was implemented. In April 1989 a new chief executive, Dr Keith Jones, was recruited from the US pharmaceutical company Merck and Co to head the new Agency. He had been the executive director, Medical Affairs, at Merck. The MCA was an executive agency, also known as a 'Next-Steps' agency, which is a part of a government department that is treated as managerially and budgetarily separate in order to carry out its executive functions. The MCA was organised into businesses – New Drugs Licensing, Abridged Licensing, Pharmacovigilance, Inspection and Enforcement, and the Pharmacopoeia. Mr C.A. Johnson had retired in January 1988, and very sadly died on 2 May after only three months of retirement. Dr Alan Rogers had taken over as secretary and scientific director in February 1988. Rogers had first been involved with the BP in 1963 as a member of one of the synthetic drugs committees. He had been a member of the BP Commission from 1978 to 1983 and had joined the staff of the BP in 1984 when the School of Pharmacy at Heriot-Watt University in Edinburgh, where he had worked, was closing.

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[18] 1986. The National Archive of the UK STAT 14/5490/ British Pharmacopoeia Commission: HMSO Steering Group Meetings 1986–1989.

[19] 1990. The National Archive of the UK STAT14/5680. HMSO Publications Steering Group Meetings 1989–1991.

Figure 4.1 Dr Alan Rogers, Secretary and Scientific Director to the British Pharmacopoeia Commission, 1988–1991
Source: Pharmaceutical Journal.

At the March 1990 meeting of the Commission Rogers reported that the staff, offices and laboratory would comprise the *Pharmacopoeia* business and that he was the new head of the *Pharmacopoeia* business. However further ways of recouping costs were under investigation. The fact that this was only a temporary reprieve was emphasised in the MCA Annual Report for 1990/1991 which noted that 'a comprehensive review was started into the purpose and functions of the Pharmacopoeia and its place in the overall arrangements for ensuring the quality of medicines'.

At the Commission meeting of 9 July 1990 the chairman of the BP Commission, Professor Ganderton, and Rogers reported on a meeting they had held with Dr Jones. They had emphasised the role of the *Pharmacopoeia* in the control and quality of medicines in the United Kingdom, and the need to maintain an effective input into the work of the *European Pharmacopoeia*. Dr Jones had expressed his appreciation of the role and standing of the BP, but had urged it to become financially self-sufficient like other businesses within the Agency. The Commission supported the effort to explore means of increasing

the BP's revenues. However whilst the rest of the Agency was able to increase fees to meet the shortfall, this option was not open to the BP.

In August 1990 a meeting was held between Rogers, Professor Ganderton, Dr Derek Calam and representatives of the Association of the British Pharmaceutical Industry to discuss the future contribution of the BP to the maintenance and enhancement of quality standards in the UK and abroad. It was agreed that the long-term aim was to strengthen the *European Pharmacopoeia* with the ultimate aim of global harmonisation. A robust and responsive BP could transfer standards to the *European Pharmacopoeia*. It had been suggested that the Commission should introduce more monographs for products at an early stage before the end of patent protection. The Commission felt that a paper should be produced explaining the *raison d'être* of the BP in both the national and European context, and Rogers agreed to draft this. In December 1990 the Commission received a draft of this document and discussed it in detail. It was revised and further discussed at the Commission meeting in March 1991. In May 1991 it was agreed to circulate the draft to the industry for comment. In July 1991 Rogers reported that over 300 copies of the final paper entitled *The British Pharmacopoeia into the 1990s* had been sent out to the industry and other organisations around the world. By October 1991 over 700 copies had been distributed. This policy statement emphasised that 'a strong national competence needed to be maintained in both Secretariat and Laboratory so that influential contributions can continue to be made at all levels in the European Pharmacopoeia Commission's work'. It also stressed that the range of the *European Pharmacopoeia* was limited and 'the British Pharmacopoeia Commission must continue to elaborate monographs in those areas that are not covered in the European Pharmacopoeia'. The statement went on 'The Commission believes in the fundamental importance of providing published standards for medicines as well as for individual ingredients, whether active or auxiliary'. A copy of the document was sent to Mrs Virginia Bottomley, the minister of state for health, who had expressed an interest in the review.

At the December 1990 BP Commission meeting the finances were reviewed. The USP was the only self-financing pharmacopoeia and a substantial part of its revenues were from the sales of reference substances. This contrasted with the BP policy which was to minimise reliance on the use of reference standards in its monographs. Also the kind of analytical development work carried out by the BP Laboratory was not followed by USP; instead it relied on public criticism of proposed methods through its publication *Pharmacopeial Forum* and from the FDA's Laboratories.

At the Commission meeting in July 1991 the Commission was advised by Rogers that the majority of monographs selected from the *British Pharmaceutical Codex* 1973 for inclusion in the BP had been revised and would be included in the 1992 *Addendum*.

In September 1991 the BP Commission was advised that the future management of the *Pharmacopoeia* business was to be split by transfer of the secretariat to the New Drugs and European Licensing Business and the Commission's laboratory staff to the Inspection and Enforcement Business. The laboratory was to be the nucleus of an MCA Laboratory. At its October meeting the Commission discussed this change. It felt that the split between the secretariat and the laboratory was not in the interest of the efficiency of the pharmacopoeial work. They questioned whether the change would impact on the strength of input into the *European Pharmacopoeia*. Rogers felt that these changes were unacceptable. He had intended to stay in his job after formal retirement but his contract was not extended. The minutes of the October BP Commission meeting record the chairman, Professor Ganderton, as saying that 'throughout his appointment Dr Rogers had pursued relentlessly his conviction of the need for publicly available standards in order to assure the quality of medicinal products throughout their shelf-life. His intellectual ability, quiet authority and sound judgement had earned him wide respect in the field of pharmacopoeial matters within the United Kingdom, Europe and overseas'. Rogers did not retire from pharmacopoeial work, he continued in his role as first vice-chairman of the European Pharmacopoeia Commission. He was elected as its chairman in 1992. However he was only able to serve part of his three-year term of office due to a brain tumour; Professor Dietrich Schnädelbach from Germany took over his role in 1994. Rogers died in December 1995.

Changes were perhaps inevitable, as although the BP Commission was slowly and meticulously reviewing its future role, little progress had been made during the previous year in balancing its books. A new broom was needed to challenge the organisation and procedures employed hitherto. Dr Robin Hutton was appointed in 1991 as the new secretary and scientific director as part of the New Drugs Licensing Business headed by Dr David Jefferys. Hutton was a chemist, the first non-pharmacist appointed as secretary and scientific director. He had worked in the pharmaceutical industry in a number of senior positions for Beecham Pharmaceuticals, Cyanamid of Great Britain and then as technical director/deputy managing director for Edwin Cooper Ltd. He then became a Superintendent Medicines Inspector in the MCA, where he had been responsible for the UK Medicines Testing Scheme, the Defective Medicines Reporting Centre, and for Good Manufacturing Practice inspection of overseas pharmaceutical manufacturing sites and contract laboratories. In a personal communication for this book, Hutton records that the decision to have separate managerial responsibility for the laboratory and the secretariat was to create practical problems for a decade until they were recombined in 2002. He goes on:

Figure 4.2 Dr Robin Hutton, Secretary and Scientific Director to the British Pharmacopoeia Commission, 1991–2001

Source: Photograph supplied by Dr Hutton.

> Further problems were also created by the decision to place the BP operation under the MHRA for management purposes but leave the responsibility for its funding with the Department of Health. On many occasions critical support operations such as IT support were denied by the MCA on the grounds that it could not be readily funded by the MCA and no mechanism existed for funds to be made available from the Department of Health.[20]

Hutton was instructed by the MCA chief executive to 'sort things out and initiate a plan to bring the operation to self-sufficiency within three months'. Hanging over his head, like the proverbial sword of Damocles, was the threat to close down the BP if he did not succeed, despite the legal requirement in the Medicines Act to publish the book. With the help of Professor Ganderton as the chairman of the Commission a start was made on making the necessary changes. Hutton was introduced at the December 1991 meeting of the Commission and explained his management objectives.

[20] 2013. Personal communication from Dr R. Hutton.

A meeting was held in December between Professor Ganderton, Dr Hutton, Dr Jefferys and Dr Jones as chief executive. Further meetings were held with members of the MCA management and an *ad hoc* meeting of several members of the BP Commission was held. A paper was tabled at the 9 March 1992 Commission meeting entitled *Objectives, Strategy and Resource Requirements for the European and British Pharmacopoeias*. Hutton struggled to introduce the necessary changes, he recounts that 'some senior members of the BP Secretariat were unable to accept the seriousness of the situation and resisted any idea of change'.[21] However he had been able to enlist the support of senior members of the BP Commission. He states that 'I was fortunate to have David Ganderton as my Chairman and Paul Turner as my Vice Chairman; also Derek Calam as a senior member of the BP Commission. They were realists who could accept the reality of the situation and adopt a combined and flexible approach to the problems that the BP operation now had to face and resolve'.[22] At Hutton's first Commission meeting a start was made on developing the plan. One key element was to try to develop monographs earlier. Drug substance monographs were developed by the *European Pharmacopoeia* and these needed to be developed sooner so that the drug product monographs could be included in the BP. One idea discussed was assignment of development of individual drug substance monographs to national pharmacopoeias to expedite the process. Another idea was for the BP laboratory to do less checking of manufacturers test methods, which would increase the output of monographs.

The March meeting of the BP Commission discussed the plan. Part of it involved making the BP more relevant to the needs of the MCA's Licensing Business by making monographs available to the licence application assessors at the time they were most needed – prior to patent expiry and prior to the first applications for the generic equivalents. Hutton argued that a new approach was needed to monograph selection and generation, using prescription volumes and patent expiry data to select the most suitable candidates. The importance of the UK contribution to the *European Pharmacopoeia* was recognised and it was important that drug substance monographs were developed at an earlier stage.

Hutton's plan was to increase the value of the BP publication to its users thereby increasing its potential sales. He had also to bring it into self-sufficiency. He carried out a review of the way that the work of the secretariat and the laboratory at Canons Park was carried out to see how efficiencies might be made. He visited the offices and laboratories of the USP in Rockville, Maryland to study the way that they produced monographs to see what lessons could be drawn from their experience. He found that the BP laboratory spent a major proportion of its time checking the analytical test methods submitted by manufacturers to

[21] 2013. Personal communication from Dr R. Hutton.

[22] 2013. Personal communication from Dr R. Hutton.

make sure that they were robust – so that the methods could be readily carried out by other laboratories which would need to use the monographs. The USP on the other hand largely accepted analytical methods submitted to it, and for the most part published these unchanged. The USP relied on feedback from other users to identify the occasional method which might need improvement. After consultation with a number of leading pharmaceutical companies to assess the level of validation of analytical methods that they would provide, an approach similar to that employed by USP was adopted. This significantly increased the number of new monographs that could be published.

Hutton also reviewed the work of the secretariat. The BP included the text of the monographs and test methods included in the *European Pharmacopoeia*. These were however edited into the particular style of the BP. In a time of austerity this was a luxury that could no longer be supported and it was decided that all the European monographs would be published largely unchanged apart from the addition of the clinical action and use statements. He also reviewed the scope of the book. Could its scope be amended to include material that might make new editions more saleable? One innovation he made was the introduction of the supplementary information chapters in the book which provided further explanation on how new monographs were introduced and other aspects.

Both of these changes increased the productivity of the staff and enabled an increase in the number of monographs in each new edition. However they did not address the fundamental financial problems. Part of the problem of funding the BP lay in its pattern of sales and the subsequent cash-flow. The sales of a new edition of the book were mainly in the first one or two years, and subsequent *Addenda* had much lower sales and thus produced much lower revenues from royalties. This can be seen from the sales of the 1980 BP and its various *Addenda* and the volumes of infrared spectra – taken from the minutes of the BP Commission/HMSO Steering Group meeting of 11 November 1987:[23]

British Pharmacopoeia 1980	24,270 copies
Addendum 1982	10,474 copies
Addendum 1983	11,003 copies
Addendum 1986	7,642 copies
Infrared Spectra Main Volume	2,233 copies
Infrared Spectra First Supplement	1,598 copies
Infrared Spectra Second Supplement	1,673 copies
Infrared Spectra Third Supplement	1,330 copies
Approved Names book	1,658 copies

[23] 1986. The National Archive of the UK STAT 14/5490/ British Pharmacopoeia Commission: HMSO Steering Group Meetings 1986–1989.

A further problem was that the UK pharmaceutical industry had undergone a series of mergers and acquisitions which created larger companies. Whereas each separate quality control and research and development departments would have previously purchased their own separate copies of the BP, the merged organisations needed a significantly lower number of copies.

The pattern of sales of the new editions – published at five-yearly intervals, and the much lower sales of the *Addenda* meant that many users were inevitably using outdated monographs and test methods. There was thus both a technical and financial case for discontinuing the annual *Addenda* in favour of an increased frequency of publication of a new edition. The move was therefore eventually made to publish the BP annually, together with the *British Pharmacopoeia (Veterinary)* and also a CD-ROM version. At the same time the price was increased substantially. The first of the annual editions was the 1998 BP. The first CD-ROM was introduced in 1993.

These changes were being made against a background of a Civil Service freeze on recruitment of staff during the early 1990s under the Conservative government of John Major. Although the number of professional staff in the Licensing Secretariat of the MCA was increasing to meet the industry's need for faster processing times for approval of new products, the BP Commission, funded by the Department of Health, was subjected to a freeze on staff recruitment and not allowed to replace anyone who left. Hutton was effectively managing to do more with much less. In 1993 there was a total of 42 staff in the BP Commission comprising 10 in the secretariat, 15 administrative staff and 17 in the BP laboratory. By 2002 this had been reduced to five in the secretariat, nine in the laboratory and five administrative staff – a total of 19. This was under half of the staff complement of 10 years earlier.

One criticism made in the 1987 Evans Cunliffe report related to the lack of benefit that the BP obtained from its apparent closeness to the licensing operation. Another innovation introduced by Hutton was to reverse the previous prohibition of Licensing Secretariat staff from being involved in the meetings of the BP Commission and its various committees. Individual members of the Licensing Secretariat were appointed to each of the technical committees to strengthen the technical input and also to ensure that the monographs, general methods and so on also reflected much more closely the regulatory needs of the pharmaceutical reviewers within the MCA.

The Cunningham Report on a Consultation on the Future of the BP and BP Veterinary

Despite Hutton's success in balancing the BP Commission's books, questions continued to be raised about the role and function of the BP. The increasing

role of the *European Pharmacopoeia* and the fact that some other national pharmacopoeias in Europe had ceased publication made the future of the BP uncertain. The BP was financed by the Department of Health but managed by the MCA. Hutton felt that he was constantly justifying the continued existence of the BP to senior department officials who lacked any real understanding of the importance of its role. In 1999, Roy Cunningham, a senior civil servant, was asked by the Department of Health to conduct a consultation into the future of the then two volumes of the BP and the companion volume the BP Veterinary. The consultation letter was circulated to the pharmaceutical industry, medical and pharmaceutical professional organisations, NHS bodies and a wide range of overseas countries. The consultation particularly concerned volume II of the BP which provided detailed requirements for finished dosage forms. Cunningham reported in September 1999 in a document entitled *Consultation on the Future of the Two Volumes of the British Pharmacopoeia and the Companion Veterinary Volume*. In the section entitled 'Background' he found that the standards in volume II were particularly important in the UK because of its large generic medicines market – roughly 20 per cent by value, 80 per cent by volume. This reflected the predominance of the NHS as a purchaser of medicines.

The results of the consultation in the Cunningham report were broadly in favour with 71 of the 99 substantive responses favouring continued publication of volume II. Seventeen were not in favour, and the remaining 11 did not offer a clear view. It was clear from the consultation that volume II was widely used abroad, especially in poorer, Commonwealth countries, developing countries generally, and in Eastern European countries. Nearly everyone felt that it set a 'gold standard' in terms of quality and scholarship. The Stationery Office (TSO) stated that more than half the sales were to overseas customers. Cunningham noted that the BP was a commercial proposition with costs for the secretariat and laboratory being recovered through the contract with TSO. He felt that the BP was an instrument of economic development and assistance to developing countries and Eastern Europe, for example by helping their regulatory authorities police markets in counterfeit drugs. He concluded that the outcome of the consultation was in favour of continued publication of volume II.

The MCA responded to the Cunningham review by recognising the support for the BP from the UK pharmaceutical industry, the expertise of the BP staff in ensuring a strong UK input into the *European Pharmacopoeia* and the support for generic prescribing. It acknowledged its important international presence with sales in 100 countries and provision of legally enforceable standards in 15 countries. On the basis of the review it was concluded that the BP publication would continue but that the Department of Health should no longer finance it. This was the first step towards it becoming a more formal part of the Medicines Control Agency.

Robin Hutton retired from the BP Commission in December 2001, but went on to set up his own GMP and quality systems consultancy. The Civil Service freeze on recruitment to BP Commission Secretariat had reduced costs. Many of the senior staff had left, thus leaving his successor with problems in resourcing the work of the committees and publishing the BP. Hutton summed up his time at the BP Commission in the words of the opening paragraph of *A Tale of Two Cities*, the historical novel by Charles Dickens published in 1859 about the years leading up to the French Revolution: 'It was the best of times, it was the worst of times.' However during his tenure as secretary and scientific director the organisation continued its successful programme of publications as we can see from the following.

British Pharmacopoeia 1988 and *Addenda*

The BP 1988 contained 2,100 monographs for drug substances, excipients and medicinal products. 495 of these are edited versions of monographs for drug substances and excipients included in the *European Pharmacopoeia*. Volume I was for medicinal substances, volume II for medicinal preparations and the appendices. This edition contained 16 new monographs for active substances and 34 new monographs for preparations. The new drugs included the beta blocker Atenolol, the hypnotic Temazepam, the antispasmodic Mebeverine and the antihypotensive Prazosin, together with their preparations. Changes had been made to the formulated preparations such as the mixtures, linctuses and syrups. In the past these had been designed for the pharmacist to make up and dispense for individual customers when he or she received a prescription. Many of these preparations were now being made by large scale production and thus needed to be stable over the longer term. The new flexible formulations allowed the manufacturer to develop more stable and possibly even more palatable products.

The 1990 *Addendum* introduced new monographs for the cytotoxic drug Cisplatin, the antibacterials Clindamycin Phosphate and Erythromycin Lactobionate, the calcium channel antihypertensive drug Nifedipine, Hypromellose eye-drops for dry eye and absorbent cotton.

The 1991 *Addendum* introduced the histamine H_1 receptor antagonist Brompheniramine Maleate for treatment of allergy, Chlortetracycline ointment, Ephedrine nasal drops, standardised senna granules and a triple vaccine against measles, mumps and rubella. The issue of the teratogenic impurity in Hexachlorophane had been mentioned before. This *Addendum* introduced a test for 2,3,7,8-tetrachloro-*p*-dioxin using Gas Chromatography in combination with Mass Spectrometry – the first time this combination technique had been

used. The limit for the impurity was not more than 0.010 parts per million. This was the most stringent impurity limit in the Pharmacopoeia.

The 1992 *Addendum* included the antiviral drug Acyclovir, the anti-emetic Buclizine Hydrochloride, the hypnotic Loprazolam, the beta-blocker Metoprolol and the excipient Stearic Acid. A monograph for Salbutamol Pressurised Inhaler for treatment of asthma was introduced. It also included dissolution tests for Cortisone Tablets, Griseofulvin Tablets and Spironolactone Tablets.

British Pharmacopoeia 1993 and *Addenda*

The BP 1993 became effective on 1 December 1993. It contained 2,040 monographs for drug substance, excipients and medicinal preparations. Volume I contained the monographs for the drug substances and excipients, volume II the monographs for dosage forms and the appendices. New monographs included the diuretic Bumetanide, the histamine H_2-receptor antagonist Cimetidine for gastric and duodenal ulcers, the antipsychotic Thioridazine, injections of the antibiotics Amoxicillin and Clindamycin and enteric coated tablets of the anticonvulsant drug Sodium Valproate for treating epilepsy. There had been detailed discussion in the European Committee for Proprietary Medicinal Products Quality Working Party and in the International Conference on Harmonisation on impurities in drug substances. The pharmacopoeias were being asked to provide more information on the identity of impurities controlled in their monographs – this would increase what is called the 'transparency' of the monographs. The BP Commission announced its intention to extend information on impurities in the BP.

The 1996 *Addenda* was published in 1995 and the 1997 *Addendum* in 1996. The 1996 Addendum had 121 new monographs including Azlocillin Sodium, the analgesic Nabumetone, the hypoglycaemic Gliclazide and the hypolipidaemic Gemfribrozil. European monographs added included Cefotaxime sodium, the antifungal Isoconazole, the antiviral Zidovudine, and a recombinant DNA vaccine for hepatitis B. One innovation was the introduction of infrared Fourier Transform spectra for certain substances. In future this instrument would be used for all new reference spectra.

The 1997 *Addendum* was published in December 1996 and was effective from June 1997. It had 100 new monographs including the anticholinergic Flavoxate, the anti-inflammatory Flurbipofen Sodium, the antivirals Foscarnet Sodium and Tribavirin and the beta-blocker Carteolol Hydrochloride. A CD-ROM was issued in November 1995.

British Pharmacopoeia 1998

This was published in 1998 and was effective from 1 December 1998. It was the sixteenth full edition of the book and the first of the new annual editions. It was part of a package consisting of the two volumes of the BP, one of the BP Veterinary and the CD-ROM of both publications. It included 94 new monographs for drug substances and excipients, 75 of which were from the *European Pharmacopoeia*. There were 42 new monographs for preparations. New monographs included Colestipol hydrochloride for hyperlipidaemia, benzydamine hydrochloride for painful inflammation of the pharynx, disodium pamidronate for the treatment of malignant hypercalcaemia and fluticasone propionate for asthma. New monographs from the European Pharmacopoeia included the fibrinolytic alteplase, the cytotoxic carmustine, the bronchodilator etamsylate and the antibacterial imipenem. In the entire new edition included 1,280 monographs from the *European Pharmacopoeia*. These are all reproduced in the text marked by the European star.

In 1998 Professor Ganderton's term of office as chairman of the BP Commission finished. He was replaced in 1998 by Professor Derek Calam.

Calam's connection with the BP dated from 1969 when he had been recruited by the National Institute for Medical Research to develop modern physico-chemical methods for analysis of biological products and had attended a meeting of the BP Hormones Committee. He had been the head of the Chemistry Division at the National Institute for Biological Standards and Control (NIBSC). NIBSC developed many analytical methods for biological products and he states that 'many of these have found their way into the BP and Ph Eur'.[24] Calam then became the European coordinator for NIBSC. In 1999 he was now also a visiting professor of the University of Strathclyde. He was the first chemist to be chairman of the BP Commission.

British Pharmacopoeia 1999

This was the second of the annual editions. It was published in April 1999. It contained 2,539 monographs and over 370 reference spectra. It was published in two volumes of the BP, one volume of the BP Veterinary and Version 3.0 of the CD-ROM of both publications. It contained 49 new monographs which were not published in previous editions. Twenty-five new BP Reference Materials were added to the collection, which then comprised 460. Sales of the reference materials remained high with 4,800 vials sold in the UK, 700 to EC countries and 2,800 elsewhere.

[24] 2014. Personal communication from Professor D. Calam.

British Pharmacopoeia 2000

The BP 2000 was published in 2000 and was effective from 1 December 2000. It contained 2,663 monographs for substances and articles used in medicine; 1,302 monographs were of national origin and 1,361 derived from the *European Pharmacopoeia*. It included 54 new monographs of national origin consisting of three substances and 51 preparations. Eighty-five new monographs derived from the 2000 supplement to the *European Pharmacopoeia*. Version 4.0 of the CD-ROM contained both the BP and BP Veterinary.

British Pharmacopoeia 2001

The fourth annual edition of the BP was published in May 2001 and was official from 1 December 2001. It contained 2,760 monographs for substances and articles used in medicine and over 390 reference spectra. It contained 43 new monographs of national origin. The package of two volumes of the BP and the BP Veterinary included version 5.0 of the CD-ROM. During the year 30 new Reference Materials were added and the collection now comprised 484.

Dr Michael Gerard 'Ged' Lee replaced Robin Hutton as secretary and scientific director on 1 January 2002. He was a pharmacist, having graduated in 1971 from the School of Pharmacy at the University of London. He received his PhD in 1975 for a thesis on metabolism of allobarbitone and mepyramine. From 1977 he had a series of jobs in NHS hospital quality assurance departments, finally becoming director of quality control at the Liverpool Pharmacy Practice Unit. He joined the Medicines Control Agency in 1999 as group manager, Laboratories and Licensing, and then became secretary and scientific director of the BP Commission in 2002. In 2004 he became group manager, Laboratories and Pharmacopoeia. He retired from the MHRA in January 2012.

Between 2002 and 2003 Lee was responsible for developing a business model for the BP as part of the MCA. Licensing was able to charge fees for its work on review and approval of marketing applications, the BP needed a different financial model. Lee developed a case balancing the revenues from sales of the BP and the reference substances against the running costs of the BP operation. Lee says that 'As a result of the uncertainty of the future of the BP in the 1990s staff numbers in both the Secretariat and the Laboratory has been allowed to decline and so the business case was an opportunity to establish these. The business planning process also allowed for future growth of the BP operation provided the income generated covered the additional costs. It was therefore a mechanism for future growth'.[25] This business case was agreed by

[25] 2014. Personal communication from Dr G.D. Lee.

Figure 4.3 Dr Michael Gerard Lee, Secretary and Scientific Director to the British Pharmacopoeia Commission, 2001–2011

Source: Photograph supplied by Dr Lee.

the MCA Board in 2002. In April 2003 the MCA merged with the Medical Devices Agency to form the Medicines and Healthcare products Regulatory Agency (MHRA). The BP was then incorporated into the MHRA trading fund. By the time Lee retired in January 2012 the BP was continuing to show a healthy balance between revenues and expenditures. The income in 2011/2012 was £2,651,000 and there was a surplus of £191,000.[26]

Lee comments that:

> Once the future of the BP had been resolved it was clear that the uncertainty and lack of development in the 1990s had created an impression amongst users and stakeholders that the role of the BP, both nationally and internationally had been reduced. It was important to re-establish the reputation and importance of the publication, particularly internationally in view of the globalisation of the pharmaceutical industry in the new millennium. India and China were leading

[26] 2012. *Medicines and Healthcare Products Regulatory Agency. Annual Report and Accounts 2011/2012.*

> players in this globalisation and so were the focus of the promotion of the publication. The BP also needed to emphasise its importance in its more traditional markets in the UK, Europe, and the Commonwealth. New monographs that promoted the development of generic medicines were important in this respect.[27]

During the next decade the role of the BP was extended by approximately 40 new monographs in the publications each year, the addition of monographs for unlicensed products, for traditional herbal medicines and for homeopathic stocks and mother tinctures.

Unlicensed medicines have always been part of clinical practice. The 1968 Medicines Act recognised that physicians should be allowed to prescribe unlicensed medicines for individual patients. This allowed them for example to prescribe for rare diseases, or as a special paediatric formulation where only a product intended for use in adults existed. This exemption from licensing was also included in the European directives. Many of these products were manufactured as 'specials' by particular UK manufacturers. However there were no published quality standards for such preparations. The BP Commission approved the role of the BP in creating quality standards for them and work started in 2006. Lee comments: 'The initiative was supported by the NHS hospital service and by pharmaceutical companies licensed to manufacture unlicensed medicines.'[28] A new general monograph on unlicensed medicines of UK origin was published in the BP 2008 together with nine individual unlicensed medicines. The general monograph included mandatory labelling requirements. Individual monographs have been published in subsequent editions of the BP.

As we have seen in Chapter 3, one of the major criticisms made of the contents of the BP prior to its 1932 edition was that there was a very poor choice of drug substances and formulated preparations, and that the ones chosen did not reflect current best medical practice. The early BP Commissions took this criticism to heart. The first BP Commission included both a Clinical Sub-Committee and a Pharmacology Sub-Committee. The early chairmen of the BP Commission were all medically qualified. The subsequent BP Commission committees usually included a Medicines and Doses Committee which could advise on what drug substances and preparations should be included. Hutton as secretary and scientific director had started to use the information from the Department of Health's computerised prescribing statistics on the most commonly prescribed products. This process continued and still forms a key part of the basis for the choice of drug substances and products to be included. In September 2004 the BP Commission was advised that the secretariat had examined the list of the top 1,000 most widely prescribed items in 2003 to identify preparations for which

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[27] 2014. Personal communication from Dr G.D. Lee.

[28] 2014. Personal communication from Dr G.D. Lee.

a monograph did not exist. A policy decision was made at this BP Commission meeting to identify the top 500 most widely prescribed items and any not subject to a monograph should be added to the work programme. In addition in 2006 a number of widely used over-the-counter products had been identified, which were available without prescription. In December 2006 the BP Commission agreed to include these in the work programme. The BP Commission Secretariat also consults its medical colleagues in the MHRA on products which have been withdrawn, or their authorisations revoked, so that the monographs for them can be removed from the next edition, although because of the legal rules under which the *Pharmacopoeia* operated these omitted monographs continued, and still continue, to be the latest official specifications.

In 2003 the BP Commission Secretariat started to collect information on a number of substances used in traditional Chinese medicine and in Ayurvedic medicine for which there were no European standards. Ayurvedic medicine originated in the Indian subcontinent and is a form of complementary and alternative medicine. Both types of medicine have become increasingly popular in the West as alternative medicines.

In 2003 the BP Commission agreed to start to produce monographs for herbal materials to support the proposed European Directive on Traditional Herbal Medicines. On 31 March 2004 Directive 2004/24/EC on traditional herbal medicinal products was adopted and it came into force on 30 April 2004. This directive set up a simplified registration procedure for traditional herbal medicines where there is a long tradition of use to show their safety and efficacy. However the directive still required the products to comply with requirements on quality. The preamble to the directive states that 'Products should comply with quality standards in relevant *European Pharmacopoeia* monographs or those in the pharmacopoeia of a Member State'. In 2004 the BP Commission set up a special advisory committee on Herbal and Complementary Medicines. Monographs for herbal materials were published from 2005 onwards. In 2006 the BP Commission Secretariat developed links with the Chinese State Food and Drugs Authority (SFDA), the Chinese Pharmacopoeia authorities, the Hong Kong regulatory authority and the Singapore Health Sciences Authority (HSA). These were to help with the development of monographs for Traditional Herbal Medicines. In 2007 a formal Memorandum of Understanding was agreed between the MHRA and the SFDA. Links were also developed in 2007 with the Drug Controller of India and the Indian Pharmacopoeia. In 2008 a Memorandum of Understanding was agreed between MHRA and the HSA. In October 2010 a formal agreement was signed to collaborate with the Chinese Pharmacopoeia to develop standards for traditional Chinese medicines.

Also in 2008 the WHO's *International Pharmacopoeia* expressed a wish to set up a formal collaboration agreement with the BP for joint production of monographs. An outline agreement was set up and a pilot study started work

on three monographs. This collaboration continued in 2009. In 2011 a formal Memorandum of Understanding was signed with the WHO to collaborate on the development of monographs for widely used formulated preparations.

Collaboration between the WHO's *International Pharmacopoeia* and the BP developed during this period with progress in 2010 towards signing a formal agreement on elaboration of monographs. During 2010 the BP staff provided feedback on draft monographs. In 2010 an agreement was made with the *Pharmacopée Française* to supply reference substances for monographs in that book.

The work of creating monographs for homeopathic stocks and mother tinctures from those in the *British Homeopathic Pharmacopoeia* was started in June 2006. Professor Woolfson as the chairman of the BP Commission states that:

> It is fair to say that many members of the BPC were not comfortable, from a scientific viewpoint, with the entire concept of homeopathy, but it was felt that people used these products and that, in their concentrated form (where they were handled by technicians and others) there should be a means of providing effective quality assurance in a safety context.[29]

The BP laboratory was on a government buildings site at Canons Park in Stanmore. In 2005 the site was being closed. The laboratory was thus required to move to the site of the Laboratory of the Government Chemist (LGC) in Teddington, London. The LGC was founded in 1842 to regulate the adulteration of tobacco. In 1875 it was appointed as a referee analyst under the 1875 Sale of Food and Drugs Act. It continues to provide expert opinion as the official Government Chemist. In 1996 it was privatised and is now owned by the management, staff and the investment group Bridgepoint. The MHRA's own laboratory which supported the work of the Medicines Inspectorate was also moved to the LGC site.

In 2006 two lay members of the BP Commission were appointed as part of a wider government initiative to add lay members to official committees. Professor David Woolfson, the chairman of the BP Commission, was involved in the formal recruitment and interview process. Most of the applicants were from various NHS trusts. He felt that 'lay members were able to assimilate the general tenor of BPC debates and make a useful contribution'.[30]

In 2010 the staff of the MHRA moved from its offices at Market Towers in Nine Elms Lane in Vauxhall to new offices in Buckingham Palace Road. The staff missed the panoramic views of the Thames and the closeness to the Oval cricket

[29] 2014. Personal communication from Professor D. Woolfson.

[30] 2014. Personal communication from Professor D. Woolfson.

ground. The new offices are open-plan and staff are not allocated a specific desk, they have to find the nearest available one to use – known as 'hot desking'. The BP Commission staff had to adapt as much as possible to paperless working.

Some highlights of editions of the BP produced under Ged Lee's direction follow.

British Pharmacopoeia 2002

This fifth annual edition of the BP was published in September 2002 as two volumes together with the single volume BP Veterinary and the CD-ROM. This edition was produced using ActiveText innovative software. It contained almost 2900 monographs and over 400 reference spectra. It was effective from 1 December 2002. Seven new BP reference substances were added to the collection during the year. The collection comprised 490 materials. In this edition some of the monographs were dual-labelled with both the recommended International Nonproprietary Name (rINN) and the British Approved Name (BAN), as part of a transition to use only the INN.

British Pharmacopoeia 2003

The sixth annual edition was published in September 2003 in a package now consisting of four volumes of the BP rather than the earlier two-volume edition, one volume of the BP Veterinary, version 7.0 of the CD-ROM of both publications, and the British Approved Names. It contained almost 3,000 monographs for substances and articles used in medicine, about 400 reference spectra and the appendices and supporting material. Volumes I and II of the BP contained the monographs on medicinal and pharmaceutical substances – the drug substances and excipients. Volume III contained the monographs on formulated preparations, blood products, radiopharmaceuticals, blood products and surgical materials. Volume IV contained the infrared reference spectra, the appendices and the supplementary chapters. It was effective from 1 December 2003. In this edition the monographs only used the INNs except for the names Adrenaline and Noradrenaline which were retained on the recommendation of the Medicines Commission for the convenience of the user from the BP 2003 to BP 2008. The Department of Health engaged in a widespread communication exercise to healthcare professionals on the changes of names for some familiar drugs.

British Pharmacopoeia 2004

The seventh annual edition was published in six volumes including the BP Veterinary and the CD-ROM. It was effective from 1 December 2004. It contained nearly 3,000 monographs including all of those in supplements 4.1 to 4.8 of the *European Pharmacopoeia*. There were five new monographs of national origin. During 2004 the BP committees and consultative groups were restructured to add two new advisory committees on Excipients and Herbal and Complementary Medicines. This latter committee took over the role of the previous Crude Drugs and Galenicals committee and advises the BP Commission on monographs for herbal materials in support of the proposed European Directive on Traditional Herbal Medicinal Products.

British Pharmacopoeia 2005

This was the eighth annual edition again published in six volumes including the BP Veterinary and Version 10.0 of the CD-ROM of both publications. It was effective from 1 December 2005. The BP contained over 3,000 monographs including supplements 5.1 and 5.2 and all the fifth edition of the *European Pharmacopoeia*. Ten new monographs were of national origin.

British Pharmacopoeia 2007

In January 2006 Professor David Woolfson took over from Calam as chairman of the BP Commission.

Woolfson graduated in pharmacy from Queen's University in Belfast, and is a registered pharmacist. He started at Queen's as a lecturer in pharmaceutical analysis, was then appointed Reader in Pharmaceutical Sciences in 1991. He was appointed to the Chair in Pharmaceutics in 1995. He is currently head of the School of Pharmacy at Queen's. He had been a member of the BP Commission since 1998.

The BP 2007 was published in August 2006 and came into effect on 1 January 2007, so there is no BP 2006. It was published as a package of the four volumes of the BP 2007, one volume of the BP Veterinary and version 11.0 of the CD-ROM of both publications. The BP contained over 3,100 monographs.

A performance-indicating requirement was added to two new monographs for formulated preparations – Alginate Raft-Forming Oral Suspension and Compound Alginate Oral Suspension. Woolfson recalls that:

> One example which caused controversy in the BPC was the development of a new monograph for raft-forming antacids, where a traditional quantitative assay was not possible or appropriate. A new *in vitro* test for raft strength was developed. This took some time as it had to be acceptable to the manufacturers of all such products, such that these products would pass the test. I believe it was the first such finished product monographs to be introduced into the BP.[31]

The BP's advisory committees were further restructured during 2006 and renamed as expert advisory groups and panels of experts. A comprehensive review of the membership of the advisory committees and panels was undertaken.

British Pharmacopoeia 2008

The BP 2008 was published in August 2007 and became effective from 1 January 2008. The package again consisted of four volumes of the BP 2008, one volume of the BP Veterinary and Version 12.0 of the CD-ROM of both publications. It contained over 3,000 monographs. It included all monographs in supplements 5.1 to 5.8 of the *European Pharmacopoeia*. For the first time the BP 2008 was also available as an e-book. The supplementary chapter on colour indicator changes was printed in colour. The text included seven monographs for herbal materials used in traditional Chinese medicines and five monographs for homeopathic stocks and mother tinctures.

British Pharmacopoeia 2009

The BP 2009 was published in August 2008 and became effective from 1 January 2009. It was part of a package consisting of the four volumes of the BP, one volume of the BP Veterinary, Version 13.0 of the CD-ROM and access to the new online version. The online version was part of the new BP website which was launched on 1 September 2008 and demonstrated at the British Pharmaceutical Conference. The website included a new section of Frequently Asked Questions (FAQs). The package contained about 3,200 monographs and 400 infrared spectra. The BP 2009 included 42 new monographs of national origin not included in previous editions.

[31] 2014. Personal communication from Professor D. Woolfson.

British Pharmacopoeia 2010

The BP 2010 was published in August 2009 and official from 1 January 2010. It was part of a package consisting of four volumes of the BP, one of the BP Veterinary, Version 14.0 of the CD-ROM and online versions of both books. An e-book was also available. It contained about 3,300 monographs and almost 400 infrared reference spectra. A new feature was introduced during the year to allow a maximum of three BP monographs to be supplied electronically, on payment of a fee, together with supporting information. The text included nine new monographs for unlicensed formulations, a new herbal material monograph and two monographs for homeopathic stocks and mother tinctures.

British Pharmacopoeia 2011

The BP 2011 was published in August 2010 and became effective from 1 January 2011. The package sold includes the now five volumes of the BP, one volume of the BP Veterinary and access to the CD-ROM and online versions. Due to the increase in the number of monographs for formulated preparations, volume III contained monographs for the general and specific monographs for formulated preparations, volume IV the monographs for specialist products such as Herbal Drugs, Blood Products, Immunological Products and Radiopharmaceuticals. Volume V contained the Infrared spectra, the Appendices and the Supplementary Chapters. It contained 52 new monographs of national origin, including 15 for unlicensed medicines, four for traditional herbal medicines, and two for homeopathic stocks and mother tinctures. In total it contained 3,400 monographs and almost 400 infrared spectra.

British Pharmacopoeia 2012

The BP 2012 was published in August 2011 and became effective on 1 January 2012. It was made available as a package of five volumes of the BP, one volume of the BP Veterinary, and access to the CD-ROM and online versions. It contained about 3,400 monographs and about 400 infrared reference spectra. It included all monographs in the seventh edition of the *European Pharmacopoeia* together with supplements 7.1 and 7.2. It contained 35 new monographs of national origin not previously published. These included nine monographs for unlicensed medicines.

In January 2012 Dr Lee retired from the MHRA, although he was then appointed to serve as a member of the current BP Commission. The new Secretary and Scientific Director is Dr Samantha Atkinson.

Figure 4.4 Dr Samantha Atkinson, Secretary and Scientific Director to the British Pharmacopoeia Commission, 2012–present
Source: Photograph supplied by Dr Atkinson.

Dr Atkinson graduated from Reading University in 2001 with a PhD in Analytical Chemistry, then worked at a number of Contract Research Organisations in a variety of roles of increasing seniority and responsibility. She joined the MHRA in 2006 as part of the Medicines Inspectorate. In 2012, she was appointed as the group manager for the British Pharmacopoeia (BP) and Laboratory Services Group. In this role, she is also the secretary and scientific director for the British Pharmacopoeia Commission and a member of the UK delegation of the European Pharmacopoeia Commission.

The balance sheet for the BP continues to be healthy – the income for 2012/2013 was £2,850,000 and there was a surplus of £188,000.[32]

At the September 2012 meeting of the BP Commission the resignation of Professor David Woolfson as Chairman of the BP Commission was announced. The Department of Health announced the appointment of Professor Kevin Taylor as the new chair of the BP Commission with effect from 1 October 2013.

[32] 2013. *Medicines and Healthcare Products Regulatory Agency. Annual Report and Accounts 2012/2013*.

Professor Taylor is the Professor of Clinical Pharmaceutics at University College of London School of Pharmacy. He was head of the Department of Pharmaceutics from 2006 to 2013. He is a pharmacist who gained his PhD from the Welsh School of Pharmacy in 1986. He joined the School of Pharmacy in London as a Teaching and Research Fellow in 1986 and was subsequently promoted to lecturer in 1988, senior lecturer in 1994, reader in 2002 and professor in 2004.

During the period 2012 to the present day, the extension of the programme of international collaboration initiated by Gerard Lee has continued. The BP Commission continues its programme of collaboration with the Chinese Pharmacopoeia on the development of monographs for traditional Chinese herbal medicines. In May 2013 a collaboration agreement with the State Pharmacopoeia of Ukraine has meant that reference to the BP monographs will be made in that pharmacopoeia. Collaboration with the WHO has continued under the collaboration agreement signed in October 2011 on monographs for formulated preparations to be included in the *International Pharmacopoeia*.

At the time of writing, two editions of the BP have been published under Samantha Atkinson's direction. Some details are given below.

British Pharmacopoeia 2013

The BP 2013 was published in August 2012 and became effective on 1 January 2013. It contained over 3,400 monographs for substances and preparations. It was available as a package of the five volumes of the BP, one volume of the BP Veterinary and access to the CD-ROM and online versions. It contained 41 new monographs of national origin of which nine were for unlicensed medicines and two for traditional herbal medicines.

British Pharmacopoeia 2014

The BP 2014 was published in August 2013 and became effective on 1 January 2014. As in previous years it consisted of a package of six volumes, five volumes of the BP 2014, one volume of the BP Veterinary 2014, access to the CD-ROM and online versions. It incorporated all of the monographs of the seventh edition of the *European Pharmacopoeia* and supplements 7.1 to 7.8. The BP 2014 contained nearly 3,500 monographs. It included 40 new monographs of national origin and 36 new monographs from the *European Pharmacopoeia*. Amongst the new monographs were three new monographs for herbals used in traditional medicine and homoeopathy, and three monographs for unlicensed formulations.

British Pharmacopoeia 2015

A special sesquicentenary edition of the BP 2015 will be produced in 2014 to mark the 150th anniversary of the first publication.

British Approved Names

As we saw in Chapter 3 Approved Names were given to drug substances and excipients by the BP Commission and they were then published as lists in the official publications the Belfast, Edinburgh and London *Gazettes*, and in the *British Medical Journal* for the benefit of prescribers. They were short distinctive names for substances for which the systematic chemical name or other scientific name is too complex for convenient use. These British Approved Names were used for the titles at the head of BP monographs. During World War II it was necessary for the BP Commission to devise Approved Names for drugs in proprietary drug substance products formerly imported into Britain by German companies, so that products containing these substances could be manufactured essentially as 'generics' in Britain. In 1940s a specific BP committee was set up to consider issues of nomenclature – Committee 11 Nomenclature under the chairmanship of Professor Gunn, who was also the chairman of the BP Commission. Successive BP Commissions since 1940s have always included a nomenclature committee. The latest is called the Expert Advisory Group on Nomenclature.

There are two guiding principles in devising or selecting British Approved Names (BANs). The first is that the name should be distinctive in sound and spelling, not inconveniently long and not liable to confusion with names in common use. The name should not conflict with trademarks. The second principle is that the name for a group of therapeutically or pharmacologically related substances should show a relationship, for example by using a common stem such as *-astine* for an antihistamine, *-bactam* for a beta-lactamase inhibitor, or *-dipine* for a calcium ion channel antagonist.

In 1968 Section 100 of the Medicines Act 1968 made it a legal requirement for the BP Commission to publish a list of suitable names which could be placed at the head of monographs of the BP. When the list has been prepared, on the recommendation of the Medicines Commission, ministers are required to publish this list.

The first edition of the book entitled *British Approved Names* was published in August 1970 by the British Pharmacopoeia Commission as a dictionary of drug names for regulatory use in the UK. The 1970 edition included all of the Approved Names issued since 1948 together with those issued earlier for substances that had not become the subject of monographs

in the BP. Supplements to the book were also published at regular intervals. Subsequent editions of the *British Approved Names* book were published at regular four-yearly intervals. More recently the *British Approved Names* book can be purchased as part of the annual package sold as the *British Pharmacopoeia* as well as being available separately. The latest text is the *British Approved Names 2012* and its two *Supplements*. This was issued as part of the BP 2014. *BAN 2012* provided the following information about each pharmaceutical substance that was included – the official nonproprietary name with a guide to its pronunciation, the systematic chemical name, the molecular formula, the molecular structure, the Chemical Abstracts Service registry number and the pharmacological action/medicinal use.

Chapter 6 of this book includes a section on the origins of the WHO International Nonproprietary Names (INNs). EC Directive 92/27/EEC mandated the use of the WHO recommended INNs throughout Europe. If there was no INN a national name could be used, and in the UK this would be the BAN. However there was conflict between many of the earlier British Approved Names and the corresponding INNs. Although these British Approved Names were technically not in conformity with the European directive, the situation was left for some years as it was felt that there would be a possibility of medication errors if there was a wholesale change in many of the existing names for drugs that were commonly prescribed. Where the INN was different to the BAN this was always identified in the BAN publication. However as products increasingly moved within the European Union, for example by parallel importation, there was also potential confusion because the name used on the imported product was different. A notice of the intention to change a number of the monograph titles to the corresponding INNs was published in the BP 2003. The MHRA published a list of the 99 old and new BANs in March 2004. Some of the name changes were small, for example Sulphacetamide to Sulfacetamide, others were more major such as Mustine to Chlormethine. Healthcare professionals – doctors, pharmacists, nurses, dentists and so on – were asked to use the new names by 30 June 2004. A large communications exercise was carried out to doctors, pharmacists and nurses with advertisements in the professional journals, posters in GP surgeries and hospitals and a patient information leaflet. Three of the BANs were retained on the advice of the Medicines Commission – Adrenaline, Noradrenaline and Lidocaine. This was because of the use of these substances in emergency medicine and the wide-spread familiarity with these particular names. However the manufacturers were encouraged to also include the INN on the label and leaflet – so-called dual labelling. Dual labelling for adrenaline and noradrenaline products was reviewed by the BP Commission in March 2007 and it was agreed that it should be continued.

Where does the Future of the BP Lie?

This question was put to Samantha Atkinson, the current secretary and scientific director of the BP Commission. In response she summarised the present role of the BP:[33]

> The current edition includes circa 3500 monographs, which are legally enforced by the UK Human Medicines Regulations 2012. Where a pharmacopoeial monograph exists, medicinal products sold or supplied in the UK must comply with the relevant monograph. All monographs and requirements of the European Pharmacopoeia (Ph. Eur.) are also reproduced in the BP.
>
> Now used in over 100 countries, the BP remains an essential reference tool (and in some cases, is the legal standard) for all individuals and organisations working within pharmaceutical research and development, manufacture and testing around the globe. Texts from the BP are also reproduced in other pharmacopoeias, which further contributes to ensuring the quality of pharmaceuticals worldwide.
>
> The BP Secretariat has strong collaborative agreements and work with a significant number of pharmacopoeial and regulatory authorities. The BP is further strengthened by the merger of the MHRA with the National Institute of Biological Standards and Control (NIBSC).
>
> The BP has a range of important functions that deliver the outcomes for the MHRA on behalf of Ministers. These functions are to:
>
> - contribute to the protection and safety of the public;
> - lead, be recognised and be trusted as an established Pharmacopoeia;
> - publish the British Pharmacopoeia, the British Pharmacopoeia (Veterinary) and the British Approved Names (BAN);
> - select, elaborate, publish and maintain the British Pharmacopoeia Monographs;
> - establish, store, sell, distribute and maintain the British Pharmacopoeia Chemical Reference Substances;
> - support regulatory functions and to protect the British Pharmacopoeia brand;
> - promote and provide authoritative standards to ensure the quality of pharmaceutical products.

In relation to the future role of the BP she stated:

[33] 2014. Personal communication from Dr S. Atkinson.

2014 sees the BP's 150th year in print and as such it is timely to consider its future. The BP must protect its strengths, embrace opportunities, address weaknesses and mitigate the threats. High level strategic strands have therefore been developed to provide a reliable platform for the BP to evolve, in a positive direction, over the coming years. These strategic strands focus on customer demands, while protecting, fostering and growing the BP business. Importantly, the BP will continue to contribute to the protection and safety of the public.

The future vision for the BP will be to:

- contribute to the protection and safety of the public;
- provide a central source for authoritative standards in the UK;
- lead the way, utilising new technological advances to ensure the content of the *Pharmacopoeia* is current and relevant. To use innovation to strengthen the BP and to reduce burden on industry, while maintaining its trusted reputation;
- become an effective streamlined operation to ensure all customer demands are met in a timely manner and to the highest standard;
- build on international relationships, to increase collaborative use of pharmacopoeial texts and to encourage harmonisation by default; and
- be recognised and valued for high quality, reliable, consistent and scientifically sound information.

Over the next 5 years, it is particularly important that the landscape in which the BP sits is fully understood. The BP must continue to evolve, adapt and respond to the changing environment and to the challenges and opportunities presented along the way.

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PART II:
The British Pharmacopoeia in International Context

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Chapter 5
British Pharmacopoeia and the *European Pharmacopoeia*

The construction of Europe is an art. It is the art of the possible.

(Jacques Chirac)[1]

The Brussels Treaty of 1948 represented the first step in the post-war reconstruction of Western European security. Among the goals of this treaty was the development of common defence structures to meet the threat from Soviet expansionism after 1945. This treaty was eventually to lead to the formation of the North Atlantic Treaty Organization (NATO). The Treaty also included provisions whereby the signatory countries – France, Belgium, the Netherlands, Luxembourg and the United Kingdom – agreed to collaborate in cultural, economic and social matters. In 1954, with the addition of Italy and the Federal Republic of Germany, the Brussels Treaty became the Western European Union.

In a speech in Zurich on 19 September 1946, Sir Winston Churchill had called for a 'kind of United States of Europe' and the creation of a Council of Europe.[1] The future structure of the Council of Europe was discussed at a specific conference of several hundred leading politicians, government representatives and others in The Hague, Netherlands, in 1948. There were two principal concepts which were discussed – an international organisation with representatives of governments, and a political forum of parliamentarians. Both ideas were combined by the creation of the Committee of Ministers and the Parliamentary Assembly under the Statute of the Council of Europe. The Council of Europe was founded on 5 May 1949 by the Treaty of London and signed by 10 states: Belgium, Denmark, France, Ireland, Italy, Luxembourg, the Netherlands, Norway, Sweden and the UK. In 1960 some of the activities of the Western European Union were transferred to the Council of Europe. On 12 August 1949, in a speech in Strasbourg, Churchill said:

> The dangers threatening us are great but great too is our strength, and there is no reason why we should not succeed in achieving our aims and establishing the structure of this united Europe whose moral concepts will be able to win the

[1] QuotesWave.com http://www.quoteswave.com/text_quotes/197071 (accessed 9 September 2014).

> respect and recognition of mankind, and whose physical strength will be such that no one will dare to hold up its peaceful journey towards the future.[2]

A pharmaceutical sub-committee proposed the establishment of a *European Pharmacopoeia* (Ph. Eur). As mentioned in Chapter 4, the European Pharmacopoeia Commission came into being in 1963 and began its work in 1964.

The first head of the Technical Secretariat to the European Pharmacopoeia Commission from October 1964 until 1985 was Mr Herbert Searle Grainger.[3] Grainger was born in Wakefield. He had served his pharmaceutical apprenticeship in Taylor's Drug Company, and then studied for his Pharmaceutical Chemist qualification at Bradford Technical College. He had a series of posts in hospital pharmacy, first at the Leeds General Infirmary, then at the Queen Elizabeth Hospital in Birmingham, finally becoming chief pharmacist at the Westminster Hospital from 1948 to 1964. A growing involvement in international affairs in the Fédération Internationale Pharmaceutique (FIP) – the International Pharmaceutical Federation – and in domestic pharmaceutical politics led him to stand and be elected to the Pharmaceutical Society's Council in 1950 and to become its president in 1961. In 1964 he had a meeting with Dr Harold Davis, chief pharmacist at the Department of Health, and Thomas Denston, the secretary to the British Pharmacopoeia Commission. He discussed with them the possibility of applying for this new job in Strasbourg. Davis felt that if the UK joined the European Community in a few years' time, the UK needed to be in on the ground floor. It would also be a challenge to start a new organisation from scratch. In September 1964 the rules of procedure of the European Pharmacopoeia Commission were adopted and Grainger applied and was appointed as the head of the Technical Secretariat. Grainger records that his first formal meeting of the new Commission in December 1964 was 'a little stiff' as the experts did not know each other and there was hesitation about accepting the others as equals. However 'one of the joys was to create an atmosphere where experts could become friends with a common purpose'.[4] Grainger died on 6 March 2008, aged 91.

The next secretary of the European Pharmacopoeia Commission was Dr Peter J. Schorn (1985–1999). Schorn's successor was Mr Peter Castle. He was born in Hull in September 1946. He graduated from Cambridge in biochemistry in 1968. He worked at the Pharmaceutical Society of Great Britain for three years and then in the animal health division of Smith Kline French in the UK. He

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[2] Council of Europe Archives. Winston Churchill speeches. http://www.coe.int/t/dgal/dit/ilcd/Archives/Selection/Churchill/Default_en.asp (accessed July 2014).

[3] 1979. Recorded oral interview by Mr C.A. Johnson with Herbert Grainger. *Royal Pharmaceutical Society Archive of Interviews*.

[4] 1979. Recorded oral interview by Mr C.A. Johnson with Herbert Grainger. *Royal Pharmaceutical Society Archive of Interviews*.

joined the Council of Europe in 1974 and became secretary to the European Pharmacopoeia Commission from 1999 until his death on 7 May 2008 at the age of 61. He had played a particular part in development of standards for biological products, particularly vaccines and blood products. Dr Hendrik de Jong, who was president of the European Commission at the time of Castle's death, said of him 'I have the greatest esteem for his important contributions to international harmonisation on a European and world level'.

The current secretary to the European Pharmacopoeia Commission is Mrs Cathie Vielle. Mrs Vielle is a pharmacy graduate from the University of Strasbourg. She held several positions in quality assurance compliance and supply-chain departments in an international pharmaceutical company before becoming head of the quality department at an international manufacturing site. She joined the EDQM in May 2009 as head of the European Pharmacopoeia Department.

At its April 1964 meeting the BP Commission discussed a letter from the British Ministry of Health together with a copy of Resolution (64)1 of the Committee of Ministers of the Council of Europe concerning the future establishment of a *European Pharmacopoeia*. The BP Commission had been involved in the preliminary discussions on the proposed new *Pharmacopoeia*. It was agreed that the BP Commission should be represented at this first meeting in April 1964, which was to be chaired by Mr Léon Robert from Luxembourg. They stressed the importance of establishing the principle of unanimity in the approval of specifications. In May 1964 Lord Cohen of Birkenhead, the chairman of the General Medical Council (GMC) Pharmacopoeia Committee and president of the GMC reported that the GMC had agreed that representatives from the British Pharmacopoeia Commission, comprising a delegation from the United Kingdom, could attend a meeting of a European Pharmacopoeia Commission.

The Convention on the Elaboration of a European Pharmacopoeia was agreed at Strasbourg on 22 July 1964. The contracting parties were France, Belgium, the Federal Republic of Germany, Luxembourg, Italy, Netherlands, Switzerland and the UK. The Convention defined that the preparation of the *Pharmacopoeia* – 'elaboration' in the words of the Convention, is undertaken by the Public Health Committee of the Council of Europe and a European Pharmacopoeia Commission. Technical and procedural decisions are taken by the Commission; other decisions are subject to the approval of the Public Health Committee. The European Pharmacopoeia Commission is composed of delegations appointed by the contracting parties, consisting of not more than three members with a similar number of alternates. The functions of the Commission were defined as:

a. to determine the general principles applicable to the elaboration of the European Pharmacopoeia;
b. to decide upon methods of analysis for that purpose;

c. to arrange for the preparation of and to adopt monographs to be included in the *European Pharmacopoeia*;
d. to recommend fixing the time limits within which its decisions of a technical character relating to the *European Pharmacopoeia* shall be implemented within the territories of the contracting parties.

Each national delegation has one vote, and on all technical matters decisions are taken by a unanimous vote of national delegations. Meetings were to be held in Strasbourg. The first formal meeting of the European Pharmacopoeia Commission was held in December 1964. It was attended by Professor Scowen as the head of the UK delegation. It established a number of groups of experts – the equivalent of the committees of the BP (now called expert advisory groups). In March 1965 the BP Commission nominated UK experts to serve on the Groups of Experts on General Biological Products, Antibiotics, Dressings and Ligatures, Inorganic Chemicals, Synthetic Organic Chemicals, Organic Chemicals Natural Products, Galenicals, Crude Drugs, Sera and Vaccines, and Blood Products. At the beginning there were 13 groups of experts. As these groups continued their work a *modus operandi* was needed to be established with regard to substances which were already the subject of monographs in the BP or the *British Pharmaceutical Codex*. At the BP Commission meeting in June 1965 it was agreed that draft monographs when they were approaching completion would be referred back to the appropriate committee in consultation with UK manufacturers and any other interested parties. A report could then be presented to the British Pharmacopoeia Commission.

Some of the tensions between a long-established national pharmacopoeia and the new Ph. Eur were evident from early reports of the UK delegation to the European Pharmacopoeia Commission, and from individual UK experts attending groups of experts meetings. In January 1966 Denston reported to the BP Commission that the opinion had been expressed at the European Pharmacopoeia Commission meeting on 11 and 12 January that national pharmacopoeias should incorporate all of the monographs included in the Ph. Eur. It was agreed that the UK would have to reserve its position, as this might mean including substances not used in the UK, or even ones viewed with disfavour. At the May 1966 European Commission meeting it was agreed that it was not necessary for national pharmacopoeias to reproduce the European specifications. One issue which was discussed at a number of BP Commission meetings was that of revision of European monographs once they were published. It was agreed that there needed to be a programme of periodical revision. In May 1966 the Swiss delegation had proposed that drugs which were the subject of monopoly patents should be excluded from the Ph. Eur. This would have effectively excluded most of the modern synthetic drugs. This was opposed by most other delegations who felt that this proposal had only been introduced for

commercial reasons, to protect the interests of the major Swiss pharmaceutical manufacturers. However by January 1967 the German delegation had also voiced its support for the proposal. The BP Commission at its meeting in January 1967 reiterated its resistance to this idea.

More important however was the quality of the monographs being produced initially by the working groups. In the same January 1967 BP Commission meeting it was felt that none of the first 14 monographs so far produced were acceptable and the secretary was asked to inform the technical secretary of the European Pharmacopoeia Commission accordingly. At the July 1967 BP Commission meeting Professor Scowen as head of the UK delegation reported that a further proposal had been made that national pharmacopoeias reproduce verbatim the European texts, this had been successfully resisted by the UK. However the legal view was that the European monograph applied whether or not there was a monograph in the BP. A suitable statement could be included in the general notices section of the next edition of the BP to emphasise the legal status of the European texts. By July 1967 more substantial overall progress had been achieved, and the European Pharmacopoeia Commission meeting had approved 50 monographs which would constitute the first volume, which it was suggested could be published in the spring of 1968. The final proofs of volume I were not received however until July 1969 and they were then checked by the BP Secretariat for editorial and typographical errors. The first volume of the Ph. Eur was published in November 1969 with a latest date for implementation of its standards set at 1 January 1972. This volume contained 76 monographs and nearly 200 pages of general notices and methods of analysis. Volume II was of the Ph. Eur was published in October 1971 to be made effective by 1 July 1973.

Another issue which was raised first at the July 1967 meeting of the European Pharmacopoeia Commission was that of general monographs for preparations such as tablets, capsules, ointments, creams and so on. Should such a general monograph apply to all preparations irrespective of whether there was an individual monograph in the book? This was to be the subject of ongoing debate for many years; particularly as in the beginning the Ph. Eur contained almost no monographs for specific preparations – unlike the BP. In March 1972 the BP Commission debated this again in relation to a general monograph on tablets. It considered that universal monographs 'would be nothing more than an elementary text-book compilation and could serve no useful purpose in the pharmacopoeia'. It felt that general monographs should apply only to the preparations of the Ph. Eur. In June 1972 the BP Commission discussed this again and reluctantly agreed that suitable general monographs could be included, but emphasised that the tests would be in the section on general analytical methods.

In 1967 the European Pharmacopoeia Commission inaugurated its first laboratory, enabling it to evaluate proposals for test methods proposed by manufacturers for new monographs or for revision of existing monographs.

In 1964 the British Pharmacopoeia Commission had been unable to recommend the ratification of the Convention as it had been established under the authority of the GMC, which owned the copyright in the BP. In April 1970, after the passage of the Medicines Act, the UK Department of Health asked the new British Pharmacopoeia Commission's advice on formal ratification. The department was advised that there was no reason for further postponement, since copyright in the BP had now been made over to the Crown. The Instrument of Ratification of the Convention was then lodged with the Secretary-General of the Council of Europe by Her Majesty's Ambassador Extraordinary on 4 December 1970. In 1972 UK health ministers issued an Order under Section 65 of the Medicines Act 1968. From 1 June 1972 the Ph. Eur replaced the BP as the primary reference text under the Medicines Act for substances or medicinal products for which no standard had been specified.

By January 1972 the possible revision of volume I was being discussed. At the BP Commission meeting it was felt that some monographs were no longer required, and others needed substantial revision, in particular to control impurities since many of the existing monographs in volume I were deficient in this respect. The Commission agreed to consult on which monographs were worth revisiting. In October 1972 Dr Hartley as chairman of the BP Commission reported that a *Supplement* to volume II had been prepared which would include amendments to volumes I and II. The monographs in volumes I and II were being reviewed. The question of revision was mentioned in the introduction to the BP 1980, where the speed of revision of the European texts was adversely compared to that which was achieved for British monographs. By 1980 there were 14 member states who had signed the Convention and it was a lengthy procedure to agree a new text with all of them and then to set a date by which the change can be made in all 14 countries.

The twelfth edition of the BP was published in 1973 with an effective date of 1 December 1973. It referred to the standards from volumes I and II of the Ph. Eur but included additional titles, and also information on storage, labelling, dose and action and use of drug substances. Thus for example the BP 1973 monograph for Aspirin merely states 'Aspirin complies with the requirements of the European Pharmacopoeia for Acidum Salicylicum'. No changes were made to the European standards. Thus users of the BP also had to purchase volumes I and II of the Ph. Eur. In September 1973 the BP Commission discussed this again in the light of complaints it had received. Dr Hartley felt that although it would be preferable to publish all the standards in the BP there might be difficulties since the Ph. Eur had legal precedence. It would also be necessary to publish the relevant appendices and details of reagents used. In January 1976 the BP

Commission noted again that readers trying to use the Ph. Eur were exasperated at having to seek information from volume to volume. It would obviously be desirable to incorporate the matter from the Ph. Eur into the BP. However it was agreed that no general change of policy could be contemplated at that time. In April 1977 the BP Commission returned to this vexed question yet again and agreed that a new complete and unified edition of the *British Pharmacopoeia* should be published in 1980 and this should include specifications from the *European Pharmacopoeia* suitably edited. This was finally accomplished in the BP 1980.

In 1975 the Scandinavian countries stopped working on their own *Nordic Pharmacopoeia* and became signatories to the Convention. From 1990 onwards countries from Eastern and Central Europe also joined. In 1994 a protocol was negotiated by Fernand Sauer from the Pharmaceutical and Veterinary Unit of the Directorate-General for Internal Market and Industrial Affairs of the European Commission which agreed which allowed the European Union to accede to the Convention. The protocol defined the respective roles of the European Union and the EU member states. Derek Calam, the chairman of the European Pharmacopoeia Commission from 1998 to 2001 comments:[5]

> At the same time, he – Sauer – played the pivotal role in establishing the European Medicines Evaluation Agency and siting it in London. When he achieved these aims, an almost immediate effect was to make the member states aware of the power of the Ph Eur to harmonise requirements for pharmaceuticals in all the members who extended beyond the smaller number of EC members. The impact was felt by the BP and MCA almost at once as the general monographs for dosage forms introduced by Ph Eur and applied as mandatory requirements across all dosage forms irrespective of the new or established status of their active ingredients helped to provide more uniform assessments of licence applications. In addition the role of EMEA in emphasising the Ph Eur requirements cannot be underestimated. Rapidly the value and importance of the national pharmacopoeial activities shot up the scale, strengthening the role of the BP Commission and the UK Delegation in Strasbourg.

At the time of writing there are 38 signatories to the European Pharmacopoeia Convention: Austria, Belgium, Bosnia and Herzogovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, the former Yugoslav Republic of Macedonia, Turkey, Ukraine, United Kingdom and the European Union.

[5] 2014. Personal communication from Professor D. Calam.

Ukraine was a signatory in 2013. Twenty seven other countries participate as observers: Albania, Algeria, Argentina, Armenia, Australia, Azerbaijan, Belarus, Brazil, Canada, China, Georgia, Israel, Kazakhstan, Madagascar, Malaysia, Moldova, Morocco, Republic of Guinea, the Russian Federation, Senegal, Singapore, South Africa, Syria, Tunisia, the United States of America, the Taiwan Food and Drug Administration and the World Health Organization. The WHO has participated in the work of the Ph. Eur since 1964.

The first edition of the Ph. Eur was published in two volumes with volume I containing general chapters, general monographs on dosage forms, methods of analysis and reagents. Volume II contains monographs on medicinal substances – drug substances and excipients. Volume I of the second edition was published in March 1980 with an implementation date of 1 January 1983 and volume II in October 1980 with an implementation date of 1 January 1983. Eighteen supplements or 'fasicules' were published between April 1981 and May 1995. The third edition was published in July 1996 with an implementation date of 1 January 1997. Four supplements were issued between 1997 and July 2000. The fourth edition was published in July 2001 with an implementation date of January 2002. Eight supplements were issued. The fifth edition was published in July 2004, with an implementation date of January 2005. The sixth edition was published in July 2007 with an implementation date of 1 January 2008. The seventh edition was published in July 2010 with an implementation date of 1 January 2011.

The eighth and latest edition of the Ph. Eur was published in July 2013 and became official on 1 January 2014. *Supplement* 8.1 was published in October 2013, *Supplement* 8.2 in January 2014, *Supplement* 8.3 in July 2014 and *Supplement* 8.4 in October 2014. Further supplements will be published during 2015 and 2016. Volumes I and II contain 2,224 monographs, 345 general chapters and 2,500 reagent descriptions. This edition covers active substances, excipients, homeopathic preparations and stocks, antibiotics, and containers. It includes texts on biologicals, blood products, vaccines and radiopharmaceuticals. It can be purchased as a book, in an online version – including on smartphones and tablets, or an electronic version in the form of a USB stick. The book version is available in English or French. The online and USB versions are bilingual.

The United Kingdom continues to send a delegation to the three meetings of the European Pharmacopoeia Commission in each year. It also supports the work of the 20 groups of experts and 50 working parties.

The presidency of the European Pharmacopoeia Commission is for a three-year period. The president for the inaugural meeting was Mr Léon Robert from Luxembourg. So far there have been three British chairmen – Mr C.A. Johnson from 1977 to 1980, Professor Alan Rogers from 1992 to 1994 and Professor Derek Calam from 1998 to 2001. During the first 50 years there have been three French chairmen, two from Luxembourg, two from the Netherlands, two from

Denmark and one each from Italy, Belgium, Germany, Ireland and Sweden. The current chairman is Dr Jean-Louis Robert from Luxembourg, the son of Léon Robert. He is also the long-standing chairman of the Quality Working Party of the European Committee for Medicinal Products for Human Use (CHMP) and the Committee for Medicinal Products for Veterinary Use (CVMP). He is thus able to integrate the regulatory needs for licensing of new medicines and the pharmacopoeia.

Drug Substance Monographs in the *European Pharmacopoeia*

In the late 1980s the Quality Working Party of the European Union's Committee for Proprietary Medicinal Products (CPMP) was considering how technical data on drug substances could be submitted to national medicines agencies in the EU in support of marketing authorisation applications for medicinal products. Some agencies accepted Drug Master Files; others did not, so there was a need for a common harmonised position for the pharmaceutical industry to avoid companies having to file different data in different EU countries. In July 1990 the CPMP adopted a guideline for a harmonised EU procedure, which at that time was called the European Drug Master File procedure – the EDMF. The EDMF could be sent to the European agencies in support of a marketing authorisation for a product and consisted of a two-part file – a so-called 'Open Part' which had also been disclosed to the product authorisation applicant and a 'Closed Part' which was disclosed only to the authorities – and which contained confidential 'know-how' information on the drug substance manufacture. Many of the EDMF submissions concerned multi-source drug substances which were out of patent and the subject of *European Pharmacopoeia* monographs. As a result the national medicines agencies receive detailed information on the methods of manufacture, specifications and other information for pharmacopoeial drug substances. The procedure is now known as the Active Substance Master File procedure (ASMF).[6]

The Technical Secretariat to the Ph. Eur was concerned that the specifications for drug substances agreed with the national agencies would be different to those in the pharmacopoeia. They therefore devised a scheme which could be used as an alternative to the EDMF scheme. This concept was discussed in 1990 with representatives from the European chemical industry and the European pharmaceutical industry in meetings chaired by Dr Agnès Artiges as chairman of the European Pharmacopoeia Commission. The proposed scheme would enable the *European Pharmacopoeia* to play an increased role in the European

[6] 2013. Guideline on Active Substance Master File Procedure. European Medicines Agency CHMP/QWP/227/02 Rev 3/Corr 31 May.

regulatory system. This proposal was to eventually lead to the Certification of Suitability of the Monographs of the European Pharmacopoeia – CEP scheme. The scheme was launched in 1993 under the legal basis of Resolution AP-CSP (93) 5 of the Council of Europe Public Health Committee of 1 July 1993, and then modified in later resolutions. The CEP scheme requires the manufacturer to submit a data package equivalent to that required in the EDMF/ASMF procedure. The manufacturer pays a fee to submit the CEP application and data and have it reviewed. The review is carried out under the supervision of the EDQM by a cadre of nominated pharmaceutical reviewers from EU national agencies. The submission has to include information on the impurity profile of the drug substance from the new supplier, and any proposals for changes to the analytical procedures. Thus the CEP procedure allows a constant review and updating of drug substance monographs as new manufacturers from India, China and elsewhere wish to start to sell them, when the originator's patent expires. As the monograph is updated the list of impurities controlled is increased to include any new ones. The impurities controlled by the monograph are all listed at the end of the text. This was agreed with the CPMP's Quality Working Party to increase the 'transparency' of the monographs, so that it was clear which impurities were controlled.

The CEP application now also has to include a declaration that the substance is made according to the requirements of the EU Good Manufacturing Practice (GMP). Manufacturers are inspected by a team of inspectors drawn from the national agencies in the EU to check their compliance with GMP. If not compliant the CEP can be suspended or revoked. A CEP certificate will be accepted by the national agencies as part of a marketing authorisation application for a product.

In 1999 the CEP application procedure was extended to excipients as well as drug substances. Bovine spongiform encephalopathy, or BSE, commonly known as 'mad cow disease', is one of a group of diseases known as Transmissible Spongiform Encephalopathies – TSEs, or prion diseases. They result from the build-up of prion proteins in the brain and nervous system. TSEs are so-called from the spongy appearance of the infected brain, and the fact that they are transmissible via infected material. Between 1986 and 2002 over 180,000 cases of BSE were confirmed in cattle in the UK. The UK government made BSE a notifiable disease in June 1988. The occurrence of BSE raised concerns about the potential transmission of the disease to man via infected animal materials used in pharmaceutical products. In 1999, the CEP procedure was extended to include products with a risk of transmissible spongiform encephalopathy whether or not they had monographs in the Ph. Eur. This enabled their certification on the basis of the Ph. Eur general chapter 5.2.8 'Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products'.

The European Department for Quality of Medicines (EDQM)

The European Directorate for Quality of Medicines (EDQM) was created in 1996 (see above). It consists of the Technical Secretariat of the European Pharmacopoeia Commission and other services which support the wider activities such as the certification of suitability[7] of monographs and the European Network of Official Control Laboratories (OCML). The Technical Secretariat supports the preparation and publication of the Ph. Eur and other publications, the experimental checking of analytical methods in the laboratory, the preparation and despatching of *European Pharmacopoeia* Reference Substances for use with the *Pharmacopoeia* analytical test procedures, and organising seminars and training on new scientific and technical subjects.

The first director of the EDQM was Dr Agnès Artiges. She was a pharmacist with degrees and PhDs in both pharmacy and law. She joined the French Ministry of Health in 1971 and held posts as head of the *Pharmacopée Française*, head of the Registration Authority for Medicinal Products and head of the sub-Directorate of Scientific and Technical Affairs. She left the French Ministry in 1993 to join the Council of Europe, and in 1996 was appointed as director of the EDQM. She retired in 2007.

In 1995 the Technical Secretariat to the European Pharmacopoeia Commission was asked by the European Union to set up a quality surveillance system for marketed medicines. This is now the European Network of Official Medicines Control Laboratories (OMCL). At the time of writing more than 100 Official Control Laboratories in nearly 40 countries participate in this scheme.

In 2007 the official name of the EDQM became 'The European Directorate for the Quality of Medicines and Healthcare'. The EDQM's current Director is Dr Susanne Keitel.

Dr Keitel is a pharmacist with a PhD in pharmaceutical technology. She worked in pharmaceutical R&D in the pharmaceutical industry for 10 years and then moved to the German Federal Institute for Drugs and Medical Devices (BfArM), where she was the division head, Pharmaceutical Quality, from 1997 to 2005. From 2005 to 2007 she was head of EU, International Affairs at the BfArM. She became the director of the EDQM in October 2007.

The EDQM consists of four departments and four divisions. The departments are the European Pharmacopoeia Department, the Publications and Multimedia Department, the Laboratory Department and the Biological Standardisation, Network of Official Control Laboratories and Healthcare Department. The divisions are the Certification of Substances Division, the Reference Standards

[7] 2014. Applications for Certificate of Suitability to the monographs of the European Pharmacopoeia. http://www.edqm.eu/en/certification-new-applications-29.html (accessed July 2014).

and Samples Division, the Public Relations and Documentation Division and the Administration and Finance Division.

Derek Calam summarises the importance of the UK's role in the EDQM as follows:[8]

> The invaluable support by the [BP] Secretariat in providing input, comments and initiatives from the UK for the work programme of the *Ph Eur* has allowed the UK to exert a powerful influence on the output from Europe in facilitating the UK Medicines Control Agency and later Medicines and Healthcare products Regulatory Agency role across the whole range of EDQM activities as it has been integrated more closely into the European medicines licensing and control systems. This has included input into the biological programme for reference materials, the control laboratories network, certification – including membership of the technical advisory boards and steering committee, and most recently the initiatives around counterfeit and falsified medicines.

The year 2014[9] was an auspicious one, as in addition to being the sesquicentenary of the first publication of the BP in 1864, it is also the 50th anniversary of the adoption of the European Pharmacopoeia Convention in 1964 and the start of work on the Ph. Eur.

[8] 2014. Personal communication from Professor D. Calam.

[9] 2014. The European Directorate for the Quality of Medicines and Healthcare. http://www.edqm.eu/en/edqm-homepage-628.html (accessed July 2014).

Chapter 6
International Harmonisation of Pharmacopoeias

After all, science is essentially international, and it is only through lack of the historical sense that national qualities have been attributed to it.

(Marie Curie)[1]

As mentioned in Chapter 1, in the nineteenth century the increasingly complex distribution chains from suppliers to patient leant themselves to problems of adulteration and counterfeiting. In the twentieth century increasing travel meant that patients needed to be provided with medicines in different countries defined to the same strengths and to the same quality standards. As the twentieth century proceeded, manufacture and distribution of drug substances, excipients and finished products became increasingly globalised. These trends have increased the pressure on the national and regional pharmacopoeia commissions to collaborate and to harmonise.

International Agreements for the Unification of Formulae for Potent Drugs

As we have seen in Chapter 2 of this book, the monographs in the early twentieth-century editions of the *British Pharmacopoeia* (BP) and other national pharmacopoeias were influenced by the First International Agreement for the Unification of Formulae of Potent Drugs resulting from the Conference called in 1902. This Agreement was ratified in 1906. A second Conference was held in Brussels in 1925 resulting in a Second International Agreement. The Agreement covered nomenclature, biological testing of arsenobenzenes, dosage forms and descriptions for 77 drug substances and preparations.[2]

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[1] Curie, M., 1926. Memorandum by Madame Curie, Member of the Committee, on the Question of International Scholarships for the Advancement of the Sciences and the Development of Laboratories, League of Nations, International Committee on Intellectual Co-operation: Sub-committee of Experts for the Instruction of Children and Youth in the Existence and Aims of the League of Nations. (Recommendations. Preamble): Issue 5, issues 9–13, 12.

[2] Madsen, T., 1937. The Scientific Work of the Health Organization of the League of Nations. Harvey Lecture, February 18, 1937. *Bull. N.Y. Acad Med*. 13(8): 439–65.

The *International Pharmacopoeia*

Many pharmacopoeial workers felt that this 1925 International Agreement should be revised and extended to cover a limited *International Pharmacopoeia*. Urdang has reviewed the development of the *International Pharmacopoeia*.[3] In 1937 the Health Organisation of the League of Nations set up a Technical Commission of Pharmacopoeial Experts. This Commission was charged with preparing a draft of a new International Agreement to be submitted to national governments by the Belgian government. The first meeting of the Technical Commission was held in Geneva in May 1938. A second meeting was held in 1939, again in Geneva, with work starting on certain monographs on important drugs used widely in a number of countries. The work was interrupted during World War II.

At the third session of the Interim Commission of the World Health Organization (WHO) held in Geneva in April 1947, it was decided to set up an expert committee on the unification of pharmacopoeias. This committee would continue the work of pharmacopoeial experts set up under the League of Nations. In 1948 the First World Health Assembly established a pharmaceutical secretariat within the WHO and agreed that an *International Pharmacopoeia* should be published in English, French and Spanish. An Expert Committee on the Unification of Pharmacopoeias was established. Seven members were appointed to the committee: Professor Rasmussen from Denmark, Professor Fahmy from Egypt, Professor Hazard from France, Professor van Os from the Netherlands, Professor Flück from Switzerland, Dr Hampshire from the UK and Dr Fullerton-Cook from the United States. Dr Hampshire was the chairman. The committee met in Geneva and then in New York. The Third World Health Assembly, held in May 1950, formally approved the publication of the *International Pharmacopoeia*. It was published in two volumes in 1951 and 1955 in English, French and Spanish.[4] A *Supplement* was issued in 1959. It included 344 monographs on drug substances, 183 monographs on dosage forms and 84 sections on tests, methods and general requirements. It was not intended to be a legal text in any country, unless adopted by the local pharmacopoeial authority. The monograph titles are in Latin.

The second edition was published in 1967 and was a complete revision of the first edition to include new chromatographic techniques, infrared spectroscopy and non-aqueous titration. One hundred and fourteen monographs from the first edition were deleted.

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[3] Urdang, G., 1951. The Development of Pharmacopoeias. A Review with Special Reference to the Pharmacopoeia Internationalis. *Bull. World Hlth. Org* 4: 577–603.

[4] 1956. The National Archive of the UK CO859/1322. Protocol for the Termination of the Brussels Agreement for the Unification of Pharmacopoeial Formulae for Potent Drugs.

In 1975 it was decided that the main purpose of the publication would be to serve the needs of the developing world and recommend simpler chemical analytical techniques.[5] Priority was given to widely used drugs and those important to the WHO programmes. The WHO Expert Committee on the Selection of Essential Drugs provided a list of drugs to be included. The essential drugs list is used by national governments to design the development of lists of medicines selected with regard to their efficacy to treat local diseases in a cost-effective way. In developing countries the cost of medicines represents between 25 and 66 per cent of health spending. The third edition consisted of five volumes. Volume I contained general methods of analysis, volumes II and III quality specifications for most of the essential drug substances, volume V contained tests and general requirements for dosage forms and a section on antimalarial drugs and dosage forms.

Volumes I and II of the fourth edition were published in 2006. Volume I contains the general notices and many of the drug substance monographs. Volume II contains the remaining drug substance and excipient monographs together with monographs for the dosage forms, the methods of analysis and reagents. These were published in print, as a CD-ROM and online.

The first *Supplement* was produced in 2008 again in these three formats. It included monographs for some additional antiretroviral substances and dosage forms (for treatment of HIV) and combination products for treatment of tuberculosis. The second *Supplement* was produced in 2011, again in the three formats. The CD-ROM of each supplement is a cumulative version.

Pharmaceutical scientists from the UK have continued to serve on the WHO expert committees which produce these new editions and supplements.

International Nonproprietary Names (INNs)

In the twentieth century drug substances used in medicine gradually moved from being largely derived from natural products to being synthetic organic drug substances. These were patented compounds and used trademarks for their commercial names for their marketing. The trademark names were much shorter than the systematic chemical names using the guidelines of the International Union for Pure and Applied Chemistry (IUPAC). The national authorities in each country started to devise simpler generic names.[6]

[5] 2008. International Pharmacopoeia. Role of the International Pharmacopoeia in Quality Assurance. *WHO Drug Information* 22(2): 113–20.

[6] Miller, L.C., 1953. International Non-Proprietary Names. *The Trade-Mark Reporter* 43(2): 133–48.

The first international conference on common, nonproprietary names was held in Geneva in 1892. A second conference was held in Liege in Belgium in 1930. In 1924 an international list of drug names was drawn up under an International Protocol. The Health Organization of the League of Nations set up after World War I also concerned itself with drug nomenclature. The World Health Organization became involved in the issue through the World Health Assembly after World War II. The Third World Health Assembly was held in Geneva in 1950. Delegates from Portugal and Greece drew attention to the confusing situation where drugs were called by different names depending on their country of origin. Resolution WHA3.11 was adopted and a new procedure was adopted. In May 1953 this led the Executive Board of the WHO to clarify the existing procedures for selection of nonproprietary names.[7] The procedure was that a notice of a proposed International Nonproprietary Name (INN) would be given in the *WHO Chronicle*, and also sent by letter to member states and to designated national pharmacopoeias. Comments or formal objections were requested within six months of publication. In the absence of any sustained objections the names were re-published as recommended INNs a year or so later.

The 1953 revised procedure was accompanied by an annex defining a set of general principles for devising INNs. The name needed to be free from any anatomical, physiological, pathological or therapeutic suggestion. An attempt should be made to form the name from a combination of syllables derived from the scientific technical name, for example by terminating the name with '*-ine*' for alkaloids, '*-oside*' for glycosides, '*-ol*' for alcohols and '*-al*' for aldehydes. The name needed to be distinctive in sound and spelling and should not in general exceed four syllables.

In Britain the BP Commission had devised the simple generic names which were also used as the titles for the monographs. These were published at regular intervals in the *British Medical Journal*. During World War II the BP Commission issued new generic names for drugs that were to be manufactured in Britain but had previously been imported before the war from German companies.

In November 1950 the American Embassy complained to the British Comptroller of Patents that some companies were attempting to register approved generic names as trademarks. The British Trade Mark Registry had an arrangement with the BP Commission whereby lists of proposed generic names were submitted to the Registry for comment. The registrar then did a search and advised any conflicts with registered trademarks.

In 1953 the BP Commission started to try to define its role in approval of generic names so that they could have international acceptability. Mr Denston as secretary to the BP Commission wrote to Mr Girling of the UK Board of

[7] 1953. Procedure for the Selection of Recommended International Non-Proprietary Names for Drugs. WHO Executive Board, Twelfth Session, EB12/19. 27 May.

Trade on 13 January 1953 stating that the BP Commission had been issuing lists of Approved Names for the last decade. Their procedure was to select a name and then communicate it to the registrar at the Patent Office. If he advised that there was no conflict with any registered Mark, and there was no objection from elsewhere, the name was published as an Approved Name. For the last year, these Approved Names had also been sent to the WHO to also give them an opportunity to comment.

A panel of experts of the WHO had been issuing proposed lists of INNs. Copies of these lists had been sent to the BP Commission and the Ministry of Health. After examining the lists of proposed names, comments were sent to WHO in Geneva of any names which were not acceptable – conflicts with registered trademarks, established usage of other names or non-compliance with certain rules of nomenclature. In April 1953 it was agreed that the proposed names on the WHO lists be cleared with the Board of Trade, and that the BP Commission would act as the official authority.

On 31 December 1953 Denston wrote to the registrar at the Patent Office indicating that to facilitate protection of names issued by the WHO as potential INNs that provided they were acceptable they would be recommended to the General Medical Council as British Approved Names.

The naming of new substances was coordinated by the WHO to ensure that a single nonproprietary name was used worldwide. Secretaries or representatives of the national nomenclature committees from France, Japan, the United States and the United Kingdom were all members of the original INN Panel of Experts and remain so to this day. The original 1953 procedure has been updated a number of times. The current WHO guideline was issued in 1997 and is entitled *Guidelines on the Use of INNs for Pharmaceutical Substances (1997)*. There are now over 7,000 INNs and between 120 and 150 are added each year. They are used in the pharmacopoeias such as the BP or the *European Pharmacopoeia*, in labelling, in the product information, advertising and promotional material. In the European Union the use of the INN is required under Directive 2001/83/EC of the European Parliament and the Council.

In the current procedure a request is made to WHO for an INN by a manufacturer or developer. The WHO Secretariat reviews the suggested name for conformity with the general rules, for similarity with any existing INNs and also conflict with trademarks. The request is then reviewed by the WHO Expert Panel and, when selected, the proposed INN is published in the *WHO Drug Information* for comments. After a time period of four months for objections, the name is given the status of a recommended INN and is then published in *WHO Drug Information*.

The 1997 WHO Guideline sets out the elements of the INN system and the principles for INN selection. An INN usually consists of what the Guideline calls 'a random, fantasy prefix' and a common stem. Substances belonging to a group

of pharmacologically related substances are given a common stem. Examples of common stems are *-astine* for antihistamines, *-caine* for local anaesthetics and *-dipine* for calcium channel blockers, nifedipine derivatives.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

In the mid-1980s the pharmaceuticals unit of the European Union's Directorate-General III, Internal Market of the European Commission, initiated a series of bilateral meetings between the European experts from the Committee for Proprietary Medicinal Products and their counterparts in the Food and Drug Administration in the United States and the Ministry of Health and Welfare in Japan. The purpose of these bilateral discussions was to try to harmonise the technical requirements in terms of quality, safety and efficacy to register medicinal products in these three regions. Harmonisation would reduce the time and effort that pharmaceutical companies spent carrying out different work programmes to obtain approval, thus reducing development costs and reducing delays in obtaining approval to market. These meetings were fruitful and some initial agreements were obtained.

The WHO Fifth International Conference of Drug Regulatory Authorities was held in the Senate Building, Luxembourg Gardens in Paris from 10 to 13 October 1989. At this conference one of the topics was international harmonisation. Fernand Sauer, the head of the pharmaceuticals unit in Directorate-General III of the European Commission, reported on the bilateral discussions with the United States and Japan.[8] Soon afterwards the authorities approached the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), to help set up trilateral discussions involving both the authorities and the pharmaceutical manufacturers in the three regions. In April 1990 a meeting was held in Brussels to plan the terms of reference for a programme of harmonisation and to set up an International Conference on Harmonisation.[9] A Steering Committee was set up to oversee the work and to define its terms of reference. The members of the Steering Committee were drawn from senior staff at the European Commission representing the European Union, the European Federation of Pharmaceutical Industries Associations, the Food and Drug Administration, the Pharmaceutical Research

[8] 1989. Fifth International Conference of Drug Regulatory Authorities. 10 to 13 October 1989. Senate Building, Luxembourg Gardens, Paris. Organized by the Pharmaceuticals and Medicines Department of the Ministry of Solidarity, Health and Welfare, France and the World Health Organization. WHO/PHA/ICDRA/9.1.

[9] 2014. History of ICH. http://www.ich.org/about/history (accessed July 2014).

and Manufacturers of America, the Japanese Ministry of Health and Welfare, and the Japanese Pharmaceutical Manufacturers Association. Staff from IFPMA provided the Secretariat to ICH. The Steering Committee agreed the terms of reference for ICH, an initial programme of work on harmonisation in the three key areas of quality, safety and efficacy and started to plan the first International Conference. The Steering Committee agreed the list of topics in the three key areas which would be the first to be considered by working groups from the regulatory agencies and the industry in the three regions. The agreed ICH process for each topic was a five-step one:

Step 1: Building consensus in joint regulator/industry Expert Working Groups.
Step 2: Agreement by the Steering Committee to release the draft consensus text for wider consultation.
Step 3: Formal regulatory consultation by the authorities in the three regions, and consolidation of comments.
Step 4: Agreement on a harmonised ICH guideline, with adoption by the regulatory agencies in the three regions.
Step 5: Implementation in the three regions.

The major ICH quality topics considered since 1990 have been Q1: Stability, Q2: Analytical Validation, Q3: Impurities, Q4: Pharmacopoeias, Q5: Quality of Biotechnology Products, Q6: Specifications, Q7: Good Manufacturing Practice, Q8: Pharmaceutical Development, Q9: Quality Risk Management, Q10: Pharmaceutical Quality Systems and Q11: Development and Manufacture of Drug Substances.

The Q4B Expert Working Group was established in November 2003 to evaluate pharmacopoeial texts that were being proposed for use by the separate Pharmacopoeial Discussion Group (PDG), for use in the three ICH regions. The Expert Working Group developed guideline Q4B which was issued in November 2007 entitled *Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions*.[10] Initially it focused on 11 General Test Chapters which had been discussed during the development of the Q6: Specifications guideline. These General Chapters were Dissolution, Disintegration, Uniformity of Dosage Units, Extractable Volume, Particulate Matter, Sterility, Microbiological Quality, Bacterial Endotoxins, Residue on Ignition/Sulphated Ash and Colour. As a result of the Q4B Expert Working Group deliberation a pharmaceutical

[10] 2007. Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions. Q4B. International Conference on Harmonization of Technical Requirements for Human Use. 1 November. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality?Q4B/Step4B_Guideline.pdf (accessed October 2014).

manufacturer can be given an assurance that the pharmacopoeial chapter in any of the three official texts in the USP, *European Pharmacopoeia* or *Japanese Pharmacopoeia* can be substituted and are regarded as interchangeable. Thus the company can generate analytical data by a single method which is accepted in all three regions.

In addition to the quality, safety and efficacy topics there is a category of multidisciplinary topics for areas which do not fit neatly into one of the categories of quality, safety and efficacy. The topics considered since 1990 have been M1: MedDRA Terminology, M2: Electronic Standards, M3: Nonclinical Safety Studies, M4: Common Technical Document (CTD), M5: Data Elements and Standards for Drug Dictionaries, M6: Gene Therapy, M7: Genotoxic Impurities, and M8: Electronic Common Technical Document (eCTD). The CTD and the eCTD define a common format for marketing authorisation applications for pharmaceutical products which can be used in all three ICH regions.

In the early years of ICH there were regular large international conferences in which the latest agreed guidelines were presented and discussed. The first ICH Conference (ICH1) was held in Brussels in November 1991, ICH2 was held in Orlando, Florida in October 1993, ICH3 was held in Yokohama in November 1995, ICH4 in Brussels in July 1997 and ICH5 in San Diego in November 2000. These large conferences have now been discontinued and the work of ICH is managed by six-monthly meetings of the Steering Committee and the Expert Working Groups. Each of these six-monthly meetings involves 10–15 expert working groups and 200–300 individual experts. The venue for these meetings alternates between Europe, Japan and the United States.

The outcome of the ICH deliberations in guidelines and standards is also rolled out to a wider group of countries via the Global Cooperation Group (GCG). This was set up in March 1999 as a sub-committee of the ICH Steering Committee. Various groups of countries started collaborating via Regional Harmonisation Initiatives (RHIs) on requirements for registration of pharmaceutical products. They were then invited to participate in the GCG discussions. RHIs included in the discussions on the GCG include Asia-Pacific Economic Cooperation, the Association of South-East Asian Nations, the East African Community, the Gulf Cooperation Council, the Pan-American Network for Drug Regulatory Harmonisation, and the South African Development Community. From June 2013 the ICH Steering Committee now has a Global Cooperation session on its agenda.

The Pharmacopoeial Discussion Group (PDG)

The PDG was initially set up in 1989 as a four-way discussion group with representatives from the *European Pharmacopoeia*, the *United States Pharmacopoeia*,

the *Japanese Pharmacopoeia* and the *British Pharmacopoeia*. However in May 1992, when the *European Pharmacopoeia* was acting as the hosts for the PDG meeting in Strasbourg, no representatives from the BP were invited. The BP Commission complained and a discussion was held with Dr Artiges as chairman of the European Pharmacopoeia Commission and Dr Schorn as its secretary. They suggested that the UK should voluntarily withdraw its delegation in the interests of European harmony. The UK rejected this proposal, but was still not invited to future meetings. The involvement of the BP Commission in the PDG discussions of the first two years has been carefully airbrushed from the official accounts of the history of the PDG.

The initial aim of the PDG was to harmonise excipient monographs and the general chapters of the *Pharmacopoeia*. Although not officially part of the ICH the PDG meets up with the ICH Steering Committee to report on its own harmonisation process. The PDG consults the manufacturers of pharmaceutical products and excipients on the programme of work.

There are seven stages in the PDG harmonisation process:[11]

Stage 1:	Identification of a subject to be harmonised. Coordinating pharmacopoeia responsible for the work.
Stage 2:	Investigation by the coordinating pharmacopoeia of existing specifications in the national pharmacopoeias and preparation of a draft proposal.
Stage 3:	Proposal for Expert Committee Review for comments by national experts and preparation of a harmonised draft document.
Stage 4:	Official Inquiry by publication in the forum of each pharmacopoeia for comment by readers and analysis by each pharmacopoeia. Comments reviewed by the coordinating pharmacopoeia and a draft harmonised document prepared with a commentary.
Stage 5:	Consensus – review by the other two national pharmacopoeias of the draft, comments and then preparation of a revised document.
Stage 6:	Regional adoption and implementation.
Stage 7:	Inter-regional acceptance. Following the Q4B process the formal notification is posted by ICH.

Although there was considerable disappointment from the regulators and industry in the three ICH regions at the glacial initial progress of pharmacopoeial

[11] 2010. Working Procedure of the Pharmacopoeial Discussion Group (PDG). Revised version (June 2010). *Pharmeuropa* 22(4): 590–92.

harmonisation, as might be expected, there has been considerable progress over the last 25 years. At the time of writing there are 11 general methods at Stage 6 – regional adoption and implementation, and one – colour instrumental method – at Stage 3 in its third revision. These general methods include dissolution, disintegration, uniformity of content/mass, tests for specified organisms and the sterility test. Sixteen general chapters are at Stage 6, and another 10 are under revision or at an earlier stage of development. These chapters include tests for flowability of powders, tablet friability, powder fineness, X-ray powder diffraction, calorimetry, amino acid determination and capillary electrophoresis. Thirty-three monographs for excipients are at Stage 6 and another 28 are under revision or at an earlier stage of development. Each of these harmonised Stage 6 texts is included in the *British Pharmacopoeia* as well as in the Ph. Eur.

International Co-operation among World Pharmacopoeias

At the 10th International Conference of Drug Regulatory Authorities (ICDRA) held in Hong Kong from 24–27 June 2002, one of the topics was harmonisation. In particular the question of the availability of specifications for new drugs which are on the WHO Essential Drugs List but are not yet included in a pharmacopoeia was discussed. This was particularly important for example for drugs for treating HIV in the developing world. A future international conference was mooted. The idea of a worldwide approach to setting pharmacopoeial specifications was further discussed at the 11th ICDRA meeting held in Madrid in 2004. These preliminary discussions led WHO to call an International Meeting of World Pharmacopoeias in Geneva from 29 February to 2 March 2012. The meeting was co-chaired by Professor A. Nicolas from France, Professor G. Pianetti, the president of the *Brazilian Pharmacopoeia*, Dr G.N. Singh the drugs controller general and secretary/scientific director of the Central Indian Laboratory and Mr N. Yasuda, the international planning director, Ministry of Health and Welfare, Japan.[12] Representatives attended from 46 national pharmacopoeia commissions, the *European Pharmacopoeia* and the African pharmacopoeias, together with the WHO which is responsible for the *International Pharmacopoeia*. An index of pharmacopoeias was produced as one of the working documents.[13] The index identified 35 national pharmacopoeias ranging from the *Farmacopea Argentina* to the *Pharmacopoeia Vietnamica*. Some countries had more than one pharmacopoeia – for example Brazil has the *Farmacopéia Brasileira* and

[12] 2012. International Meeting of World Pharmacopoeias, Geneva, 29 February – 2 March 2012. Meeting Report. WHO QAS/12.467. March.

[13] 2012. Index of Pharmacopoeias. Working Document QAS/11.453. WHO.

the *Farmacopéia Homeopática Brasileira* for homeopathic products. Similarly Germany has the *Deutsche Arzneibuch* and the *Deutsches Homöopathisches Arzneibuch*. The African countries have the *African Pharmacopoeia* produced by the Committee on Scientific and Technical Research, African Union based in Nigeria, and the *African Herbal Pharmacopoeia* produced by the Association for African Medicinal Plant Standards based in Mauritius.

The conference recognised the increasing globalisation of the trade in drug substances, excipients, intermediates, bulk and finished pharmaceutical products. It was felt that the pharmacopoeias had to respond to the problems of adulteration and falsification by characterisation of the products and control of impurities. The pharmacopoeias were extending their scope to include new biological products, herbal medicines, traditional Chinese, Ayurvedic and homeopathic medicines. Effective networking between the pharmacopoeias would enable them to harmonise the development of pharmaceutical texts. The conference suggested the development of a guideline on 'Good Pharmacopoeial Practices' (GPhP). An initial drafting group was formed composed of Argentina, Brazil, the *European Pharmacopoeia*, India, Japan, Mexico, the Russian Federation, Ukraine and the *United States Pharmacopoeia*, with editorial help being provided by the United Kingdom. This guideline would be developed under the auspices of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

The Second International Meeting of World Pharmacopoeias was held in New Delhi, India on 18–19 April 2013, co-hosted by the Indian Pharmacopoeia Commission and the WHO. A WHO concept paper on Good Pharmacopoeial Practices was discussed and circulated for comments in May 2013. Pharmacopoeial standards developed via GPhP would ensure that analytical tests were adequately validated and suitable reference standards provided to support them. Such standards could enable work-sharing between pharmacopoeias and mutual acceptance of monographs.

Bilateral Harmonisation and Co-operation Agreements

USP

There has been close cooperation between the BP and the USP Committee of Revision almost since the first edition of the BP in 1864. In the early days the two organisations exchanged copies of new editions and exchanged ideas on matters of mutual interest. In 1927 Professor Fullerton Cooke, the chairman of the Committee of Revision of the USP, gave evidence to the MacMillan Sub-committee which considered the organisation and operation of the *British Pharmacopoeia*, suggesting the USP might serve as a model for the BP. When

the BP Commission was established in 1928 it again established a close working relationship with the USP, and this has continued to this day with a mutual programme of visits of senior staff, exchange of ideas and information on new monographs and tests.

The programme of harmonisation of pharmacopoeial monographs for excipients and general tests in the PDG has been limited, as the Ph. Eur includes very few monographs for specific dosage forms – and these are only for some biological products. The BP has been able in its programme of bilateral harmonisation to start work on a pilot programme for some specific product dosage forms. Arguably this programme of bilateral cooperation and harmonisation could be even more important than the PDG programme, as patients don't take drug substances or excipients, they take specific medicinal products. Following an informal harmonisation process between USP and the BP, and with the co-operation of the manufacturer and simultaneous submissions of data to both the BP and the USP, the new monographs for the glaucoma products Dorzolamide Eye Drops and Dorzolamide and Timolol Eye Drops were evaluated and published in the 2013 edition of the BP. The analytical methods in these monographs are harmonised for the two *Pharmacopoeias,* thus lessening the regulatory burden for manufacturers.

Chinese Pharmacopoeia

The BP Commission is continuing its collaboration with the *Chinese Pharmacopoeia* on the development of monographs for Traditional Chinese Herbal Medicines and mutually agreed projects.

State Pharmacopoeia of Ukraine

Following the signing of a Collaboration Agreement in May 2013, reference to the *British Pharmacopoeia* monographs will be made in the *State Pharmacopoeia of Ukraine*.

World Health Organization

Following the signing of a Collaboration Agreement in October 2011, the BP Commission is continuing to exchange information with the WHO relating to the *International Pharmacopoeia* and to collaborate on the development of monographs for formulated preparations.

PART III:
Change and Continuity

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Chapter 7
Changes in Therapeutics 1864–2014

Life is short, the art is long, occasion suddain, experience dangerous, judgement difficult.

(Hippocrates)[1]

Many of the early chemical drugs such as the alkaloids were isolated and purified from their plant sources. Towards the end of the nineteenth century other organic synthetic chemical drugs started to be developed. Hoechst introduced the analgesics phenazone and amidopyrine in 1888. In 1887 Bayer introduced the analgesic phenacetin. Large scale manufacture of drug products started in the nineteenth century in Britain, for example when Luke Howard manufactured mercurial preparations and quinine products.[2] The chemotherapeutic revolution began in Germany at the end of the nineteenth century when Paul Ehrlich started screening organic compounds for activity against the *Treponema* infections which caused syphilis, testing them in animal models and then evaluating them in clinical trials. His work led to the discovery of Salvarsan and other organoarsenical drugs. Drug research and development in Britain started at a similar time with the establishment of Burroughs Wellcome, which sold a wide range of medicinal products, particularly early tablet products under its Tabloid brand. During the inter-war years a number of the major continental and American pharmaceutical companies developed and launched new drug products. World War II provided a huge impetus to the development of antibiotic products to treat the wounds and infections in the casualties of war. During the war the Allied countries were unable to import drugs formerly made in Germany so that British chemical manufacturers started to make what were essentially generic versions of these products. Some of these had to be tested clinically to assess their equivalence to the originator products. After the war other pharmaceutical companies such as Imperial Chemical Industries (now AstraZeneca), started programmes of drug development. The National Health Service (NHS) started in Britain on 5 July 1948 and made medicines available to all for the first time. This created a very large new market for the new medicines

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[1] The Aphorisms of Hippocrates, Aphorism 1 in *The Aphorisms of Hippocrates Prince of Physicians*, anonymous translator, 1655. London: Printed for Humphrey Mosely at the Princes Arms in St Paul's Church yard.

[2] 2005. Slinn, J. The development of the pharmaceutical industry in *Making Medicines, a brief history of pharmacy and pharmaceuticals.* Pharmaceutical Press.

which were being developed. Aneurin Bevan, the architect of the NHS and the minister of health in the post-war Labour government, complained about 'the cascades of medicines pouring down British throats – and they are not even bringing the bottles back'.[3] The drugs bill under pressure from the huge new demand for medicines had spiralled in two years from £13 million to £41 million.[4] For comparison, in 2013, 1.0 billion NHS prescription items were dispensed in England outside hospitals at a cost of £8.6 billion.[5]

Textbooks of pharmacology usually list drugs with their pharmacokinetic properties, the main targets in the body for their pharmacological activities and the clinical indications for which they are included. They give information on the route of administration. They often imply simplistically that the safety and efficacy of any drug is mainly related to its intrinsic properties. Medical students are taught about the drugs they will prescribe for patients – but patients don't take drugs, they take medicinal products. The efficacy and safety of a drug is inextricably linked to its quality and the way in which the drug is delivered to the body from the particular pharmaceutical dosage form. This chapter will give some details of the discovery and development of some of the key drugs, their introduction into the pharmacopoeia, and how the quality of the drugs and their dosage forms relate to their safety and efficacy in daily use.

Drugs and their preparations are included in the *British Pharmacopoeia* (BP) on the basis of their wide use by prescribers in general practice or in hospitals. The review of the contents of the BP is carried out by the Secretariat to the BP Commission using the NHS Prescription Cost Analyses which are published by the Health and Social Care Information Centre. Figure 7.1 gives the current top 20 drugs ranked in order of the numbers of prescription items dispensed in the community in 2013. This chapter includes details of the discovery of some of these classes of drugs and the chronology of the inclusion of some of their monographs in the pharmacopoeia.

However before dealing with the modern drugs it is useful to review how monographs for some of the drugs included in the early editions of the BP have evolved. The active constituents of many of the herbal drugs were identified and isolated in the nineteenth century, and it is interesting to note how these herbal drugs of potentially variable composition sometimes continued to be widely prescribed by ultra-conservative physicians for many decades alongside their better defined and specified active principles. The

[3] Kynaston, D., 2007. Jolly Good as a Whole, 39. In *Austerity Britain 1948–51, Smoke in the Valley*. London: Bloomsbury Publishing.

[4] Anderson, S., 2006. From Bespoke to 'Off-the-Peg'. In *From Physick to Pharmacology*, edited by Louise Curth. Aldershot: Ashgate.

[5] 2014. Prescription Cost Analysis, England 2013 [NS], *Health and Social Security Information Centre*, April 3. http://www.hsic.gov.uk/catalogue/PUB13887 (accessed July 2014).

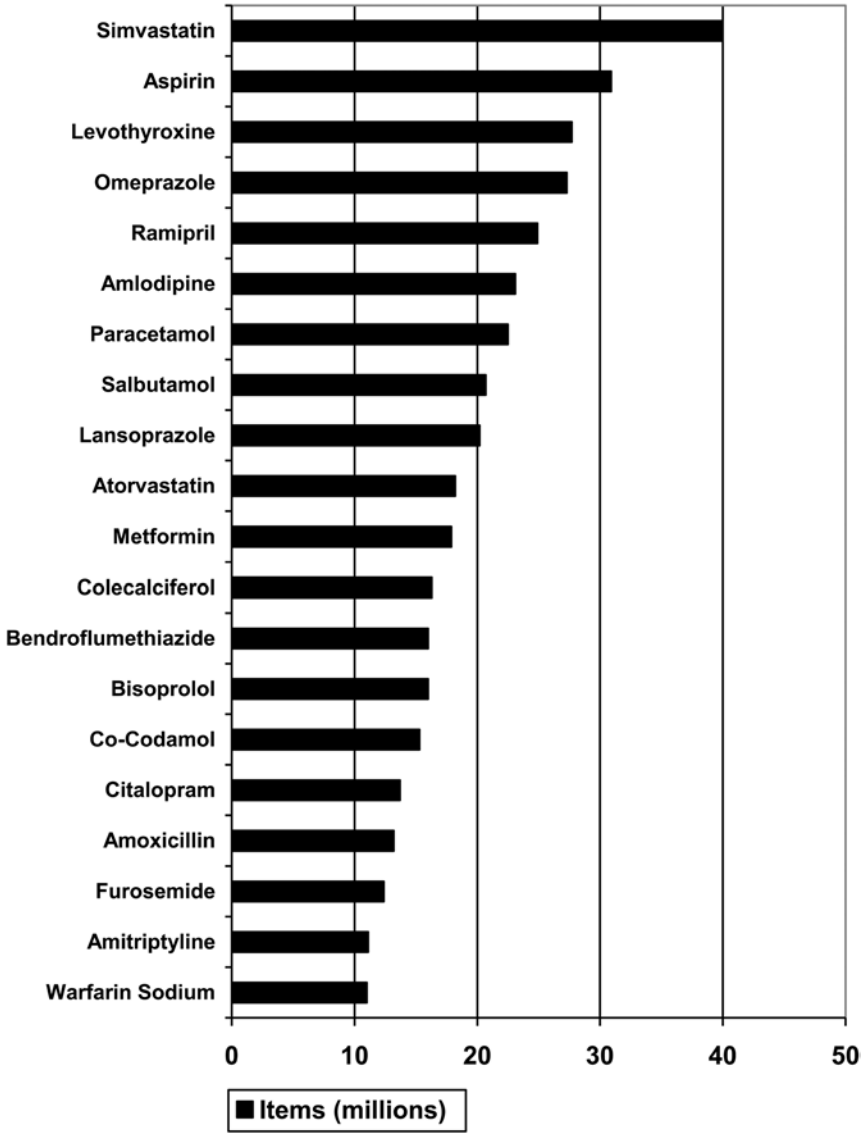

Figure 7.1 Prescription cost analysis: England 2013 (top 20 chemicals by items)

Source:

BP Commission was therefore obliged to continue to provide monographs for these herbal drugs and their products. Opium, for example, is still used nearly 200 years after the isolation and identification of morphine. Cinchona preparations continued to be used for 160 years after the discovery of quinine as the active principle. However, sometimes the opposite is true. Dioscorides described the use of seeds of Colchicum for treatment of gout in *De Materia Medica* in AD 70.[6] Both Colchicum corm and seeds were included in the 1836 *London Pharmacopoeia* and then in the 1864 BP. Although colchicine alkaloid was isolated from Colchicum seeds in 1820 by Caventou and Pelletier, it was not until the 1948 BP that Colchicina (colchicine alkaloid) was included for the first time as a separate monograph. Colchicine is still sometimes used for treatment of gout refractory to other treatments.

As mentioned in Chapter 1, some of the drugs used in ancient Egypt included linseed (*Linum usitassimum*), coriander (*Coriandrum sativum*), anise (*Anethum graveolens*), *Styrax benzoin*, *Citrullus colocynthus*, garlic (*Allium sativum*) and honey. All of these are included in the current 2014 BP.

Opium and its Alkaloids

Opium had been used in Greek and Arab medicine from the earliest times. Dioscorides mentions it in *De Materia Medica*. Paracelsus reintroduced it into Europe as Laudanum, which was a composition of opium in alcohol or wine. Opium is obtained from the opium poppy (*Papaver somniferum*), which is widely cultivated in Asia, Iran, Turkey and now in Afghanistan. After the poppy has bloomed, the unripe seed capsules are incised, and the milky fluid which forms is removed and dried. This is compressed into the cakes of raw opium. The 1618 *London Pharmacopoeia* included both Laudanum and Pilulae de Cynoglosso (hound's tooth pills), which also contained opium. Thomas Sydenham (1624–1689), the famous English physician, simplified Paracelsus's Laudanum composition by making it a mixture of opium and alcohol – this was included in the 1864 BP as Tincture of Opium. Until its use was controlled, Laudanum was widely abused as it could be readily purchased. The writer and commentator William Cobbett (1763–1835) in the notes to volume II of his 1830 book *Rural Rides*[7] commented that women working in the nineteenth-century manufacturers often had to farm out their children to older women who kept them quiet by feeding them doses of 'Godfrey's cordial', 'mother's quietness',

[6] Beck, L., 2005. *De Materia Medica, Pedanius Dioscorides of Anazarbus*, translated by Lily Beck. Hildesheim and New York: Olms-Weidmann.

[7] Cobbett, W., 1853. Notes to Volume II, 30 It is a great error etc. in *Rural Rides*, Dent's Double Volumes 1934 edition. London: J.M. Dent & Sons Ltd.

'infant's cordial', or 'soothing syrup'. Godfrey's cordial contained '1½ ounces of pure laudanum to the quart'. The 1864 BP also contained Opium Plaster, Opium Extract, Opium Liniment, Opium Pills, Lead and Opium Pills, Ipecacuanha and Opium Powder, Aromatic Powder of Chalk and Opium, Powder of Kino and Opium, Tincture of Opium, Camphorated Tincture of Opium, Opium Wine and Ointment of Galls and Opium. Ipecacuanha and Opium Powder was also called 'Dover's Powder' after its inventor Thomas Dover, a physician and sea captain, who included the recipe in his book *The Ancient Physician's Legacy to His Country* first published in 1732.

In 1806 the young pharmacy apprentice Friedrich Wilhelm Sertürner (1783–1841), working in Paderborn in Westphalia, Germany isolated a chemical from opium which, when administered to dogs, caused a profound sleep.[8] He called the drug 'morpheum' after Morpheus the Greek god of dreams. The drug was later renamed morphine. The 1864 BP included details of the extraction of morphine from opium and a monograph for Morphine Hydrochloras (hydrochloride). This edition also included Solution of Morphine, Morphine Lozenges, and Morphine and Ipecacuanha Lozenges. Morphine is an effective painkiller by mouth, but it was also given by injection. Alexander Wood (1817–1884), who was the secretary to the Royal College of Physicians in Edinburgh, is given credit for inventing the hypodermic syringe with its hollow needle in 1853. It was first used to inject morphine.[9] The 1867 BP included Hypodermic Injection of Morphine. The injection was made by dissolving morphine hydrochloride in water, then adding ammonia to precipitate morphine base. This was filtered and washed and allowed to drain. Acetic acid was then used to dissolve the morphine base. The product was then filtered and preserved in a stoppered bottle. The 1898 BP contains a different formulation, with Morphine Tartrate dissolved in recently boiled cooled water. It is only in the 1932 BP that the first mention is made of the need for a process of sterilisation of the injection solution or the container. The monograph for Morphine Tartrate stated that the injection is sterilised either by Tyndallisation – heating for one hour at 80°C for three successive days, or by filtration using a sterile bacteria-proof filter and then filling into sterilised glass containers. It is only in this edition that a sterility test was introduced with a test for both aerobic and anaerobic microorganisms. The 1948 BP had a monograph for Morphine Sulphate Injection. Tyndallisation as a process of sterilisation had by then been discredited and the monograph stated that the product was to be sterilised either by heating with a bactericide or by filtration. The 1953 BP

[8] Raviña, E., 2011. Antiquity, 11–12. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

[9] Wood, A., 1858. Treatment of Neuralgic Pain by Narcotic Injections. *Br. Med. J*. 28 August 1(87): 721–3.

includes 0.1 per cent sodium metabisulphite as an antioxidant to improve the stability of the morphine.

Poppy Capsules were also official in the 1864 edition – the nearly ripe capsules of the white poppy *Papaver somniferum*, dried and without its seeds. This was cultivated in Britain but only contained a small amount of morphine. Decoction of Poppies – an aqueous extract – and Syrup of Poppies were both official. As we saw in Chapter 2, Syrup of Poppies was the eighth most commonly prescribed pharmaceutical product in 1895. Opium and Tincture of Opium still remain official in the 2014 BP as medicinal substances. Two preparations are still official – Opiate Squill Linctus and Paediatric Opiate Squill Linctus. Opiate Squill Linctus is a cough remedy which is more commonly known as Gee's Linctus. It was devised by Samuel Gee (1839–1911) who was a physician at St Bartholomew's Hospital. A number of morphine preparations are official in the 2014 BP: Kaolin and Morphine Mixture – used for treating diarrhoea, Morphine Suppositories, Morphine Tablets, Prolonged-release Morphine Tablets, Morphine Sulfate Injection, and Morphine and Atropine Injection.

Codeine is another alkaloid present in opium. It was extracted in 1832 by the French pharmacist Professor Pierre-Jean Robiquet at the École de Pharmacie in Paris.[10] It is less effective as an analgesic than morphine but is also less prone to abuse. One of its other main uses is as an antitussive – cough suppressant. Codeine is the methyl ether of morphine and is now manufactured by methylation of morphine. It was first included in the 1885 BP. The 1898 BP included both Codeine and Codeine Phosphate. It was not until the 1948 BP that preparations of codeine were included – Tablets of Codeine Phosphate and Compound Tablets of Codeine – which contained Aspirin, Phenacetin and Codeine Phosphate. Soluble Compound Codeine Tablets first appear in the 1963 BP. The 2014 BP now includes Codeine, Codeine Hydrochloride, and Codeine Phosphate as drug substances; Codeine Linctus, Paediatric Codeine Linctus, Codeine Phosphate Injection, Codeine Phosphate Oral Solution, Codeine Phosphate Tablets, Paracetamol, Codeine Phosphate and Caffeine Capsules, and Paracetamol, Codeine and Caffeine Tablets as preparations. In England in 2013, Co-Codamol – a combination of Codeine Phosphate and Paracetamol – was the fifteenth most commonly prescribed product in the community.

Diamorphine or heroin was first synthesised in 1874 by Charles Alder Wright a chemistry and physics teacher at St Mary's Hospital Medical School – it is diacetylmorphine. It was developed and tested in 1888 by Heinrich Dreser a chemist working at Bayer. It was initially developed as a cough suppressant and a substitute for morphine that could be used to treat morphine addiction.

[10] Robiquet, P.J., 1832. Nouvelles observations sur les principaux produits de l'opium. *Annales de chimie et de physique* 51: 225–67.

However reports soon appeared of its addictive properties. It was banned in the United States in 1924 but has continued to be available in Britain as a prescription drug for the treatment of severe pain. The injection is mentioned in the 1932 BP. The monograph for the drug substance was deleted from the 1953 BP, but reinstated in the 1963 BP. This edition also included a monograph for Diamorphine Injection. The 2014 BP still includes both monographs.

Cannabis Indica or Marijuana

Cannabis or Marijuana is another drug that was used as a medicine in antiquity.[11] It was included in the 1864 BP as *Cannabis Indica* – Indian Hemp. It seems to have been used as a hypnotic. Two preparations are included in the 1864 BP – Extract of Cannabis and Tincture of Cannabis. It was included in subsequent pharmacopoeias but then omitted from the 1932 BP. Cannabis is the most widely used illegal drug in Britain, it is classified as Class B under the Misuse of Drugs Act 1971 – this means that it is illegal to possess, supply or produce this drug. The maximum penalty for supply and production is up to 14 years in prison, an unlimited fine or both.

Sativex, an oromucosal spray produced by G.W. Pharma Ltd. has now been approved in many European countries for treatment of spasticity in adults due to multiple sclerosis. Sativex is a solution of extracts from Cannabis which contains delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Trials are ongoing to extend its use to relief of cancer pain and neuropathy (neurological pain). Cannabis or its constituent cannabinoids are not official in the current BP.

Cinchona and Quinine

The 1677 *London Pharmacopoeia* introduced Peruvian bark for the treatment of fever. Jesuit priests in Peru in the sixteenth century had observed the local population using the bark of the cinchona tree to reduce the shaking caused by severe chills. In 1630 Juan Lopez de Canizares, the Spanish corregidor of Loxa in Ecuador – then part of Peru – was taken ill with an intermittent fever and this was cured by the local Indians who told him about the bark and how to administer it.[12] The Jesuits sent supplies of the bark to Spain. In 1639 a Jesuit priest, subsequently a cardinal, took the bark back to Rome. From Italy it reached

[11] Grant, B., 2012. Medical Marijuana: Smoke, Fire and Science. *The Scientist* July 2012: 36–7.

[12] Packard, R.M., 2007. *The Making of a Tropical Disease*. Baltimore: Johns Hopkins University Press.

the Netherlands and England. The English apothecary Robert Talbor used it to cure King Charles II.[13, 14] Talbor was then sent by the King to France to cure the Dauphin of an ague. It was taken up by Thomas Sydenham (1624–1689) and became a fashionable Society remedy. The technique used by Sertürner for production of morphine was then applied by other chemists to a variety of herbal drugs to produce what were originally called 'alkalies' – what we now call alkaloids. In 1820 the French chemists Pierre-Joseph Pelletier (1788–1842) and Joseph Bienaimé Caventou (1795–1877) isolated quinine,[15] and in 1826 they produced 1800 kg of quinine sulphate from 150 tons of cinchona bark. The 1836 *London Pharmacopoeia* included Disulphate of Quina in the section of 'Alkalies'. The 1864 BP included *Cinchona Flava* – Yellow Cinchona Bark, *Cinchona Pallida* – Pale Cinchona Bark, *Cinchona Rubra* – Red Cinchona Bark, and Sulphate of Quinia. The 1864 BP also included a Decoction of Yellow Cinchona – an aqueous extract, a Liquid Extract of Yellow Cinchona, and a Tincture of Yellow Cinchona – an alcoholic extract. The 1885 BP contained both Quinine Sulphate and Quinine Hydrochloride salts. One of the therapeutic indications was for the treatment of ague – a malarial fever, but it was also used in lower doses as a tonic. Commercial tonic waters containing quinine were first produced in 1863 and are still being manufactured today as 'mixers' with gin. Three quinine preparations were listed in the 1885 BP – Ferri et Quininae Citras, Tinctura Quininae Ammoniata and Vinum Quininae – Quinine Wine. Malaria is a mosquito-transmitted disease caused by the parasite *Plasmodium*. Malaria was a major source of sickness and death along the coasts and estuaries in England from the seventeenth century onwards. Quinine remained a major drug for treatment of malaria until the 1940s when it was largely replaced by chloroquine. However as chloroquine-resistant strains of *Plasmodium falciparum* – the most common cause of malaria – have emerged, it has come into use again as a treatment. Quinine Wine or Orange Quinine Wine remained a popular and widely advertised treatment for influenza until well into the 1930s. An advertisement in *The Western Times* newspaper of 15 January 1937 by the Devon and Somerset Stores Ltd in Exeter[16] stated 'Influenza! The best Preventative: Orange Quinine Wine. Prepared in strict accordance with the requirements of the British Pharmacopoeia'. Cinchona was included in the 1932 BP but was omitted from the 1948 edition. The 2014 BP includes three quinine

[13] Keeble, T.W., 1997. A Cure for the Ague: The Contribution of Roger Talbor (1642–81). *J Royal Soc. Med.* 90: 285–90.

[14] Siegel, R.E. and Poynter, F.N.L., 1962. Robert Talbor, Charles II, and Cinchona – A Contemporary Document. *Med. Hist.* 6(1): 82–5.

[15] Raviña, E., 2011. Plant Sources: Derivatives and Related Drugs, 126–9. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

[16] 1937. Advertisement for Orange Quinine Wine from Devon and Somerset Stores Ltd., Exeter. *The Western Times* 11 January.

salts – Quinine Bisulfate, Quinine Dihydrochloride and Quinine Sulfate. Three preparations are listed – Quinine Bisulfate Tablets, Quinine Sulfate Tablets and Quinine Dihydrochloride Infusion. The monographs for the official quinine tablets all now include a rotating basket dissolution test to help control their bioavailability – until the 1970s these tablets were all sugar coated. Because of the high water solubility of the drug the tablet cores needed a protective coating of shellac before the layers of sugar syrup coating were applied. The shellac layer varied in thickness, and it toughened as it aged, thus making the dissolution of batches of the tablets variable and often extended.

Iron Salts

In 1681 Thomas Sydenham used pills containing iron filings, and then wine to treat chlorosis – iron-deficiency anaemia. In 1832 the French physician Pierre Blaud (1774–1858) introduced his pill containing ferrous sulphate and potassium carbonate called 'Blaud's pills'. A modification of his formula was included in the 1864 BP as Pills of Carbonate of Iron. A number of other iron salts were also included in that edition: Citrate of Iron and Ammonia, Citrate of Iron and Quinia, Iodide or Iron, Magnetic Oxide of Iron, Solution of Perchloride of Iron, Solution of Pernitrate of Iron, Peroxide of Iron, Hydrated Peroxide of Iron, Phosphate of Iron, Sulphate of Iron, Reduced Iron and Tartrated Iron. Some of these would have been made into pills by dispensing pharmacists. The 1883 edition of Martindale and Westcott's *Extra Pharmacopoeia*[17] lists Pilulae Ferri Hypophosphitis cum Strychni, Pilulae Ferri Iodi, Pilulae Ferri, Quiniae et Strychniae Phosph. and Pilulae Ferri Redacti. The 1885 BP contains an Aromatic Mixture of Iron – made with iron wire, Compound Mixture of Iron, Pill of Carbonate of Iron, and Pill of Iodide of Iron. The 1898 BP omits the Iron Iodide and Iron Carbonate pills and only included an Iron Pill made with Ferrous Sulphate. Ferrous Sulphate Tablets do not appear in the BP until the 1953 BP as Tablets of Exsiccated Ferrous Sulphate, which contained 200 mg of ferrous sulphate as a sugar-coated tablet. The 2014 BP now contains three iron salts: Ferrous Fumarate, Ferrous Gluconate and Ferrous Sulphate. It includes the following preparations: Ferrous Fumarate Capsules, Ferrous Fumarate Oral Suspension, Ferrous Fumarate Tablets, Ferrous Fumarate and Folic Acid Tablets, Ferrous Gluconate Tablets, Paediatric Ferrous Sulphate Oral Solution, Ferrous Sulphate Tablets and Prolonged-release Ferrous Sulphate Tablets.

[17] Martindale, W. and Westcott, W.W., 1883. *The Extra Pharmacopoeia of Unofffficial Drugs and Chemical and Pharmaceutical Preparations*. London: H.K. Lewis.

Salicin and Aspirin

Infusions of the bark and leaves of the willow tree – the genus *Salix* – were used for hundreds of years to relieve pain and fever. They are mentioned in Egyptian papyri and Hippocrates described their use in 400 BC. Salix was included in the *London Pharmacopoeia* of 1618. In 1763 the Reverend Edward Stone wrote to the Earl of Macclesfield, the Lord President of the Royal Society, on the use of dried, powdered willow bark in the treatment of agues (fevers). His letter was printed in *Philosophical Transactions*[18] and is one of the first accounts of a clinical trial. He stated: 'I have continued to use it as a remedy for agues and intermitting disorders for five years successively and successfully. It hath been given I believe to fifty persons, and has never failed in the cure.' In 1826 Joseph Buchner isolated crystals of salicin (salicylic acid). The use of salicylate medicines increased but their use was limited by their gastric irritation side effect. In 1853 Charles Gerhardt prepared acetylsalicylic acid by mixing acetyl chloride with sodium salicylate.[19] Other chemists repeated Gerhardt's work and produced impure acetylsalicylic acid. In 1894 the young chemist Felix Hoffman joined the pharmaceutical group at the German company Friedrich Bayer and Company. In 1897 Hoffman found a better way to synthesise acetylsalicylic acid from salicylic acid by refluxing with acetic anhydride. Bayer named the drug 'aspirin'. Instead of providing the drug substance to pharmacists to make into pills Bayer manufactured and sold their own compressed tablets of aspirin. Acetylsalicylic Acid first appeared in the 1914 BP as a medicinal substance and has been in every edition since then. The 1945 *Addendum* to the 1932 BP included the first monograph for Acetylsalicylic Acid Tablets. The 1948 BP included monographs for Tablets of Acetylsalicylic Acid with Ipecacuanha and Opium – Aspirin and Dover's Powder, Tablets of Acetylsalicylic Acid and Phenacetin, and Compound Tablets of Codeine – containing Acetylsalicylic Acid, Phenacetin and Codeine Phosphate.

The 2014 BP contains monographs for Aspirin Tablets, Dispersible Aspirin Tablets, Effervescent Soluble Aspirin Tablets, Gastro-resistant Aspirin Tablets and Aspirin and Caffeine Tablets. Aspirin is now known to work by affecting the production of prostaglandins which are responsible for pain and fever.[20] Aspirin is also now recommended because of its effect on blood platelet aggregation

[18] Stone, W., 1763. An Account of the Success of the Bark of the Willow in the Cure of Agues. In a Letter to the Right Honourable George Earl of Macclesfield, President of the R.S. from the Rev. Edmund Stone, of Chipping-Norton in Oxfordshire. *Philosophical Transactions* 53(1763): 195–200.

[19] Gerhardt, T., 1853. Recherches sur les acides organiques anhydrides. *Annales de chimie et de physique* 37: 285–342.

[20] Jefferys, D., 2005. *Aspirin: The Remarkable Story of a Wonder Drug*, 226–33. New York: Bloomsbury Publishing.

which reduces the risk of thrombosis in patients with cardiovascular disease and following by-pass surgery. Aspirin was the second most frequently prescribed drug in the community in England in 2013 with 30.9 million items.

Smallpox Vaccine

Smallpox is one of the earliest pathogenic diseases to afflict Europe. The plague of Antonine during the reign of Marcus Aurelius from 165 AD is reported to have accounted for the deaths of almost seven million people. It affected all sectors of society and even if those affected did not die they were often left with disfiguring scars. In the eighteenth century the practice of variolation was introduced – inoculating non-immune individuals with fresh matter taken from a ripe smallpox pustule. The main English advocate for this practice was Lady Mary Wortley Montague, and she persuaded the Royal Court to use it for the royal family. However a small number of those inoculated died of the disease or from another disease caused by using contaminated pustules.

Edward Jenner was born in May 1749 in Berkeley, Gloucestershire.[21] He was the son of the vicar of Berkeley. When he was 13 he was apprenticed to the country surgeon Mr Ludlow of Sodbury. In 1764 he was apprenticed to George Hardwicke. After completing his apprenticeship at the age of 21 he became a student of the surgeon John Hunter at St George's Hospital in London. In 1773 he returned to Gloucestershire to practice medicine.

It was during his apprenticeship with Mr Ludlow that he heard stories of the protective effect of smallpox in dairymaids who had contracted cowpox – a much milder disease. In 1796 having heard about cowpox amongst the milkers at a farm near Berkeley he took some of the fluid from a vesicle on the hand of the milkmaid Sarah Nelmes. On 14 May he inoculated an eight-year-old boy, James Phipps. On 2 July he inoculated the boy with smallpox to demonstrate that the cowpoxing had made him resistant to the disease. In 1797 Jenner sent a communication on his experiment to the Royal Society, but his paper was rejected. He continued to add some more cases and in July 1798 published a booklet entitled *An inquiry into the causes and effects of the variolae vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire and known by the name of Cow Pox*.[22] His ideas met with mixed reaction, but others began to try vaccination with cowpox. Dr William

[21] Creighton, C., 1889. *Jenner and Vaccination: A Strange Chapter of Medical History*. London: Swan Sonnenschein and Co.

[22] Jenner, E., 1798. *An inquiry into the causes and effects of the variolae vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of cow pox*. London.

Woodville who was the physician to the Smallpox and Inoculation Hospitals in London was one of the most practised inoculators and both he and Jenner supplied lymph to others. Jenner received honour and public recognition for his work, and was awarded two separate grants by parliament as a reward.

The vaccination of all children within three months of birth was made compulsory under the 1853 Vaccination Act. The 1867 Vaccination Act made Poor-Law guardians responsible for control of vaccination. Vaccinators were paid one to three shillings per child vaccinated in a district. The 1873 Act made vaccination compulsory.

The first official monograph for Vaccinum Vacciniae, Vaccine Lymph was in the 1932 BP, over 130 years after the publication of the first edition of Jenner's booklet. The monograph described it as the substance which was obtained from the vesicles produced by the inoculation of vaccinia virus on the skin of healthy animals. The lymph was treated with glycerol to reduce the numbers of living bacteria. It was tested to ensure the absence of gas-producing anaerobic microorganisms and of haemolytic streptococci. The monograph included a potency test on the skin of rabbits where a solution had to produce the characteristic vesicles. In the 1948 BP monograph additional tests for the absence of *Bacillus anthracis*, *Bacterium coli*, *Clostridium tetani* and beta-haemolytic streptococci were added. By the 1953 BP preparation of Smallpox Vaccine was also allowed using membranes of the chick embryo inoculated with the vaccinia virus. The 1963 BP allowed dried Smallpox Vaccine to be produced by centrifuging and then drying from the frozen state. In 1967 the World Health Organization began a global campaign to eliminate the disease. On 8 May 1980 the World Health Assembly announced that the world was free from smallpox and recommended that all countries cease vaccination programmes. Although the *European Pharmacopoeia* monograph remained official for some time, Smallpox Vaccine was omitted from the 1993 BP.

Colecalciferol

Hippocrates mentioned the use of fish oils in medicine. In the eighteenth century cod liver oil was used both internally and externally for the treatment of rheumatism. The 1864 BP includes Oleum Morrhuae (Cod Liver Oil). The BP has included monographs for Cod Liver Oil ever since the first edition.

Rickets is a disease of childhood shown as bow legs – a deformity of the long bones in the legs as the child begins to walk caused by soft weak bones. The British physician Edward Mellanby was born in 1884 in West Hartlepool.[23]

[23] Rajakumar, K., 2003. Vitamin D, Cod-Liver Oil, Sunlight and Rickets: A Historical Perspective. *Pediatrics* 112(2): 132–5.

He studied medicine at St Thomas's Hospital in London. He lectured at King's College for Women. He began researching the causes for rickets in 1914. Mellanby fed a group of dogs a diet of porridge and also kept them indoors. The dogs developed rickets, which Mellanby was able to treat by adding cod liver oil to their diet. He concluded that a component of cod liver oil prevented rickets. In 1922 the American biochemist Elmer McCollum tested degraded cod liver oil in which the vitamin A had been destroyed. He found that the degraded oil was still able to cure rickets in dogs. He named the active component vitamin D.

The 1932 BP monograph for Cod Liver Oil did not include any assay for Vitamin A or D. The preface to this edition stated that the British Pharmacopoeia Commission felt that the oil was sufficiently well characterised without the need for any assays as different lots of the commercial material contained sufficient for therapeutic purposes. However a biological assay for Antirachitic Vitamin – vitamin D – was included where the potency of vitamin D in the oil needed to be stated. The assay consisted of exposing a group of young rats to a diet designed to cause rickets. The degree of rickets was determined by X-rays and then the rats were divided into two groups, one receiving a Standard Preparation and the other the test product. After 10 to 14 days the rats were killed and the bones compared to assess the degree of healing of the rickets in the two groups. By the time of the 1948 BP opinions had clearly changed about the need to characterise cod liver oil, as the monograph now included assays for both Vitamin A and Vitamin D; it contained in 1 gram not less than 600 Units of vitamin A activity and not less than 85 Units of antirachitic activity – vitamin D.

As the author of this book can testify, after World War II children in austerity Britain were routinely fed spoonfuls of Cod Liver Oil and Malt 'to build you up'. The 1948 BP included a monograph for Extract of Malt with Cod Liver Oil. This contained 10 to 15 per cent of cod liver oil, the syrupy malt extract counteracting to some extent the unpleasant fishy taste of the oil. This product disappeared from commerce, but it has now been revived by Potter's Herbal in its original form and also now in butterscotch and honey flavours.

Several forms of vitamin D exist. The two major forms are vitamin D_2 or calciferol, and vitamin D_3 or colecalciferol – originally named cholecalciferol. The structure of vitamin D_2 was identified in 1932 and D_3 in 1936. Vitamin D_3 is produced naturally in the skin on exposure to sunlight from ultraviolet irradiation of the precursor 7-dehydrocholesterol. Vitamin D_2 is produced by irradiation of ergosterol.

The 1953 BP contained monographs for Concentrated Solution of Vitamin D and Concentrated Solution of Vitamins A and D. The Concentrated Solution of Vitamin D contained 10,000 Units of antirachitic activity – vitamin D in 1 gram. The assay used was the biological assay using young rats mentioned previously. A number of potential sources of vitamin D were mentioned as being suitable – Calciferol; from a fish-liver oil rich in vitamin D; from the

unsaponifiable matter of such oil; from a concentrate prepared by partial saponification, distillation or extraction of such an oil; or any other source found in fish livers. This edition also contained monographs for Calciferol – vitamin D_2, Solution of Calciferol containing 3000 Units of antirachitic activity per 1 gram, and Calciferol Tablets.

The 1977 *Addendum* to the 1973 BP included a new monograph for Cholecalciferol (vitamin D_3). The tests in the monograph were all physical or chemical, no biological assay was involved. The 1980 BP included a revised monograph with a limit test for 7-dehydrocholesterol which is an impurity arising from the use of this material in the manufacture. This edition also included a monograph for Ergocalciferol (vitamin D_2).

The 1993 BP included the *European Pharmacopoeia* monographs for Ergocalciferol, Cholecalciferol, Cholecalciferol Concentrate – Oily Form, Cholecalciferol Concentrate – Powder Form and Cholecalciferol Concentrate – Water Dispersible Form. A liquid chromatographic assay was now included in the Cholecalciferol monograph. The following product monographs were included: Calciferol Injection, Calciferol Oral Solution and Calciferol Tablets. Each product was allowed to contain either Cholecalciferol (vitamin D_3) or Ergocalciferol (vitamin D_2). In this edition the *European Pharmacopoeia* monograph for Cod Liver Oil had a liquid chromatographic assay for ergocalciferol and cholecalciferol.

The 2014 BP includes monographs for Colecalciferol, Colecalciferol Concentrate – Oily Form, Colecalciferol Concentrate – Powder Form, Colecalciferol Concentrate – Water-dispersible Form, and Ergocalciferol. There are monographs for the following preparations: Calcium and Colecalciferol Tablets, Chewable Calcium and Colecalciferol Tablets, Calcium and Ergocalciferol Tablets, Chewable Calcium and Ergocalciferol Tablets, Colecalciferol Injection, Colecalciferol Tablets, Ergocalciferol Injection, and Ergocalciferol Tablets.

In 2013 the Chief Medical Officer for England, Dame Sally Davies, issued a report entitled *Our Children Deserve Better: Prevention Pays*.[24] The report highlighted the growing problem of vitamin deficiency which was illustrated by the return of rickets caused by a lack of vitamin D. The report stated that 'Vitamin D deficiency has a prevalence of around 12% with as many as 40% of young children having levels below the accepted optimum threshold.'

Calcium and vitamin D is commonly prescribed for patients with osteoporosis and osteopenia to help prevent hip fractures. It is fair to say that there is considerable controversy about the possible wider role of vitamin D in healthcare outside the prevention of rickets, and research is still continuing.

[24] 2013. *Annual Report of the Chief Medical Officer 2012. Our Children Deserve Better: Prevention Pays*. Department of Health.

Colecalciferol is included in the 2013 top 20 list of the most widely prescribed drugs in the community in England.

The 2014 BP includes three monographs for cod liver oil: Cod Liver Oil Type A, Cod Liver, Cod Liver Oil Type B and Farmed Cod Liver Oil. Farmed cod liver oil has only an upper limit for vitamin D_3 content of 50 Units per gram; the other two types have between 60 and 250 Units per gram.

Glyceryl Trinitrate and Related Organic Nitrates

Ascanio Sobrero, a chemistry teacher at the University of Turin, was the first to synthesise glyceryl trinitrate or nitroglycerin.[25] He found that minute amounts of this drug caused violent headaches. In 1867 the Scottish surgeon Thomas Brunton investigated the use of amyl nitrate to relieve angina pectoris in his patients. However the effect was only short-lasting. In 1877 the physician William Murrell found that glyceryl trinitrate could replace amyl nitrate, the vasodilation effect was slower in onset but lasted longer. Tablets of Nitroglycerin were first included in the 1885 BP and consisted of one hundredth of a grain – 600 micrograms – of pure nitroglycerin in tablets of chocolate. These were the first and only official tablets in the BP until the 1940s.

The 2014 BP now includes Glyceryl Trinitrate Solution as the medicinal substance, and Glyceryl Trinitrate Ointment – for the management of pain associated with anal fissures, Glyceryl Trinitrate Sublingual Spray, Glyceryl Trinitrate Tablets and Glyceryl Trinitrate Transdermal Patches.

Longer acting vasodilators such as isosorbide mononitrate and pentaerythritol tetranitrate are also now available. The 2014 BP includes monographs for Diluted Isosorbide Dinitrate and Isosorbide Mononitrate as medicinal substances, Isosorbide Dinitrate Injection, Isosorbide Dinitrate Tablets, Isosorbide Dinitrate Sublingual Tablets, Prolonged-release Isosorbide Mononitrate Capsules, Isosorbide Mononitrate Tablets, and Prolonged-release Isosorbide Mononitrate Tablets.

The mechanism of action of the organic nitrates was elucidated in the 1970s. Ferid Murad from the University of Texas showed that nitric oxide (NO) was released from nitroglycerin.[26] Robert F. Furchgott at the State University of New York_had discovered endothelial-derived relaxing factor in 1978, a substance from endothelial cells which relaxes blood vessels.[27] By 1986 he identified that

[25] Marsh, N. and Marsh, A., 2000. A Short History of Nitroglycerine and Nitric Oxide in Pharmacology and Physiology. *Clinical and Experimental Pharmacology and Physiology* 27: 313–19.

[26] 1998. Ferid Murad: Nobel Prize. http://www.nobelprize.org/nobel_prize/medicine/laureates/1998/murad-bio.html (accessed July 2014).

[27] 1998. Robert Furchgott: Nobel Prize. http://www.nobelprize.org/medicine/laureates/1998/furchgott-autobio.html (accessed July 2014).

this factor was NO. He shared the Nobel Prize in 1998 with Louis Ignarro from the University of California School of Medicine[28] and Ferid Murad.

Salvarsan and the Arsphenamines

Paul Ehrlich, one of the founding fathers of modern medicine,[29] was born in Strehlen in Upper Silesia in Germany in 1854. He studied medicine at the Universities of Breslau, Strasbourg, Freiburg-im-Breisgau and Leipzig. He obtained his MD with a dissertation on the staining of animal tissues. In 1890 Robert Koch appointed Ehrlich as one of his assistants at the new Institute for Infectious Diseases in Berlin. The Institute moved to Frankfurt in 1898 with Ehrlich as its director. He started working on chemotherapy, looking for chemical compounds which might selectively bind to pathogenic microorganisms – what Ehrlich called 'magic bullets'. He started by screening the activity of hundreds of chemicals against *Trypanosoma* infections.

In 1909 he was joined by Sachahiro Hata who had developed a method to infect rabbits with the protozoal infection *Treponema pallidum,* which is the causative organism for syphilis. Amongst the drugs they evaluated was an arsenical compound which had already been tested for other purposes. This was the 606th compound investigated. It was found to be effective in animals and was then tested in clinical trials. This drug was arsphenamine whose trade name was Salvarsan. Arsphenamine base was insoluble and unstable and had to be marketed as the hydrochloride. This had to be neutralised before it was administered. A more stable salt was obtained in 1912 – neoarsphenamine. This was manufactured by Hoechst. Ehrlich was awarded the Nobel Prize in 1908. He died in August 1915. Part of Ehrlich's scientific legacy is that he had established a method of discovering new drugs by developing experimental animal models for testing new compounds, screening of a wide range of chemical compounds, then testing promising candidate compounds clinically in patients.

During World War I imported drugs from Germany were unavailable and Burroughs Wellcome was able to manufacture arsphenamine which it marketed as Kharsivan.[30] However there was dispute about the clinical safety and efficacy of the British product, and physicians were asked to keep accurate records of cases in which the new preparations were used to monitor efficacy and adverse reactions. The effect of the experience of drug synthesis and commercial manufacture of

[28] 1998. Louis Ignarro: Nobel Prize. http://www.nobelprize.org/medicine/laureates/1998/ignarro-facts.html (accessed July 2014).

[29] Bosch, F. and Rosich, L., 2008. The Contribution of Paul Ehrlich to Pharmacology: A Tribute on the Occasion of the Centenary of His Nobel Prize. *Pharmacology* 8(23): 171–9.

[30] Williams, K.J., 2009. The Introduction of 'Chemotherapy' using Arsphenamines – the First Magic Bullet. *J. Royal Soc. Med.* 102(8): 343–8.

synthetic substitutes for imported drugs was to stimulate the growth of the British pharmaceutical industry during World War I and afterwards.

Monographs for Neoarsphenamine and Sulpharsphenamine were included in the BP 1932. The products were both presented as a solid in a hermetically sealed glass phial. They were reconstituted for injection with Sterilised Water for Intravenous Injections. Neoarsphenamine and Sulpharsphenamine were controlled under the 1925 Therapeutic Substances Act, as although both were chemicals they were impure, and in the absence of suitable analytical control methods for impurities they needed biological tests for both the absence of undue toxicity and for therapeutic potency. The test for absence of undue toxicity involved two separate tests in mice and rats. The first involved injecting intravenously a group of 10 mice, if not more than two died in three days the sample passed. If more than two died the test was repeated in a second group of mice. If the number of deaths in both the first and second groups was not greater than eight, the sample passed. The test in rats involved injecting intravenously a group of five rats. If not more than one of the rats died within seven days the sample passed. The therapeutic potency test involved a series of mice or rats which were infected with *Trypanosoma equiperdum*. The sample was tested at different doses, each of which was administered to groups of five animals. The result was compared to the effects of a Standard Preparation of Neoarsphenamine or Sulpharsphenamine obtained from the National Institute for Medical Research then located in Hampstead, London. The blood of the animals was inspected microscopically for trypanosomes on the day after injection and each successive day for a week. The sample passed the test if it had a curative action not less than the Standard Preparation.

Both Neoarsphenamine and Sulpharsphenamine and their injections were omitted from the BP in 1958 as by then their use in treating syphilis had been superseded by penicillin preparations which were easier to use and less toxic.

Digitalis and Digoxin

William Withering was born at Wellington in Shropshire in 1741.[31] He was educated at home and then apprenticed to a local medical practitioner. In 1762 he went to study anatomy and chemistry at Edinburgh University. After graduating in 1766 he undertook a trip to Paris with a friend and then set up medical practice in Stafford. He was appointed to the new Stafford Infirmary as one of its first physicians. Medical practice in Stafford was not well-remunerated and in 1775 he was invited by Erasmus Darwin to move to work at

[31] Lee, M.R., 2001. William Withering (1741–1799): A Birmingham Lunatic. *Proc. R. Coll. Physicians Edinburg*. 31: 77–83.

the Birmingham General Hospital. Erasmus Darwin was a physician, inventor and poet. He was the grandfather of Charles Darwin and Francis Galton. He was also a member of the Lunar Society of Birmingham, which was founded in 1766. They were a group of eighteenth-century amateur experimenters who met monthly at the Monday night nearest to the full moon. Withering was invited to join the Lunar Society, which included Darwin, James Watt, John Baskerville and Matthew Boulton.[32] When Withering was first appointed to his post in Birmingham he drove back every week to see patients in Stafford. During one stop to change horses, he was asked to see an old woman with dropsy – the oedema and swelling of tissues in the body caused by heart or kidney failure. He found that she had recovered and she attributed this to an herb tea made to an old family recipe. He enquired about the constituents and concluded that the recovery was due to the presence of *Digitalis* in the tea. *Digitalis*, the foxglove, had been used for centuries and it had been mentioned by both Dioscorides and Galen in their books. Withering then started a scientific investigation into this herb in his Birmingham patients. He found that the powdered dried leaf was more effective than the root or the fresh leaf and was able to determine the effective dose. In 1785 he published his *An Account of the Foxglove*. Withering died in October 1799.

The 1864 BP included both the dried leaf of *Digitalis purpurea* and Digitalin, which it was claimed as the active constituent obtained from Digitalis. Digitalin is a complex mixture of the cardiac glycosides of Digitalis. Glycoside drugs contain a sugar molecule. Digitalin was included in the 1867 BP but then omitted from the 1885 BP. The 1914 BP included Digitalis Folia – Digitalis leaves.

Digitalis was one of the examples of a badly controlled drug which was quoted in evidence to the Committee of Civil Research Sub-committee – the MacMillan Sub-committee, which enquired into the *British Pharmacopoeia* in 1926. The new BP Commission established in 1928 set up a number of sub-committees to consider particular topics, one of which was the control of the herbal drugs *Digitalis* and *Strophanthus*. Sir Henry Dale, the director of the National Institute for Medical Research and a future Nobel Prize winner, was one of the members of this sub-committee, which reported in May 1931. In the 1932 BP the monograph for Powdered Digitalis was revised to include a biological assay as recommended by the sub-committee. The biological assay involved a comparison of its activity on cardiac muscle compared to a Standard Preparation of Digitalis. The Standard Preparation was a mixture of dried, powdered Digitalis leaves in sealed vials which could be obtained from the National Institute of Medical Research in Hampstead, London. Several animal models were official – involving use of frogs, guinea pigs or cats. Using frogs,

[32] Uglow, J., 2003. Plants and Passions. In *The Lunar Men. The Friends who made the Future*. London: Faber & Faber.

a dose was chosen to kill about half of a test group. Injections were then given into two groups of frogs, one with the Standard Preparation, the other with the sample. The potency was calculated using the percentage mortality of the two groups of frogs. For cats and guinea pigs, the groups of anaesthetised animals were injected into the vein with the Standard and sample until the heart stopped. Again the average lethal dose was calculated.

In 1930 Dr Sidney Smith from Burroughs Wellcome Laboratories isolated the glycoside digoxin from *Digitalis lanata* leaves.[33] The initial clinical studies with digoxin were carried out with a liquid formulation by Wayne. These studies, reported in 1933, showed that digoxin was well absorbed and that the average dose was 0.5 mg per day. Digoxin increased the force of contraction of heart muscle and improved the blood flow to the organs. It is a drug with a low safety margin – the ratio of effective dose to toxic dose.

Digoxin was added to the BP in 1941 in the fourth *Addendum* to the 1932 BP. The 1948 BP included a monograph for Prepared Digitalis – a standardised powder adjusted to contain 10 Units in 1 gram using the biological assay. It also included the monograph for Digoxin as a drug substance controlled by its Melting Point and Specific Rotation but without any assay. Monographs were also included for Tablets of Prepared Digitalis (assayed biologically) and Digoxin Tablets (assayed chemically) by producing a green colour by reaction with sulphuric acid and then a colorimetric assay. The 1953 and 1958 editions of the BP continued to include monographs for Digitalis Leaf, Prepared Digitalis, Digoxin, Digoxin Injection, Tablets of Prepared Digitalis, and Digoxin Tablets. In 1963 a monograph for Digitoxin a longer acting cardiac glycoside was also included, together with a monograph for Digitoxin Tablets. A new formulation for Digoxin Injection was included in the 1968 BP. The monograph for Digoxin Tablets in the 1973 BP was improved by the addition of a Content Uniformity Test – tablet to tablet variability in content of digoxin had been shown to be a problem because of the difficulties of mixing in the small amounts of digoxin into the excipients in the commercial 0.25 mg strength tablets. The new test ensured that the content of each tablet was between 80 and 120 per cent of the average, except that one tablet was allowed to be between 75 and 125 per cent of the average.

By the 1970s there were over 20 brands of digoxin 0.25 mg. About half the patients were being treated with Burroughs Wellcome's brand Lanoxin, which was the first digoxin tablet on the market. In 1969 the manufacturing process for Lanoxin tablets was changed and this led to a two-fold decrease in bioavailability. From 1970 to 1972 low digoxin plasma levels were reported and cardiologists

[33] Raviña, E., 2011. 4.1 Plant Sources – Derivatives and Related Drugs, 109–10. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

found that many patients were under-digitalised.[34, 35, 36] The differences were associated with differences in the rate of release of the digoxin into solution as measured by an *in vitro* dissolution test – what was then called a solution rate test. In 1972 Burroughs Wellcome changed the method of tablet manufacture back again to improve the bioavailability of Lanoxin tablets. In 1972 the Council of the Pharmaceutical Society after consulting the Committee on Safety of Medicines advised pharmacists not to dispense Lanoxin on 'open' prescriptions – ones where the brand was not specified. A number of investigations into the dissolution and bioavailability were then reported on Lanoxin and also other brands of digoxin. Chapter 8 discusses this issue in more detail. The 1980 BP included a dissolution test to help address the issue of varying bioavailability from the tablets.[37] However it still also included monographs for Prepared Digitalis Tablets and Digotoxin Tablets. The monograph for Digitoxin Tablets, which were less widely used, did not include a dissolution test. Digitalis Tablets were finally omitted from the BP in the 1993 edition – nearly 50 years after their introduction in the 1948 BP.

The 2014 BP includes monographs for Digoxin, Digoxin Tablets, Digoxin Injection, Paediatric Digoxin Injection and Paediatric Digoxin Oral Solution. It also includes monographs for Digitoxin and Digitoxin Tablets.

Thyroid and its Constituents

In 1873 the English physician Sir William Withey Gull, who was at that time the Resident Physician at Guy's Hospital, published a paper entitled 'On a cretinoid state supervening in adult life in women'. The paper described the symptoms and changed appearance of a Miss B who had a thyroid deficiency.[38] In 1888 W.M. Ord renamed this condition myxoedema – hypothyroidism. In 1891 the physician George Redmayne Murray evaluated the treatment of myxoedema with subcutaneous injections prepared from an extract of fresh

[34] Johnson, B.F., Fowle, A.S., Lader, S., Fox, J and Munro-Faure, A,D., 1973. Biological Availability of Digoxin from Lanoxin Produced in the United Kingdom. *Br. Med. J.* 4: 323–6.

[35] Shaw, T.D.R., Howard, M.R., and Hamer, J., 1974. Recent Changes in Biological Availability of Digoxin. Effect of an Alteration in 'Lanoxin' Tablets. *British Heart Journal* 36: 85–9.

[36] Shaw, T.D.R., 1974. The Digoxin Affair. *Postgrad. Med. J.* 50: 98–102.

[37] Shaw, T.D.R., Raymond, K., Howard, M.R and Hamer, J, 1973. Therapeutic Non-equivalence of Digoxin Tablets in the United Kingdom. Correlation with Tablet Dissolution Rate. *Br. Med. J.* 4: 763–6.

[38] Slater, S., 2011. The Discovery of Thyroid Replacement Therapy. Part 2. The Critical 19th Century. *J. Royal Soc. Med.* 104(2): 59–63.

sheep thyroid which he injected into a 46-year-old woman with myxoedema. After three months the patient was dramatically better. He followed up with further cases. Other physicians evaluated treatment with whole sheep thyroid or an oral thyroid extract, and this latter became the treatment route of choice. Dry Thyroid was first introduced as a medicinal substance in the 1898 BP. It was described as a powder prepared from fresh and healthy thyroid gland of the sheep. The healthy glands were minced and dried at a temperature of 32.2°C to 37.8°C. The fat was removed by treatment with petroleum spirit, and the powder was then dried. The specification in the monograph merely describes it as 'a light dull-brown powder, with a very faint meat-like odour and taste'. The clinical indication for the product was treatment of hypothyroidism. In December 1914 thyroxine, the principal hormone in thyroid, was isolated by the American chemist Edward Kendall working at the Mayo Clinic. Its structure was determined by Harington in 1926.

The 1932 BP included both Thyroid – Dry Thyroid, and Thyroxine Sodium. Thyroid by then could be prepared from oxen, sheep or pigs and had a specification of 0.1 per cent of iodine in combination as thyroxine and not more than 10 per cent of the content of total iodine. Curiously the 1948 BP omitted Thyroxine Sodium but retained Thyroid and Thyroid Tablets, again defined the Thyroid as containing 0.1 per cent thyroxine. This was presumably because thyroxine was much more expensive than Thyroid as it took 3 tons of pigs' thyroid to isolate just 33 grams of thyroxine.[39] A team of Glaxo chemists synthesised it in 1949. In the 1958 BP Thyroxine Sodium reappeared.

In 1952 a trace contaminant in thyroxine was identified by Gross and Pitt-Rivers as liothyronine. It was more potent than thyroxine and it was a metabolite of thyroxine. Liothyronine Sodium and Liothyronine Tablets were added in the 1960 *Addendum* to the 1958 BP. Until recently it was mainly used in the management of myxoedema coma, but has now been advocated for routine management of myxoedema.

The introduction to the 1963 BP stated that the use of thyroxine had by then become widely established. However Thyroid and Thyroid Tablets were still widely used by the more conservative physicians. The BP Commission expressed concern that the then current analytical methods were not always adequate to measure the activity of samples. The 1963 BP introduced an assay based on determination of total iodine in thyroid in combination with a limit test for inorganic iodide, but reservations were expressed about the adequacy of these tests. They were regarded as an interim measure whilst a biological assay was being developed. In 1978 11 physicians wrote a letter to the *British Medical Journal* stating that 'We continue to see patients who have been diagnosed as

[39] Slater, S., 2011. The Discovery of Thyroid Replacement Therapy. Part 3: A Complete Transformation. *J. Royal Soc. Med*. 104(3): 100–106.

having myxoedema and who are being treated with apparently adequate doses of thyroid extract but who are clinically and biochemically hypothyroid'.[40] They stated that 'we see no reason for the retention of thyroid extract, which we consider to be dangerous'.

Thyroid and Thyroid Tablets were omitted from the 1980 BP and each subsequent edition. Curiously, there is now an almost underground swell of opinion amongst patients who prefer 'natural' products to use Dried Thyroid Tablets, sometimes described as Natural Desiccated Thyroid and these are available on prescription but are not licensed in Britain. Some tablets are imported from the United States as 'Armour Thyroid'.

In 2011 the Medicines and Healthcare Products Regulatory Agency (MHRA) started a review on the bioavailability and dissolution of levothyroxine. During the preceding five years there had been an increase in the number of reports from healthcare professionals of inconsistency in the efficacy of different makes of Levothyroxine Tablets. In particular some of the adverse drug reaction reports received between December 2011 and February 2012 for Teva's 100 microgram tablet were supported by patient results which showed that the levels of thyroid stimulating hormone (TSH), the marker for thyroid disease, were not in the target range. The Teva marketing authorisation was suspended in February 2012.[41, 42] The BP 2014 monograph for Levothyroxine Tablets now contains a dissolution test using the rotating paddle at 100 rpm, with 500 mL of water at 37°C as the dissolution medium. Not less than 75 per cent of the declared content must be released after 45 minutes.

The 2014 BP now contains monographs for Levothyroxine Sodium, Liothyronine Sodium, Levothyroxine Oral Solution, Levothyroxine Tablets and Liothyronine Tablets.

Penicillin

Alexander Fleming was a Scottish farmer's son from Ayrshire.[43] He was born in August 1881. He had a two-year scholarship to Kilmarncock Academy before

[40] van't Hoff, W., Hoffenberg, R., London, D.R., Hall, R., Joplin, G,F., Besser, G.M., Stafforth, J.S., Jenkins, J., Himsworth, R.L., and Sonksen, P., 1978. Letter on Thyroid Extract. *Br. Med. J.* July 15: 200.

[41] 2012. Teva Levothyroxine 100 Microgram Tablets: Potential Reduced Efficacy – Suspension of Marketing Authorization. *Drug Safety Update* 5(8): March 2012.

[42] 2013. MHRA Report: Levothyroxine Tablet Products: A Review of Clinical and Quality Considerations. 7 January 2013.

[43] Worboys, M., 2011. Fleming, Sir Alexander (1885–1955). In the *Oxford Dictionary of National Biography*. Oxford: Oxford University Press.

studying at the Royal Polytechnic Institution. He inherited some money and then studied medicine at St Mary's Hospital Medical School, graduating in 1906. He then joined the research department at the university, gained a BSc in Bacteriology and became a lecturer at St Mary's. He served in World War I as a captain in the Royal Army Medical Corps. He returned to St Mary's where he was made Professor of Bacteriology. His area of research was antibacterial agents as he had witnessed many deaths due to sepsis of infected wounds during the war. In 1928 he was investigating *Staphylococci* and left a stack of cultures on his bench whilst he was away on a family holiday. When he returned he saw that one culture was contaminated with a fungus which had destroyed the surrounding Staphylococcal colonies. He then grew the contaminating mould and found that it killed a number of pathogenic bacteria. He identified the mould as a *Penicillium* and named the substance it produced 'penicillin'. The work was published in the *British Journal of Experimental Pathology* in 1929. He was however unable to isolate and purify the new compound. Howard Florey and Ernst Chain at the Sir William Dunn School of Pathology in Oxford started researching how to manufacture and isolate penicillin.[44] Its chemical structure was identified by Edward Abraham in the Oxford team. Florey asked British manufacturers to help produce penicillin, but they were unable to assist in the wartime conditions. Florey therefore travelled to the United States in 1941 and was able to get help from a US Department of Agriculture research laboratory in Peoria, Illinois. They were able to improve the manufacturing yield by changing to a deep fermentation process. A consortium of 21 US companies then started manufacture. By 1944 enough penicillin was being produced to treat the Allied war wounded. Fleming, Chain and Florey were awarded a Nobel Prize in 1945.

Penicillin was included as a monograph in the 1948 BP and was described as either the Sodium Salt or Calcium Salt. A number of preparations were also included – Cremor Penicillini, Cremor Penicillini Sterilisatus, Injectio Penicillini, Injectio Penicillini Oleosa, Oculentum Penicillini, Trochischi Penicillini and Unguentum Penicillini. The drug substance was assayed microbiologically against a suitable strain of *Staphylococcus* compared to a Standard Preparation issued by the Medical Research Council. The potency was expressed in Units.

Monographs for Benzylpenicillin and Procaine Benzylpenicillin were included in the 1951 *Addendum* to the 1948 BP. Benzylpenicillin is otherwise known as Penicillin G. The 1953 BP included monographs for Cream of Penicillin, Eye Ointment of Penicillin, Injection of Penicillin, Lozenges of Penicillin, Ointment of Penicillin and Tablets of Penicillin. Tablets of Penicillin contained Benzylpenicillin, but the other preparations could contain either

[44] Raviña, E., 2011. 4.2. Drugs from Microbiological Sources, 254–64. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

Amorphous Penicillin or Benzylpenicillin. Benzylpenicillin was assayed by titration with iodine for total penicillins and gravimetrically for benzylpenicillin.

By the time of the 1958 BP a number of monographs for other penicillin derivatives had been added – Benzathine Penicillin and Phenoxymethylpenicillin – the latter was otherwise known as Penicillin V. Penicillin V had been described in 1948 as the first oral penicillin and was first synthesised in 1957 by John Sheehan and K.R. Henery-Logan at the Massachusetts Institute of Technology.

From 1954 researchers at Beecham Research Laboratories had been studying the biosynthesis of Benzylpenicillin.[45] The isolation of 6-aminopenicillanic acid enabled the creation of a range of semisynthetic penicillins by Beecham and other manufacturers. These new penicillins could be designed to resist the β-lactamase enzymes produced by bacteria and which broke down the earlier penicillins. The aminobenzylpenicillins, ampicillin and amoxycillin, were developed by Beecham during the 1960s. Ampicillin and Ampicillin Trihydrate were include in the 1964 *Addendum* to the 1963 BP. Monographs were also included in this *Addendum* for Ampicillin Capsules, Ampicillin Injection and Ampicillin Trihydrate. A monograph for Amoxycillin Trihydrate was included in the 1980 BP. Amoxicillin, with its slight change of spelling, is still in the top 20 most prescribed drugs in England in 2013 with over 13 million items prescribed.

The 2014 BP contains monographs for Amoxicillin Sodium, Amoxicillin Trihydrate, Ampicillin, Ampicillin Sodium, Ampicillin Trihydrate, Bacampicillin Hydrochloride, Benzathine Benzylpenicillin, Cloxacillin Sodium, Dicloxacillin Sodium, Flucloxacillin Magnesium Octahydrate, Flucloxacillin Sodium, Oxacillin Sodium Monohydrate, Phenoxymethylpenicillin, Phenoxymethylpenicillin Potassium, Piperacillin, Piperacillin Sodium, Pivampicillin, Procaine Benzylpenicillin, Sultamicillin, Sultamicillin Tosylate Dihydrate, Ticarcillin and their preparations.

Insulin

Diabetes had been described for hundreds of years. The word in Greek describes the symptom of frequency of urination. In the 1670s the urine of diabetics was found to contain sugar. In 1889 the role of the pancreas in diabetes was identified by von Bering and Minkowski. Various scientists had tried to isolate the hormone which was thought to be implicated in control of diabetes. In 1921 Frederick Banting, a Canadian surgeon, approached Professor John McLeod at the University of Toronto with an idea as to how the hormone might be

[45] Raviña, E., 2011. 4.2. Drugs from Microbiological Sources, 254–64. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

extracted from the pancreas.[46] He was given access to McLeod's laboratory. He enlisted the help of a young student, Charles Best. They tied off the pancreatic ducts in a dog. After two months they removed the pancreas and macerated it in a saline solution. They then injected a suspension of this material into another diabetic dog and managed to stabilise the blood glucose levels. With the help of McLeod they then started a programme to prepare insulin concentrates using pancreases obtained from slaughtered animals – pigs and cows. A biochemist, James Collip, refined the extraction and purification techniques. A young diabetic was treated with an insulin precipitate and this controlled his diabetes. An agreement was reached with the US pharmaceutical company Eli Lilly for industrial manufacture. In 1923 Lilly started commercial production. Banting and McLeod were awarded the Nobel Prize for Medicine in 1923. Banting shared his prize money with Best; McLeod did the same with Collip.

One of the criticisms levelled by the Medical Research Council at the General Medical Council during the course of the enquiry in 1926 by the Committee of Civil Research Sub-Committee on the *British Pharmacopoeia* chaired by Hugh Macmillan KC was that the *Pharmacopoeia* did not introduce new life-saving drugs into the book as early as possible. Insulin was one example where the Medical Research Council had been involved in devising a biological standard but where there was no pharmacopoeial monograph. Insulin was also controlled under the Therapeutic Substances Act 1925. A monograph on Insulin was added to the 1932 BP when it was produced by the new BP Commission. The monograph included a biological assay. This was carried out by comparing the dose of a sample of insulin necessary to produce hypoglycaemia in rabbits or convulsions in mice with the dose of a Standard Preparation of Insulin as prepared by the National Institute for Medical Research in Hampstead, London.

Insulin is a peptide hormone which reacts with basic proteins. At the end of the 1930s Hans Hagedorn from the Danish company Nordisk developed a series of insulin complexes with protamines: these were less soluble, absorbed more slowly and therefore longer acting.[47] Absorption was even slower when insulin-protamine-zinc suspensions were used. A monograph for Injection of Protamine Zinc Insulin was introduced in the seventh *Addendum* to the 1932 BP which was official from 12 February 1945. Globin Zinc Insulin was introduced in the 1953 BP. The 1955 *Addendum* added monographs for Insulin Zinc Suspension, Insulin Zinc Suspension (Amorphous) and Insulin

[46] Simoni, R.D., Hill, R.L. and Vaughan, M., 2002. The Discovery of Insulin: The Work of Frederick Banting and Charles Best. *Journal of Biological Chemistry* 277, e15. http://www.jbc.org/content/277/26/e15 (accessed July 2014).

[47] Raviña, E., 2011. Animal Sources and Related Drugs, 223–4. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

Zinc Suspension (Crystalline). The 1963 BP added a monograph for Isophane Insulin Injection.

The insulins from pigs and cows were purified from the 1960s onwards by gel filtration chromatography or gel electrophoresis to reduce protein impurities. However these animal-derived insulins were still prone to cause immunogenic reactions during the long-term treatment of diabetic patients. It was clear that the development of a human insulin product was desirable. Two different commercial ways of doing this were developed. The first was by the Danish company Novo in 1980 by replacing the terminal alanine amino acid in pig insulin with threonine. The second, also in 1980, was by the US company Genentech using recombinant DNA technology. A monograph for Human Insulin appeared in the 1988 BP and applied to both methods of production. This new monograph included tests for pro-insulin like immunoreactivity and for proteins of higher molecular weight. The assay was carried out by liquid chromatography using the European Pharmacopoeia Chemical Reference Substance for human insulin. There was no biological assay although this was retained for the insulin and insulin derivatives from pig and cow which were still official.

In the late 1990s and early years of the 2000s the so-called 'designer insulins' were developed by changing some of the amino acids or amino acid sequences.[48] The 2014 BP now includes Insulin Aspart which is short-acting, Insulin Glargine which is longer lasting than conventional insulin, and Insulin Lispro which is again short-acting. The monographs for Insulin, Biphasic Insulin, Isophane Insulin, Protamine Zinc Insulin and Insulin Zinc Suspension all allow the use of human, pig or cow (bovine) insulin. However human insulin products are now the standard treatment. Chemical assays are now used throughout these monographs both for impurities and for the assays.

Sulpha Drugs

In 1931 Gerhard Domagk, the Director of Research in Experimental Pathology and Bateriology at I.G. Farben in Elberfeld started a programme of *in vitro* and *in vivo* research to test a series of azo dyes as antimicrobials.[49] In 1932 he identified a compound called Prontosil which was effective in protecting mice and rabbits against staphylococcal and streptococcal infections. The compound was patented and the results published in 1935. In the same year a team of researchers at the Institut Pasteur found that in the body the drug was converted

[48] 1964. Obituary: G. Domagk. *Br. Med. J.* May 2 1(5391): 1189.

[49] Raviña, E., 2011. 2.5. Fathers of Chemotherapy, 48–50. In *The Evolution of Drug Discovery*. Wiley-VCH Verlag GmbH and Co., KGaA.

to sulphanilamide and this was responsible for its antibacterial activity. Prontosil was thus a prodrug. Sulfanilamide was a known compound and therefore not patentable. It was then used clinically for a range of streptococcal infections including pneumonia, for treatment of meningitis and gonorrhoea. Domagk was nominated for a Nobel Prize in 1938 and this was awarded in 1939. However Hitler had forbidden any German to accept a Nobel Prize, so he was forced to decline the honour. He received the Nobel Prize gold medal in 1947.[50]

Other sulphonamides were then developed. In 1937 May and Baker discovered sulphapyridine which was also useful in treating infections causing pneumonia, meningitis and gonorrhoea. It was known as M&B 693. It was used to treat an attack of pneumonia contracted by Winston Churchill, the wartime prime minister, when he visited Tunisia in December 1943. He referred to this in a wartime radio broadcast, saying 'This admirable M&B from which I did not suffer any inconvenience, was used at the earliest moment and, after a week's fever, the invaders were repulsed'. M&B 693 was widely used during World War II both as a powder wound dressing and a tablet.

The solubility of the early sulphonamides was very pH dependent, and they were prone to crystallise in the kidneys causing severe damage. The newer sulphonamides such as sulphadiazine, which were developed subsequently, were more highly ionised and thus more soluble. The sulphonamides were the first effective treatment of bacterial infections.

Sulphanilamide was introduced into the 1941 fourth *Addendum* to the 1932 BP. The 1945 seventh *Addendum* included a number of other sulpha drugs – Sulphacetamide, Soluble Sulphacetamide, Sulphadiazine, Soluble Sulphadiazine, Sulphaguanidine, Sulphathiazole and Sulphathiazole Sodium. This *Addendum* also included Tablets of Sulphadiazine, Sulphaguanidine, Sulphanilamide and Sulphapyridine.

The 2014 BP includes monographs for Sulfacetamide Sodium, Sulfadiazine, Sulfadoxine, Sulfurazole, Sulfaguanidine, Sulfamethizole, Sulfamethoxazole, Sulfasalazine, Sulfathiazole, and Sulfinpyrazone. There are only three preparations listed: Sulfadiazine Injection, Sulfasalazine Tablets and Gastro-resistant Sulfasalazine Tablets. Sulfasalazine is broken down in the gut to mesalazine (an anti-inflammatory) and sulfapyridine (an antibacterial). It is indicated for the treatment of ulcerative colitis and Crohn's disease and also for rheumatoid arthritis which has failed to respond to non-steroidal anti-inflammatory drugs.

[50] 1964. Obituary: G. Domagk. *Br. Med. J.* May 2 1(5391): 1189.

Streptomycin

Selman Waksman was born in 1888 in Nova Pryluka, then part of Russia, now in the Ukraine.[51] He emigrated to the United States in 1910, gained his BSc at Rutgers College in 1915, and went on to study for his PhD in Biochemistry at the University of California, which was awarded in 1918. He joined the faculty at Rutgers University in the Department of Biochemistry and Microbiology. Waksman coined the term antibiotic in 1942 and defined it as a substance produced by a microorganism that has the ability to inhibit the growth of another microorganism or cause its death. He led a team in the 1940s as part of the global effort to discover new antibiotics. In 1943 after his discharge from the army, one of his PhD students, Albert Schatz, was screening actinomycete organisms for activity against the tuberculosis bacillus – *Mycobacterium tuberculosis*. Schatz isolated some strains of *Streptomyces griseus* from soil samples and from a swab from the trachea of a healthy chicken and found that they inhibited the TB bacillus. He then produced the streptomycin which was used in the first toxicity studies and then clinical studies. Waksman, as his supervisor, however claimed sole credit for the discovery and was awarded the Nobel Prize in 1952. The recent book by Peter Pringle, *Experiment Eleven: Deceit and Betrayal in the Discovery of a Wonder Drug*,[52] sets out the story of the discovery of streptomycin and the roles of Waksman and Schatz. In 1949 Waksman and H.A. Lechevalier isolated another aminoglycoside antibiotic, neomycin, from a *Streptomcyces fradiae* culture.[53]

Streptomycin Hydrochloride and Streptomycin Sulphate were included in the 1951 *Addendum* to the 1948 BP. The *Addendum* also included Injections of Streptomycin and Calcium Chloride, Streptomycin Sulphate and Streptomycin Hydrochloride. The monograph included a test for undue toxicity in a group of five mice – none should die, but if one dies then the test could be repeated in a further group of five mice, where none should die. A test for histamine-like substances was carried out by intravenously injecting a cat – the fall in blood pressure should be less than that caused by a solution of histamine phosphate. The assay was a microbiological one. The 1951 *Addendum* also included monographs for Dihydrostreptomycin and Dihydrostreptomycin Injection. The 1955 *Addendum* deleted Streptomycin Hydrochloride, Streptomycin Calcium Chloride and their injections. Dihydrostreptomycin caused ototoxicity, which could lead to hearing loss, and this was much greater than with streptomycin.

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[51] 1952. Selman Waksman: Nobel Prize. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1952/waksaman-bio.html (accessed July 2014).

[52] Pringle, P., 2012. *Experiment Eleven: Deceit and Betrayal in The Discovery of the Cure for Tuberculosis*. London: Bloomsbury Publishing.

[53] Waksman, S., 1950. Streptomycin and Neomycin. An Antibiotic Approach to Tuberculosis. *Br. Med. J.* Sept 9: 595–600.

Dihydrostreptomycin and its injection were therefore omitted in the 1960 *Addendum* to the 1963 BP.

The 2014 BP still contains monographs for Streptomycin Sulphate and Streptomycin Sulphate Injection. The monograph stipulates that if tested the substance will not cause undue toxicity. A microbiological assay is still used. The drug is still used for the treatment of tuberculosis in combination with other drugs.

Tetracyclines

Benjamin Minge Duggar was born in 1872 in Gallion, Alabama, in the United States.[54] He graduated with a BS in 1891 from Alabama Polytechnic Institute and with a PhD from Cornell in 1898. By 1944 he had retired from his post as a plant physiologist from the University of Wisconsin and worked as a consultant for the US pharmaceutical company Lederle Laboratories in Pearl River, New York researching antibiotics from microorganisms in soil samples. In 1945 he received a soil sample from Professor William Albrecht at the University of Missouri. From this sample Duggar isolated an unknown actinomycete which he called *Streptomyces aurofaciens* because it produced a bright yellow crystalline compound. The new compound was chlortetracycline, the first of the new series of tetracyclines which were orally active against a wide range of Gram-negative and Gram-positive organisms. Lederle began industrial fermentation to produce the antibiotic in 1948 and marketed it in 1949 as Aureomycin. In 1951 a team led by Alexander Finlay at Pfizer found another actinomycete called *Streptomyces rimosus* in a soil sample from Terre Haut, Indiana.[55] This produced oxytetracycline. Although the chemistry was difficult, this was to lead to a series of semi-synthetic tetracyclines in the 1950s and 1960s – tetracycline, demethylchlortetracycline, doxycycline and minocycline.

The 1958 BP included Chlortetracycline Hydrochloride, Chlortetracycline Capsules – which were soft shell gelatin capsules, Chlortetracycline Injection, Oxytetracycline Dihydrate, Oxytetracycline Hydrochloride, Oxytetracycline Tablets, Oxytetracycline and Procaine Injection, Oxytetracycline Injection, Tetracycline Hydrochloride, Tetracycline and Procaine Injection, Tetracycline Capsules, Tetracycline Injection and Tetracycline Tablets. All of the substances and their preparations were assayed microbiologically.

The 1963 BP included Demethylchlortetracycline Hydrochloride and Demethylchlortetracycline Capsules. Again both the substance and the

[54] Keith, G.W., 1957. Benjamin Minge Duggar: 1872–1956. *Mycologia* 49(3): 434–8.

[55] Raviña, E., 2011. 4.3. Drugs from Microbiological Sources. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

preparation were assayed microbiologically. Oxytetracycline Capsules were added in the 1968 BP. The 1973 BP added monographs for Lymecycline – a water-soluble combination of tetracycline, lysine and formaldehyde, Lymecycline Capsules and Lymecycline and Procaine Injection. Monographs for Doxycycline Hydrochloride and Doxycycline Capsules were added in the 1971 *Addendum* to the 1968 BP.

The 1980 BP introduced a dissolution test for Chlortetracycline Capsules, Oxytetracycline Capsules, Oxytetracycline Tablets, Tetracycline Capsules and Tetracycline Tablets. In the case of the tablets these were originally sugar-coated by applying successive coats of sugar syrup to a tablet core protected by means of a shellac layer. The shellac coating was often variable in thickness and tended to toughen on ageing. Thus batch variation in dissolution of the tablets was a potential quality issue. The 1980 monographs allowed the tablets to be either sugar or film coated. Film-coating with a cellulosic polymer was a much more reproducible process.

In the 1960s a number of clinical literature reports related Fanconi syndrome – a renal disease (presenting with renal tubular acidosis, hypophosphatemia and hypokalemia) – to the use of outdated or degraded tetracycline products. This was related to the levels of epi-anhydro-tetracycline. The 1993 BP included Related Substances tests for a number of the impurities and degradation products in the tetracyclines. The monograph for Tetracycline Hydrochloride included limits for the 4-epianhydro, 4-epi, anydro impurities and degradation products. The 1982 *Addendum* to the 1980 BP introduced a high pressure liquid chromatographic assay to replace the microbiological assay in the monograph for Oxytetracycline Calcium.

Tetracycline products are still used clinically although they are only partly absorbed orally, resulting in changes in the intestinal flora which can give rise to diarrhoea. Also bacterial resistance has reduced their usefulness. The substances included in the 2014 BP are Chlortetracycline Hydrochloride, Demeclocycline Hydrochloride, Doxycycline Hyclate, Doxycycline Monohydrate, Lymecycline, Minocycline Hydrochloride and Dihydrate, Oxytetracycline Dihydrate, Oxytetracycline Calcium, Oxytetracycline Hydrochloride, Tetracycline, Tetracycline Hydrochloride and their various preparations. The assay for all of the drugs and their preparations is now a liquid chromatographic method.

Chloramphenicol

The successful development of streptomycin by Waksman and Schatz stimulated research on new antibiotics from *Actinomyces* from soil samples. Chloramphenicol was a new antibiotic produced by cultures of an actinomycete isolated from soil by John Ehrlich and his colleagues from the University of

Illinois in 1947. The soil samples from which the strains were isolated were collected from a field near Caracas, Venezuela and from a compost soil sample from the horticultural farm of the Illinois Agricultural Experiment Station at Urbana, respectively. This actinomycete was a new species – *Streptomyces venezuela*.[56] The drug was developed commercially by Parke-Davis and marketed in 1949 as a broad spectrum antibiotic. Controulis and his colleagues at Parke-Davis were able to synthesise the drug in 1949.[57]

Chloramphenicol was included in the 1951 *Addendum* to the BP 1948. Capsules of Chloramphenicol were included in the 1953 BP. The monograph for Chloramphenicol included tests for Identification, Light Absorption, Melting Point, Specific Rotation, Lead, Loss on Drying and Sulphated Ash. However curiously no assay was included, it was not until the 1968 BP that a titrimetric assay was included.

The current uses of chloramphenicol are limited because of its haemotoxicity – blood toxicity; the drug can cause bone-marrow depression and aplastic anaemia. Its current use is for life-threatening conditions including typhoid, bacterial meningitis and Rocky Mountain spotted fever. However these toxicity limitations do not apply to the same extent to topical preparations. The 2014 BP includes Chloramphenicol, Chloramphenicol Palmitate, Chloramphenicol Sodium Succinate, Chloramphenicol Capsules, Chloramphenicol Ear Drops, Choramphenicol Eye Drops, Chloramphenicol Eye Ointment and Chloramphenicol Sodium Succinate Injection.

Beta-Blockers

In 1948 Professor Raymond Alquist at the Medical College of Georgia hypothesised that drugs such as adrenaline/noradrenaline acted on two different receptor sites which he termed the alpha and beta receptors. In the early 1960s Dr James Black and his associates were working at Imperial Chemical Industries (ICI) in the UK on a series of compounds which would block the beta receptors and would reduce the heart's requirement for oxygen and thus treat angina.[58] In 1963 the first beta-blocker was marketed – pronethalol. However its use was limited to life-threatening conditions. Another drug, propranolol, was also being tested clinically in 1964 and this was launched onto the market. It was used for treatment of angina, hypertension and arrhythmias. In 1970

[56] Ehrlich, J., Gottlieb, D., Burkholder, P.R., Anderson, L., and Pridham, T.G., 1948. Streptomyces venezuelae N. Sp., the Source of Choromycetin. *J. Bacteriology* 56(4): 467–77.

[57] Countroulis, J., Rebstcock, M.C., and Crooks, H.M., 1949. Chloramphenicol (Choromycetin). V. Synthesis. *J. Am. Chem. Soc.* 71(7): 2463–8.

[58] Quirke, E., 2006. Putting Theory into Practice: James Black, Receptor Theory and the Development of the Beta-Blockers at ICI, 158–1978. *Medical History* 50(1): 69–92.

another ICI beta-blocker drug was launched – practolol – but this had to be subsequently withdrawn as it caused 'dry eye' syndrome where the patients are unable to secrete tears to lubricate the eye.

ICI continued to develop beta-blockers and in the mid-1970s marketed atenolol. Other companies also began to compete in this market. The Swedish company Hässle marketed metoprolol, E. Merck marketed bisoprolol, and Frosst-Merck marketed timolol.

Glaucoma is caused when fluid drainage of aqueous humour from the front chamber of the eye fails to keep up with its production from the rear chamber. The intraocular pressure then builds up, compressing the optic nerve and leading to blindness. Timolol eye-drops are used to treat glaucoma by reducing the production of fluid and hence reducing the intraocular pressure.

Monographs for Propranolol Hydrochloride, Propranolol Injection and Propranolol Tablets were introduced in the 1968 BP. Practolol, Practolol Injection and Practolol Tablets were included in the 1973 BP. Practolol and Practolol Injection were still included in the 1980 BP but Practolol Tablets were now omitted. The other practolol preparations were omitted from later editions.

The 2014 BP contains monographs for 17 separate beta-blocker drugs and their various preparations – including injections, tablets, capsules, eye-drops, suspension and solutions. The drug monographs are Acebutolol Hydrochloride, Alprenolol Hydrochloride, Atenolol, Betaxolol, Bisoprolol Fumarate, Carteolol Hydrochloride, Celiprolol Hydrochloride, Levobunolol Hydrochloride, Metipranolol, Metoprolol Succcinate, Nadolol, Oxprenolol Hydrochloride, Penbutolol Sulfate, Pindolol, Propranolol Hydrochloride and Timolol Maleate.

As mentioned, bisoprolol fumarate was developed by E. Merck in Darmstadt, Germany. It is the 14th most widely prescribed drug (by numbers of prescriptions) in England. Bisoprolol is both lipid and water-soluble, its water solubility means that it has a lower incidence of central nervous system side effects because it diffuses less readily into the brain compared to many other beta-blockers. It is cardio-selective thus making it an ideal drug for treatment of cardiac disease. The 2014 BP includes a monograph for Bisoprolol Tablets.

Calcium Channel Blockers

The University College Hospital physician and physiologist Sydney Ringer (1836–1910) published four papers in the *Journal of Physiology* in the early 1880s. These showed the importance of calcium in the contraction of the frog's heart.[59] Albrecht Fleckstein (1917–1992), Professor of Physiology at the University of

[59] Miller, J.D., 2004. Sydney Ringer; Physiological Saline, Calcium and the Contraction of the Heart. *The Journal of Physiology* 555: 585–7.

Freiburg, showed that drugs can alter cardiac contraction by reducing the entry of calcium into the heart muscle cells, thus enabling their use in the treatment of hypertension. The herb bisnaga or khella is the derived from the fruits and seeds of *Amni visnaga*, which is a member of the carrot family. It was used in Egypt for renal colic and as a diuretic. Its active constituent is khellin. In 1948 Gelb von Anrep from the University of Cairo showed that khella relieved the pain from colic but also was effective in treatment of angina. Friedrich Bossert and Wulf Vater at Bayer AG made a series of modifications of the structure of khellin and this led to the discovery of nifedipine.[60] Fleckstein found that it was effective as a calcium channel blocker. Nifedipine was marketed in 1982.

Other calcium channel blockers followed based on the 1,4-dihydropyridine chemical structure of nifedipine – verapamil, diltiazem and amlodipine. Amlodipine was patented by Pfizer in 1982 as the maleate salt; most of the clinical trials were carried out using this salt. However problems arose with chemical instability due to an interaction between the amine group of amlodipine and maleic acid to form an impurity which was biologically active. The maleate salt was also difficult to tablet. Pfizer therefore marketed the drug as the besylate salt. Amlodipine is claimed by Pfizer to be the world's best-selling antihypertensive drug. It was included in the top 20 list of most prescribed medicines in the community in England in 2013. However its volume of prescription is exceeded by another antihypertensive, the ACE antagonist Ramipril (see below).

The 2014 BP includes monographs for Nifedipine, Nifedipine Capsules, Prolonged-release Nifedipine Capsules, Prolonged-release Nifedipine Tablets, Verapamil Hydrochloride, Prolonged-release Verapamil Capsules, Verapamil Injection, Verapamil Tablets, Prolonged-release Verapamil Tablets, Diltiazem, Prolonged-release Diltiazem Tablets, Felodipine, Prolonged-release Felodipine Tablets and Amlodipine Besilate.

ACE Inhibitors

The renin-angiotensin system is one of the mechanisms involved with the regulation of blood pressure. Renin is an enzyme which breaks down angiotensinogen to produce angiotensin I. This is converted by angiotensin converting enzyme (ACE) into angiotensin II which constricts blood vessels. It also stimulates the release of aldosterone which is also involved in regulation of blood pressure. Researchers at the Squibb Institute for Medical Research studied

[60] Raviña, E., 2011. 4.1. Plant Sources: Derivatives and Related Drugs, 149–52. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

the converting enzyme and developed the first ACE inhibitor, captopril, which was marketed in 1981.[61] Other ACE inhibitors such as enalapril followed.[62]

The BP 2014 now contains monographs for 11 ACE inhibitors and their preparations. These are Benezepril Hydrochloride, Captopril, Cilazapril, Enalapril Maleate, Fosinopril Sodium, Lisinopril Dihydrate, Perindopril Erbumine, Quinapril Hydrochloride, Ramipril, Spirapril Hydrochloride Monohydrate and Trandolapril. Ramipril was in the top 20 of the most widely prescribed drugs in England in 2013. The 2014 BP includes monographs for Ramipril Capsules and Ramipril Tablets.

Diuretics

Inorganic mercurial compounds such as mercurous chloride – calomel – were used historically for treatment of syphilis. They also had diuretic properties. They acted by reducing the reabsorption of sodium in the ascending loop of Henle in the kidney. In the twentieth century organomercurials were introduced for the treatment of syphilis. These also showed diuretic properties and the observation led to the development of organomercurial diuretics. Mersalyl was first included in the 1936 *Addendum* to the 1932 BP. It was given by injection or in tablets for treatment of cardiac oedema. It was often given in combination with theophylline to reduce irritancy and prevent the decomposition of the organomercurial complex. However this class of diuretics was toxic and could lead to mercurial nephrotic syndrome. Mersalyl was omitted from the 1958 BP.

The observation that some of the antibacterial sulphonamides also had a diuretic action led to structural modification to find new compounds.[63] One of the first of these was acetazolamide which was developed by R. Roblin and J. Clapp at Lederle Laboratories in the United States; this was marketed in 1953 and included in the 1958 BP. Karl Beyer and his team at Merck Sharp and Dohme in the United States also developed a series of sulphonamides to evaluate, and this led to the development of chlorothiazide. Monographs for Chlorothiazide and Chlorothiazide Tablets were included in the 1960 *Addendum* to the 1958 BP. Beyer realised that a diuretic could also be useful in managing hypertension and this increased the market for this class of drugs. Furosemide was developed by Heinrich Ruschig of Hoechst in Germany in the 1960s. Frusemide – as the

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[61] Raviña, E., 2011. 6.1. Searching for the Ideal Antihypertensive Agent, 407–14. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

[62] Mondoa, F., Sromonsky, J.A. and Walker, J.F., 1985. Enalapril in Hypertension and Congestive Heart Failure: Overall Review of Efficacy and Safety. *Drugs* 30(Suppl. 1): 82–9.

[63] Raviña, E., 2011. 3.7. Structural Variations on Sulfanilamide, 69–75. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

drug was then known – was first introduced into the 1968 BP together with Frusemide Tablets.

The 2014 BP includes a number of thiazide diuretics – Bendroflumethiazide, Cyclopenthiazide, Hydroflumethiazide, Polythiazide and their tablet preparations. It also includes Furosemide, Furosemide Injection and Furosemide Tablets. Bendroflumethiazide and Furosemide were among the top 20 most frequently prescribed drugs in the community in England in 2013.

Bronchodilators

Bronchodilators are drugs that open the airways during an asthma attack. Adrenaline was used for the treatment of asthma in the first half of the twentieth century. Monographs for Adrenalin and Hydrochloric Solution of Adrenalin were included in the 1914 BP. The solution could be given by subcutaneous injection. The *British Pharmaceutical Codex* also contained monographs for a number of nebuliser solutions containing adrenaline for treatment of asthma by inhalation.

Isoprenaline was an adrenergic drug introduced in the UK for treatment of bronchial asthma and emphysema; it was a more powerful bronchodilator than adrenaline. The monograph for Isoprenaline Sulphate was included in the 1951 *Addendum* to the 1948 BP, and the 1953 BP included a monograph for Isoprenaline Sulphate Tablets. There were also a number of commercial nebuliser spray solutions for inhalation. However it is also has a powerful cardiac stimulating effect and it could easily be overdosed. In the 1960s there was an epidemic of deaths associated with a high strength isoprenaline inhalation product – isoprenaline forte.[64] The 2014 BP still contains monographs for Isoprenaline Hydrochloride, Isoprenaline Sulfate and Isoprenaline Injection.

In 1948 Raymond Ahlquist at Emory University in Atlanta, Georgia suggested that there were two types of adrenergic receptors – α and β. In 1967 A.M. Lands and his co-workers from the Sterling-Winthrop Research Institute in Rensselaer, New York found that the β receptors could be classified into two sub-types – β_1 receptors responsible for the cardiac stimulation and β_2 receptors responsible for the bronchodilator effects.[65] Also in 1967 David Hartley and his colleagues at the British company Allen and Hanburys Ltd discovered salbutamol which is selective for β_2 receptors and therefore had more bronchodilator than

[64] Pearce, N. and Hensley, M.J., 1998. Epidemiological Studies of Beta Agonists and Asthma Deaths. *Epidemiological Reviews* 20(2): 173–86.

[65] Lands, A.M., Arnold, A, McAuliff, J.P., Luduena, F.P., and Brown, T.G., 1967. Differentiation of Receptor Systems activated by Sympathomimetic Amines. Letters to Nature. *Nature* 214: 597–8.

cardiac stimulant properties.[66] In Sweden, Kjell Wetterlin and his colleagues at Astra Co. discovered terbutaline. Monographs for Salbutamol Sulphate and Salbutamol Tablets were included in the 1973 BP.

Metered dose inhalers were introduced commercially in the early 1960s. At the time isoprenaline was the most commonly used drug for treatment of asthma. However salbutamol inhalers rapidly became more widely used when introduced due to the safety concerns about isoprenaline. The 1993 BP contains a monograph for Salbutamol Pressurised Inhalation. For deposition in the lung a particle size of drug in the range 2 to 5 μm is essential, and the monograph specified the use of two alternative impinger devices to measure the percentage of the dose emitted from the aerosol valve after actuation which is in the correct particle size range.

Salbutamol was the eighth most commonly prescribed drug in the community in England in 2013. The 2014 BP includes monographs for Salbutamol, Salbutamol Sulphate as drug substances, Prolonged-release Salbutamol Capsules, Salbutamol Injection, Salbutamol Nebuliser Solution, Salbutamol Oral Solution, Salbutamol Inhalation Powder, Salbutamol Powder Predispensed, Salbutamol Pressurised Inhalation, Salbutamol Tablets and Prolonged-release Salbutamol Tablets.

The monographs for Salbutamol Inhalation Powder and Salbutamol Powder Predispensed are designed to control the metered dry powder inhalers which are marketed. Appendix XIIC in volume V of the 2014 BP is entitled Consistency of Formulated Preparations. It includes a section on Preparations for Inhalation Assessment of Fine Particles. This is the *European Pharmacopoeia* method 2.9.18. It includes a number of different devices, impingers and impactors, which can be used to check the control of the fine particle size in the therapeutic range for effective inhalation of 2 to 5 μm.

The 'Statins'

Arteriosclerosis had been identified in the nineteenth century. The relationship between cholesterol and arteriosclerosis was identified by Adolf Windaus in 1910 who analysed atherosclerotic plaques and found a concentration 20 times more than that in normal aorta.[67] In 1913 Nikolai Anichkov showed that cholesterol alone caused the atheromatous changes in the vascular wall.[68] In the 1950s John Gofman at the University of California used the ultracentrifuge to separate

[66] Raviña, E., 2011. 5.2 Receptor-Based Drug Discovery, 329–30. In *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH Verlag GmbH and Co., KGaA.

[67] Windaus, A., 1910. Uber der Gehalt normaler und atheromatoser Aorten an Cholesterol und Cholesterinester. *Zeitschrift Physiol. Chemie* 67: 174.

[68] Konstantinov, I.E., Mejevoi, N. and Anichkov, N.M., 2006. N. Anichkov and His Theory of Atherosclerosis. *Tex. Heart Inst. J.* 33(4): 417–23.

plasma lipoproteins by flotation. He found that heart attacks correlated with high levels of cholesterol and particularly with levels of low density lipoproteins. The steps in the synthesis of cholesterol in the body were worked out in the 1950s and early 1960s and the role of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase enzyme was identified as the rate controlling enzyme in the synthesis. In the 1980s Akira Endo and his colleagues working at Sankyo identified a metabolite produced by *Pencillium citrinum* mould which inhibited cholesterol synthesis – they called this compactin.[69] In 1978 Akira Yamamoto at the Osaka University Hospital evaluated compactin in a series of patients with familial hypercholesterolaemia and found it to be safe and effective in lowering their cholesterol levels. However because of concerns about occurrence of lymphomas at high doses in rats and monkeys the development programme was discontinued. Other pharmaceutical companies were then inspired to search for what became known as other statin drugs. Merck began clinical studies on lovastatin in 1980 and it was approved in the United States in 1987.[70] Merck subsequently developed simvastatin. Atorvastatin was synthesised by Bruce D. Roth and his colleagues at Parke Davis Research in the early 1990s. Both simvastatin and atorvastatin are in the top 20 list of most frequently UK prescribed drugs.

The 2014 BP includes monographs for Atorvastatin Calcium Trihydrate, Cilastatin, Fluvastatin, Lovastatin, Pravastatin, and Simvastatin. Monographs for Pravastatin Tablets and Simvastatin Tablets are in included in volume III Formulated Preparations. A monograph for Atorvastatin Tablets is under development.

Selective Serotonin Re-Uptake Inhibitors – Antidepressants

The French military surgeon Henry Laborit investigated a number of compounds for use in anaesthesia.[71] He collaborated with Specia Laboratories at Rhône-Poulenc and found that chlorpromazine was useful in treating schizophrenia and psychosis. It was marketed in 1952. Other companies explored chemical variations on the chlorpromazine molecule. One variant – imipramine – was marketed by Geigy in 1958 as an antidepressant and is a tricyclic drug. Imipramine and Imipramine Tablets were included in the 1963 BP. Amitriptyline was developed by Merck and is a chemical variant of the imipramine molecule. It is

[69] Endo, A., 2010. A Historical Perspective on the Discovery of Statins. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* 86(5): 484–93.

[70] Endo, A., 2010. A Historical Perspective on the Discovery of Statins. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* 86(5): 484–93.

[71] Ban, T.A., 2007. Fifty Years of Chlorpromazine: A Historical Perspective. *Neuropsychiatr. Dis. Treat.* 3(4): 495–500.

still widely used and was still in the top 20 most widely prescribed drugs in the community in England in 2013. Monographs for Amitriptyline, Amitriptyline Tablets and Amitriptyline Injection were included in the 1966 *Addendum* to the 1963 BP.

In the 1960s a number of companies were investigating the mode of action of the tricyclic antidepressants to try to find newer compounds with fewer side effects. The first compound with serotonin – 5-hydroxytryptamine – uptake inhibitor with antidepressant properties which was marketed in 1982 was zimelidine, but was withdrawn two years later. Eli Lilly marketed fluoxetine in the United States in 1987 under the trade name Prozac. In the 1990s other serotonin re-uptake inhibitors were also marketed – citalopram, paroxetine, sertraline and venlafaxine. Citalopram is marketed for the treatment of major depressive episodes and panic disorder.

The 2014 BP includes monographs for Imipramine, Imipramine Tablets, Amitriptyline Embonate, Amitriptyline Hydrochloride, Amitriptyline Tablets, Sertraline Hydrochloride, Sertraline Tablets, Fluoxetine Hydrochloride, Fluoxetine Capsules, Fluoxetine Oral Solution, Anhydrous Paroxetine, Paroxetine Hydrochloride Hemihydrate, Paroxetine Tablets, Citalopram Hydrobromide, Citalopram Hydrochloride, Venlafaxine Hydrochloride, Prolonged-release Venlafaxine Capsules, Venlafaxine Tablets and Prolonged-release Venlafaxine Tablets. Citalopram was in the list of the top 20 most widely prescribed drugs in the community in England in 2013. Amitriptyline was also in the top 20 list.

Proton Pump Inhibitors

Historically belladonna and atropine products were used to inhibit gastric secretion. Mixtures containing belladonna and antacids such as Aluminium Hydroxide and Belladonna Mixture were widely prescribed.

Histamine had been identified as a chemical mediator for gastric secretion. In the 1960s a team at Smith Kline and French in the UK under the direction of James Black began research on histamine antagonists. This led to the discovery of cimetidine the first H_2-histamine receptor antagonist.[72] In the late 1960s Ivan Östholm and his team at the Swedish company Hässle (part of Astra) initiated a research programme to find a drug to inhibit gastric secretion that acted within the parietal cells that produce hydrochloric acid. In 1979 they synthesised

[72] Brimblecombe, R.W., Duncan, W.A.M., Durant, G.J., Ganellin, C.R., Parsons, M.E., and Black, J.W., 1975. The Pharmacology of Cimetidine, a New Histamine H_2. Receptor Antagonist. *Br. J. Clin. Pharmacol.* 53(3): 435–6.

omeprazole and it was approved about 10 years later.[73] It is a prodrug which is activated by the gastric acid and converted to sulfenamide which inactivates the proton pump in the parietal cells. The drug would be inactivated in the stomach and it is therefore formulated as gastro-resistant capsules or tablets. The 2014 BP includes monographs for Omeprazole, Omeprazole Magnesium, Omeprazole Sodium, Gastro-resistant Omeprazole Capsules, Omeprazole Oral Suspension and Gastro-resistant Omeprazole Tablets. The monographs for the capsules and tablets include a two-stage dissolution test using the rotating paddle method at 100 rpm. Two different dissolution media are used, the first stage is at pH 4.5 for 45 minutes and then after adjusting the pH to 6.8 the second state is a further 45 minutes. No more than 10 per cent of the stated amount is released in the first stage and at the final stage not less than 65 per cent of the stated amount.

Omeprazole was the fourth most commonly prescribed drug in the community in England in 2013. Other proton pump inhibitors are structural modifications of the omeprazole molecule. Lansoprazole was also in the top 20 most widely prescribed drugs in England in 2013. The 2014 BP includes monographs for Lansoprazole, Gastro-resistant Lansoprazole Capsules and Gastro-resistant Lansoprazole Tablets. Again the monographs for the capsules and tablets include a two-stage dissolution test.

Metformin Hydrochloride

In 1929 Slotta and Tschesche discovered the sugar-lowering action of this drug in rabbits. In 1950 a Philippine physician Eusebio Garcia used metformin to treat influenza and discovered that it also lowered the blood sugar. The French diabetologist Jean Sterne was studying the properties of galegine, an alkaloid from *Galega officinalis* (French lilac or goat's rue). He noted the report from Garcia and investigated it clinically for the treatment of diabetes.[74] Metformin was approved in the UK in 1958. It is the world's most widely prescribed oral antidiabetic drug. It was the eleventh most widely prescribed drug in England in 2013.

Metformin Hydrochloride and Metformin Tablets were added to the BP in the *Addendum* 1969 to the 1963 BP. A dissolution test was added to the Metformin Tablet monograph in the 1980 BP. Metformin Oral Solution and Metformin Tablets are included in the 2014 BP.

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[73] Östholm, I., 1995. *Drug Discovery: A Pharmacists Story*. Apotekarsocieteten/Swedish Pharmaceutical Society, Stockholm.

[74] Bailey, J.J.C.J. and Turner, R.C., 1996. Metformin. *New England J. Med.* 334(9): 574–9.

Sodium Warfarin

In the 1920s attacks of fatal bleeding occurred in cattle in North Dakota and Alberta in Canada. The Canadian veterinary surgeon F.W. Schofield identified the cause of the disease as being due to hay containing mouldy sweet clover. He separated some good clover from damaged clover and fed samples of each to a different rabbit. The damaged clover killed the rabbit from a fatal bleed. In the 1930s Professor Karl Paul Link at the University of Wisconsin started trying to identify the causative chemical.[75] One of his students, Harold Campbell, isolated a small amount, and then Mark Stahmann was able to produce enough material for chemical identification to be made.[76] The compound was identified as dicoumarol. During World War II, Link prepared a range of other coumarin derivatives. The most effective of these derivatives, warfarin, was marketed in 1948 as a rat and mouse poison. The name of the drug is derived from WARF – Wisconsin Alumni Research Foundation. The drug was marketed in the 1950s for humans as an anticoagulant.

Monographs for Warfarin and Warfarin Tablets were included in the 1963 BP. Because of the critical nature of the dosing of warfarin – achieving the right anticoagulant dose without untoward risk of bleeding, a dissolution test was added as soon as the methodology became established. The monograph in the 1980 BP included the dissolution test. The 1980 BP included monographs for Warfarin Sodium, Warfarin Sodium Clathrate, Warfarin Oral Suspension and Warfarin Tablets. The 2014 BP contains the same monographs.

[75] Pirmohamed, M., 2006. Warfarin: Almost 60 Years Old and Still Causing Problems. *Br. J. Clin. Pharmacol.* 625(5): 509–11.

[76] Stahmann, M.A., Heubner, C.F. and Link, K.P., 1941. Studies on Hemorrhagic Sweet Clover Disease. V. Identification and Synthesis of the Hemorrhagic Agent. *J. Biol. Chem*. 138: 513–27.

Chapter 8
Changes in Analytical Methods 1864–2014

An essential condition for any fruitful research is the possession of suitable methods. Any scientific progress is progress in the method.

(Mikhail Tswett)[1]

Chapter 1 mentioned that the 1836 edition of the *London Pharmacopoeia* included for the first time short notes on how to check the purity of chemicals for use in medicinal products. By this date the chemical remedies had increased in number and importance. The tests included identity tests, limit tests, solubilities and specific gravities. The fourth–fifth-century Greek alchemist Synesios introduced the use of a hydrometer for measuring the density of liquids. He called his device a hydroscopium.[2] However his invention was forgotten and the great Anglo-Irish chemist Robert Boyle (1627–1691) rediscovered the principles. Boyle was born in Munster, Ireland, the fourteenth child of Richard Boyle, the first Earl of Cork. He was educated at Eton College with his brother, and thereafter travelled widely to France, Switzerland and Italy where he studied. He set up a laboratory in Stalbridge, Dorset in 1649. In late 1655 he moved to Oxford joining a group of philosophers based at Wadham College. He was present at the first meeting of the Royal Society and was active in its meetings. In 1668 he moved to London in a house in Pall Mall equipped with a laboratory. In 1690 Boyle published *Medicina Hydrostatica or Hydrostaticks applied to the Materia Medica*, in which he described the use of specific gravity as a means of detecting drug adulteration.[3]

The monographs in the 1864 edition of the *British Pharmacopoeia* (BP) built on this earlier experience and used a variety of analytical methods to control drug substances, excipients and preparations. The monographs included inorganic chemicals, herbal drugs and drugs such as the alkaloids which had

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[1] Mikhail Tswett, *Chromatographic Adsorption Analysis. Selected Works*. V.G. Berezkin, translated by Mary Masson, 1990. London: Ellis Horwood Series in Analytical Chemistry.

[2] Szabadvary, F., 1966. *History of Analytical Chemistry*, translated by Gyula Svehla. Oxford: Pergamon Press.

[3] Boyle, R., 1690. *Medicina Hydrostatica or Hydrostaticks Applied to the Materia Medica Shewing How by the Weight that divers Bodies, used in Physick, have in water; one may discover Whether they be Genuine or Adulterate*. Printed for /Samuel Smith at the Sign of the Princes Arms, in St Paul's Church-Yard.

been extracted and purified from their botanical sources. The tests under the heading 'Characters' in the monographs often included tests to identify adulteration. For example the Acacia monograph specified that a sample did not become blue when iodine solution is added – this test would identify starch or starch-containing material as an adulterant. Other tests to limit adulterants and impurities included melting points and specific gravities – particularly of liquids. As Chapter 2 indicated, adulteration and counterfeiting of drug substances was rife in the nineteenth century. Therefore the BP monographs played a vital role in providing analysts with suitable means of detection.

The analytical methods in the BP stem from a number of sources. Some were derived from fundamental and applied research in academic, government and industrial laboratories (see below). Many of the methods in the early editions of the BP derived from work done in the laboratories of the Pharmaceutical Society of Great Britain and its Department of Pharmaceutical Sciences. Others came from pharmaceutical companies developed in support of their own products, from the BP Commission's own laboratory or other of the European official laboratories in the case of *European Pharmacopoeia* monographs.

Many of the methods stem from the fundamental research of investigators who developed completely novel analytical techniques. The twelfth-century French scholar and philosopher Bernard of Chartres, later reiterated by Isaac Newton, is reported as comparing us to 'dwarfs perched on the shoulders of giants ... we see more and further than our predecessors, not because we have keener vision or greater height, but because we are lifted up and borne on their gigantic stature'.[4] The current BP monographs can be said to be built on the scientific advances made by giants such as Robert Boyle, Robert Bunsen, Mikhail Tswett, J.J. Thomson, Arnold Beckman, Archer Martin and Richard Synge, Edward Purcell, and Csaba Horvath. Some of these key advances are discussed in relation to the development of BP monographs in this chapter.

Metric System in Pharmaceutical Analysis

The 1864 BP used the Imperial system of weights and measures for the analytical methods. For example the Volumetric Solution of Nitrate of Silver was defined as having 148.75 grains of Nitrate of Silver in one pint of Distilled Water. The 1885 BP moved to the use of the metric system of Weights and Measures in parallel with the Imperial system for volumetric solutions and titrations. The Fahrenheit scale was used for temperature, but the Centigrade equivalent was given in parentheses. By the 1914 edition the thermometric scale used was now Centigrade. Modern analysts used to working in a warm laboratory may be

[4] Troyan, S.D., 2004. *Medieval Rhetoric: A Casebook*, 10. London: Routledge.

interested to note that the volumetric glassware used was graduated at 15.5°C; modern glassware is graduated at 20°C. The 1914 edition defined all of the volumetric solutions using the metric system in terms of normality – thus the Solution of Hydrochloric Acid used was either N/1 or N/10 – normal or one-tenth normal. Normality is used as a measure of the concentration, and is defined as being the gram equivalent weight of the substance per litre of solution. The gram equivalent weight is a measure of the reactive capacity. For Hydrochloric Acid volumetric solution an N/1 solution contained 36.48 grams of HCl in 1,000 millilitres.

The early metric system was based on three units: the centimetre, the gram and the second. This system was called the CGS system. The Système International d'Unités was adopted in 1960 by the international authority on units of measurement, the General Conference on Weights and Measures. This is called the SI system. It is based on seven units – the metre, kilogram, second, ampere, kelvin, candela and the mole. The 1980 BP announced that the *Pharmacopoeia* had moved to the SI system of units. Normality was replaced by molarity for volumetric solutions in this edition.

Volumetric Analysis

The great Anglo-Irish scientist Robert Boyle has already been mentioned in respect of his work on the use of specific gravity to detect adulteration in medicinal substances. In 1663 he also published a description of the use of an indicator in the reaction between acids and based. He used the fluorescent blue aqueous extract from *Lignum nephreticum* which disappeared in acid but reappeared when potash was added. Boyle was able to estimate the strength of an alkali or acid by the amount required to restore or destroy this blue colour. *Lignum nephreticum* or 'kidney wood' is wood from the Mexican kidneywood tree *Eysenhardtia polystacha*.[5]

Volumetric analysis is considered to have originated in France in the eighteenth century.[6] François-Antoine-Henri Descroizelles (1751–1825) was born in Dieppe. His family had been pharmacists for four generations. Henri studied chemistry in Dieppe and Paris. He developed the first burette in 1791, and published a paper on acid-base titrations in 1806 entitled '*Notices sur les alcalis du commerce*'. His design was improved by Joseph Louis Gay-Lussac, the great French chemist and physicist. Gay-Lussac (1778–1850) was born in

[5] 1977. *A History of Analytical Chemistry*, edited by H.A. Laitinen and G.W. Ewing. Washington: Division of Analytical Chemistry of the American Chemical Society.

[6] Szabadvary, F., 1966. *History of Analytical Chemistry*, 208–240, translated by Gyula Svehla. Oxford: Pergamon Press.

the town of Saint-Leonard in the Limousin in France. He studied and worked under Berthollet at the École Polytechique in Paris. He published a paper in 1824 where he coined the terms 'burette' and 'pipette'. The first text book on titrimetry was written by the German chemist Karl Leonhard Heinrich Schwarz (1824–1890). He was born in Eisleben and studied in Paris. Schwarz's book was entitled *Praktische Anleitung zu Maasanalysen (Titrir-Methode)* and was published in Braunschweig in 1850. The German chemist Karl Friedrich Mohr (1806–1879) was born into the family of a Koblenz pharmacist. He studied in Heidelberg, Berlin and Bonn before returning to work in the family business. He published his better known and more extensive book on volumetric analysis in 1855, *Lehrbuch der chemisch-analytischen Titrir-methode* (*Textbook of Titration Methods in Chemical Analysis*). Mohr also improved the design of the burette by adding a tip at the bottom and a metal clip – a 'Mohr's clip' – which made it much easier to use.

Many of the inorganic chemical monographs in the BP 1864, such as acetic acid, arsenious acid and hydrocyanic acid, included volumetric titrations for the assay, but only gave an absolute theoretical value – at 100 per cent. No range of assay limits was considered. The 1864 BP gave sparse details of the apparatus to be used for the volumetric analyses apart from mentioning the use of an alcimeter – a tube which 'holds 100 grains of distilled water at 60°, and and is divided into 100 parts of equal capacity'. The 1867 edition of the BP which was edited by Theophilus Redwood and Mr Warrington improved the descriptions of the analytical methods in many of the monographs. The new edition employed volumetric titration in 25 of the monographs. For the first time it contained a detailed description of the apparatus – flask, a graduated cylinder and a burette. Again however, only the theoretical values – 100 per cent – were stated in the monographs. By the 1885 BP further details on volumetric analysis were included with details of indicators such as mucilage of starch used for its intense blue colour with iodine, a solution of ferricyanide of potassium used for its blue precipitate with ferrous salts, litmus used for its red colour with acids and blue colour with alkalis, potassium chromate used to give a red colour with silver nitrate, and tincture of phenolphthalein to give an intense colour with sodium or potassium hydroxide. The 1914 BP also introduced a series of tests for fixed oils, fats, waxes and beeswax and volatile oils. The tests were all given in Appendix VII to the BP. Many of these tests involved titration or gravimetric analysis.

One of the early textbooks on pharmaceutical analysis was written by Charles Hampshire in the early years of the twentieth century. The second edition of his *Volumetric Analysis for Students of Pharmaceutical and General Chemistry*

was published in 1919[7] and included chapters on acidimetry and alkalimetry, determinations involving oxidation and reduction, and precipitation reactions. Hampshire revised his book when he became the secretary to the British Pharmacopoeia Commission after the publication of the 1932 BP. The new edition of his book included the methods in the monographs in the 1932 edition.[8]

It had been known since the early twentieth century that colour changes for indicators and the reactions of bases and acids can occur in non-aqueous solvents. In 1912 Folin and Flanders published a paper on titration of acids in benzene, chloroform and chloroform-ethanol mixtures.[9] In 1927 Conant and Hall at Harvard University published their studies of the behaviour of weak bases in glacial acetic acid.[10, 11] In the 1940s more extensive studies were carried out, and the use of non-aqueous titration was gradually adopted in the BP. The assay for Cinchocaine Hydrochloride in the 1958 BP was by titration with perchloric acid in glacial acetic acid.

Gravimetric Analysis

Gravimetric analyses were also quite commonly employed in early editions of the BP. For example an extraction, then drying and weighing, was part of the monographs for opium and cinchona bark to determine the amount of alkaloid present. The 1864 BP monograph for opium specified that 6–8 per cent of morphine should be present, and for cinchona bark that it should contain not less than 2 per cent quinine. Experience with the testing of batches of drugs would often lead to a tightening of the specification in the monograph. The monograph for opium in the 1885 BP, again using a gravimetric assay, stated that '100 parts of dry powdered opium shall yield not less than 9.5 parts and not more than 10.5 parts of morphine'. The monograph stated that the opium must be that obtained in Asia Minor. The 1867 textbook entitled *An Introduction*

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[7] Hampshire, C.H., 1919. *Volumetric Analysis for Students of Pharmaceutical and General Chemistry*. Second Edition. London: J & A Churchill.

[8] Hampshire, C.H., 1933. *Volumetric Analysis for Students of Pharmaceutical and General Chemistry*. Fifth Edition. London: J & A Churchill.

[9] Folin, O. and Flanders, F., 1912. Is Ionization as Indicated by Conductivity a Necessary Prerequisite for the Combination of Acids with Bases. *J. Am. Chem. Soc.* 34(6): 774–9.

[10] Hall, N.F. and Conant, J.B., 1927. A Study of Superacid Solutions I: The Use of the Chloranil Electrode in Glacial Acetic Acid and The Strength of Weak Bases. *J. Am. Chem. Soc.* 49(12): 3047–61.

[11] Conant, J.B. and Hall, N.F., 1927. A Study of Superacid Solutions II: A Chemical Investigation of the Hydrogen Ion Activity of Acetic Acid Solution. *J. Am. Chem. Soc.* 49(12): 3062–70.

to Pharmaceutical Chemistry by Professor John Attfield[12] gave a number of examples of gravimetric analysis such as barium determined as the sulphate, magnesium by converting to magnesium oxide, aluminium converted to the hydroxide and then weighed as the oxide, and bismuth as the sulphide.

Optical Rotation

In the 1867 BP the monograph for Acidum Carbolicum (phenol) contains the following specification: 'It does not affect the plane of polarisation of a ray of polarised light', which is the first reference in the BP to an optical rotation test, albeit one where the details of the apparatus and method are not given. Simple polarimeters had been in use since the 1820s. The 1914 BP included more details of the test in Appendix VIII for Determination of Optical Rotation where it also defined the specific optical rotation.

Identification Tests

The early editions of the BP from 1885 all included a section entitled Characters and Tests. These were a variety of tests which helped to identify the particular medicinal substance. Organoleptic testing for appearance, colour, smell and taste were widely used. Thus Chloroform was described as being 'a limpid colourless liquid, of an agreeable ethereal odour, and a sweet taste'. Even potent poisons were defined in terms of their taste, so for example Strychnine was described as 'being sparingly soluble in water, but communicating to it an intensely bitter taste'. Unsurprisingly, with modern health and safety considerations, tests for taste were omitted from the BP by a General Notice in the 1973 BP excluding taste as an official standard. The introduction to the 2001 BP announced that tests for the presence or absence of a particular odour would also be omitted. Appearance of a medicinal substance was clearly important from the early editions of the BP. The herbal ingredients were described in detail in terms of their botanical source and a detailed histological description was provided. Inorganic and organic chemicals were described in terms of their crystalline morphology. For example the monograph for Iron Sulphate in the 1885 BP described it as 'oblique rhombic prisms, of a pale greenish-blue colour'. By the 1932 BP the headings in the monographs had been further refined and 'Characters' described appearance and solubility in several solvents.

[12] Attfield, J., 1867. *An Introduction to Pharmaceutical Chemistry*. London: John van Voorst.

As with the current BP the substances were described in terms of their solubility profile. In the 1885 BP they were described as being soluble or sparingly soluble in water, alcohol, chloroform, and acid and alkali solutions.

Other physical properties were also used for identification and purity testing. Amyl Nitrite in the 1932 BP was described as having a specific gravity of between 0.874 and 0.884, and a boiling point of not less than 85 per cent distilling between 90°C and 100°C. Barbitone was described in its 1932 BP monograph as having a melting point between 189°C and 192°C. Melting points are both an identification test and a measure of any possible impurities present, as these will usually lower the melting point and also increase the melting range.

Chemical reactions were also used for identification in individual monographs. The 1885 BP monograph for Ammonium Chloride – Sal Ammoniac – included a test for the aqueous solution by reacting with silver nitrate to form a 'copious curdy precipitate' of silver chloride. The 1914 BP included the detail of these reactions and tests in Appendix IV. The preface to this edition stated that for convenience all of these tests were brought together in this appendix rather than 'being many times repeated in the text'. The 1914 BP included 38 of these qualitative tests for 'basic and acidic radicals'. The 1932 BP included these tests under the heading of 'Tests for Identity' in monographs. By the 1948 BP many monographs contained numerous chemical identification tests. The monograph for Morphine Sulphate for example contained eight separate chemical identification tests. The 1958 BP retained all these chemical tests but added two instrumental ones – a UV spectrophotometric test to determine the extinction of a 0.01 per cent solution at 285 mμ and the specific optical rotation of a 2 per cent solution. The BP and the *European Pharmacopoeia* gradually moved to the use of instrumental methods as the main means of identification for organic drug substances. The 1963 BP introduced the use of infrared (IR) absorption spectroscopy for identification tests, firstly by comparing the spectrum of the test sample with that of a chemical reference standard. The 1977 BP Veterinary introduced the use of published IR spectra instead of chemical reference standards. The 1980 BP included a companion volume of published IR spectra. The 1980 BP monograph for the beta-blocker Oxprenolol Hydrochloride included four identity tests – an infrared spectrum, determination of the UV absorption maximum and light absorption, determination of the melting point of oxprenolol base, and a test to show the presence of a chloride salt. The 2014 *European Pharmacopoeia* monograph for Morphine Sulfate uses an IR spectrophotometric method – the spectrum of the sample is considered to be concordant with the published reference spectrum if the absorption maxima of the principal bands in the sample correspond in position, relative intensities and shape to those in the published reference spectrum.

Edward Purcell (1912–1997) graduated in electrical engineering at Purdue University and then obtained his MA and PhD at Harvard. After World War II

he returned to Harvard and in 1946 he discovered nuclear magnetic resonance (NMR) with his colleagues Pound and Torrey.[13] He was awarded the Nobel Prize in 1952 in Physics with Felix Bloch of Stanford University[14] who had independently discovered the principles. However NMR spectrometers were very expensive and were not used routinely in quality control. The 1980 BP introduced the use of NMR as an identification test for corticosteroid sodium phosphates such as Dexamethasone Sodium Phosphate where an IR identity test was not suitable. The NMR spectrum was compared with that from a reference standard and had to be concordant with it. However the test was optional and could be omitted if a combination of other identification tests were carried out. The use of NMR was extended and is now used in the *European Pharmacopoeia* monographs for a wide range of drugs and excipients. It is used in the identification tests for Buserelin, Farmed Cod Liver Oil, Goserelin, Heparin Sodium, Heparin Calcium, Low Molecular Weight Heparins, Premextred Disodium Heptahydrate, Farmed Salmon Oil, Tobramycin and Medronic Acid for Radiopharmaceutical Preparations. It is used for the assay of Hydroxypropylbetadex and Hydroxypropyl Starch, and for the characterisation of some surfactants such as Lauromacrogol 400 and Poloxamer.

Impurity Control

It has sometimes been asserted that there were no specific limits on impurities in drug substances in the BP until well into the twentieth century. However the monograph for Quinine Sulphate in the 1885 BP included limit tests for cinchonine and cinchonidine, quinidine and cupreine. The tests relied on separation of these impurities and then drying and weighing them. The monograph specifies that 'Sulphate of Quinine should not contain much more than five per cent of sulphates of other cinchona alkaloids'. By the time of the 1898 BP the limits in the Quinine Sulphate monograph had been tightened to 'should not afford any appreciable reaction characteristic of cinchonine, quinidine, cupreine or amorphous alkaloid, and should not yield more than a total of 3 per cent of crystals of impure cinchonidine'.

In 1746 the English chemist John Roebuck, working in Birmingham, designed a process for production of sulphuric acid using lead-lined chambers. These could be made much larger than the glass containers used earlier and this

[13] 1952. Edward Purcell: Nobel Prize. http://www.nobelprize.org/nobel_prizes/laureates/1952/purcell-bio.html (accessed July 2014).

[14] 1952. Felix Bloch: Nobel Prize. http://www.nobelprize.org/nobel_prizes/laureates/1952/bloch-bio.html (accessed July 2014).

enabled the scale of production to be dramatically increased.[15] The process was further developed by Gay-Lussac in the nineteenth century. It was called the 'lead chamber process'. However one of the disadvantages of the process is that the lead lining was contaminated with arsenic and other materials which then in turn contaminated the acid with lead and arsenic. If sulphuric acid was used in the manufacture of an inorganic or organic drug it could introduce trace levels of lead or arsenic. The 1914 BP introduced limits for both of these metals in a wide range of inorganic and synthetic drugs in Appendices V and VI. The limits of lead ranged from 0.5 to 25 parts per million. The limits for arsenic ranged from 1.4 to 1,000 parts per million. The test for lead was a colorimetric one using the reaction with potassium cyanide. The level of arsenic was determined by the production of a yellow stain on mercuric chloride paper. Many monographs in the current 2014 edition of the BP continue to have stringent tests for arsenic and lead even though the commercial use of lead chamber sulphuric acid was discontinued decades ago. The 1914 BP also introduced limit tests for chlorides, for sulphates and for iron in many pharmaceutical substances.

The 1932 BP introduced a series of tests in Appendix XII for ash, including acid-insoluble ash and water-soluble ash. These tests involved incineration and then gravimetric assay. A test for sulphated ash was added in the 1948 BP.

The 1932 BP also included some tests for specific named impurities. Appendix IX included details of the tests for absence of cotton-seed oil in other oils, sesame oil in other oils and arachis oil in other oils. Some of the other monographs contained limits for specific impurities. For example the monograph for Cresol had a limit of not more than 0.5 per cent by volume of hydrocarbon oil and not more than 0.1 per cent by volume of volatile bases calculated as pyridine.

The 1948 BP included some monographs with specific limits for named impurities, such as that for Acetylsalicylic Acid (Aspirin) with a colorimetric test for Salicylic Acid. There were tests for acetone and aldehyde, methyl alcohol, peroxides, sulphurous acid and other free acids in the monograph for Anaesthetic Ether. However in this edition some drug substance monographs still lacked an assay and many lacked any impurity tests apart from perhaps a limit for lead and an ash content. Even as late as 1980 some monographs such as that for Amylobarbitone still lacked an assay. For some monographs such as that for Clofibrate it was argued that an assay was unnecessary as the drug was identified by specific tests including infrared, and there were tests to control all likely impurities. However monographs were constantly being updated and in the 1993 BP the *European Pharmacopoeia* monograph for Amylobarbitone contained an assay by non-aqueous titration.

[15] Kiefer, D.M., 2001. Sulfuric Acid: Pumping up the Volume. http://pubs.acs.org/subscribe/archive/tcaw/10/i09/html/09chemch.html (accessed July 2014).

Up to the 1990s it was common for impurity tests to be rather general ones for so-called 'related substances'. The introduction to the 1993 BP stated that the tests for related substances were usually included in monographs for synthetic, organic medicinal substances. They might be specific or general and may control impurities or degradation products. Specific tests were included where a particular impurity needed to be controlled on toxicity grounds – such as the thin layer chromatography (TLC) test for the genotoxic impurity hydrazine in the monographs for Isoniazid used in the treatment of tuberculosis. The 1993 BP announced a change in policy in that both the BP and European Pharmacopoeia Commissions had decided, following request from users, that monographs would in future state the identity of impurities known to be controlled by the monograph. The vague reference to 'users' rather concealed the concerns raised by the medicines regulatory agencies in Europe and the United States that when new manufacturers of existing synthetic chemical drug substances started selling their materials when the originator's patent expired, their drug would often be made using a different synthetic route or under different manufacturing conditions, thus leading to a different impurity profile. If there were new impurities the possibility of toxicity would need to be considered. As an example of the new format of monographs, the new *European Pharmacopoeia* monograph for the cytotoxic drug Cytarabine contained the statement 'The impurities limited by this monograph include uracil arabinoside and uridine'. The new monographs were designated as 'transparent' monographs. This policy has been implemented in subsequent editions of the British and European pharmacopoeias.

In the 1980s the philosophy for setting the monograph specification for drug substance was that, provided there was a variety of analytical techniques used for identification and control of impurities, it was sufficient for the assay to be a non-specific one – such as for example a non-aqueous titration. The introduction to the 1993 BP mentions that manufacturers often use stability-indicating methods of assay such as liquid chromatography, but that it was felt that this does not provide adequate assurance of quality for an independent analyst. However manufacturers who validate and utilise stability-specific methods for assay such as high pressure liquid chromatography (HPLC) have often been unwilling to change their methods so the pharmacopoeia has increasingly adopted such methods in its monographs.

Spectrophotometry[16]

In 1873 the physiologist Carl Vierordt devised apparatus for obtaining absorption spectra. He used it to determine the spectra of many coloured materials such as chromate and fuchsine, and to publish tables of extinction values – measures of how strongly they absorb light at a particular wavelength. Photoelectric detectors were patented by Wilhelm Berg in 1911 who used them in a photoelectric colorimeter. Early colorimeter instruments were manufactured by Klett and the Fisher Scientific Company. In 1935 Arnold J. Beckman formed a company called National Technical Laboratories which developed a spectrophotometer which could be used over the ultraviolet (UV) and visible spectrum. In 1941 they started selling the Beckman DU spectrophotometer which was a workhorse in countless laboratories for decades. It continued in production until 1976. It used a prism monochromator, a hydrogen lamp for the ultraviolet spectrum and an incandescent lamp for the visible spectrum.

The 1936 *Addendum* to the 1932 BP introduced the use of the UV absorption spectrophotometer as an alternative method for determination of vitamin A in cod liver oil. However the biological assay was still regarded as the definitive method. The method was used in several monographs in the 1948 BP. In the monograph for Halibut Liver Oil the test was used to control for whale-liver oil by comparing the absorption at two wavelengths of 300 and 328 mμ, the absorption at 328 mμ being not greater than 75 per cent of that at 400 mμ. The method was also used to determine the Vitamin A content in Concentrated Solution of Vitamin A and in Concentrated Solution of Vitamin A and D. It was used in the monograph for Calciferol where the extinction coefficient was defined as not less than 460 at 265 mμ. The use of UV spectrophotometry rapidly increased in subsequent editions of the BP both as part of identification tests and in assays.

Professor Harrison M. Randall (1870–1969) of the University of Michigan led a team of investigators who began to carry out an intensive programme in the 1920s to develop IR spectrophotometry and apply it to chemical problems. They published spectra of hydrocarbons and other compounds and stimulated research by others. Difficulties with the design of instruments were gradually overcome. Perkin Elmer introduced a recording instrument in 1944 and Baird Associates a recording double beam optical null recording spectrophotometer in 1947. In 1957 Perkin Elmer introduced their model 137 which was a low cost bench instrument which made the use of IR spectrophotometry accessible to every chemical laboratory. The 1963 BP introduced the use of infrared absorption

[16] 1977. *A History of Analytical Chemistry*, 138–57, edited by H.A. Laitinen and G.W. Ewing. Washington: Division of Analytical Chemistry of the American Chemical Society.

spectra in the range 2.5 μ to 15 μ, that is 4,000 to 66 cm^{-1}, for identification tests. The test required the comparison of the spectra of an Authentic Specimen or British Chemical Reference Substance with that of the test batch. The 1977 BP Veterinary introduced the use of published infrared spectra instead of chemical reference standards. The 1980 BP included a companion volume of published infrared spectra. The reference spectra are now included in the main volumes of the BP.

Dispersive IR spectrophotometers such as those mentioned earlier work by shining a light beam at a sample and measuring how much light is absorbed, and then repeating for different wavelengths. A Fourier Transform Infrared (FTIR) machine works by shining a beam with many wavelengths at the sample and then measuring how much is absorbed by the sample. The beam is modified to contain different frequencies and the measurement is repeated. This is done many times. A computer analysis then combines all of the data using the mathematical Fourier transform algorithm – named in honour of the French mathematician and physicist Jean Baptiste Fourier (1768–1830). FTIR was only practicable when commercial mini-computers were available in the mid-1960s. The first commercial FTIR was the Digilab FTS-14 in 1969. The 1996 *Addendum* included FTIR spectra for diflucortolone valerate and the free base of naftidofuryl oxalate. It announced that in future publications all new published infrared spectra would be on an FTIR instrument.

As mentioned earlier in the section of this chapter on Identification, Edward Purcell discovered nuclear magnetic resonance (NMR) with his colleagues Pound and Torrey in 1946. He was awarded the Nobel Prize in Physics with Felix Bloch of Stanford University who had independently discovered the principles. It was first used as an identity test for corticosteroid sodium phosphate monographs in the 1980 BP. By 1993 the cost of the commercial instruments had reduced so that it was more commonly used by manufacturers. It was used in a number of monographs and described in Appendix IIC to the BP 1993.

The German chemist Robert Bunsen (1811–1899) was born in Göttingen in Westphalia.[17] He attended school in Holzminden and then after obtaining his PhD lectured at Göttingen, at Kassel and Marburg. In 1852 he came to the University of Heidelberg. In 1859 he worked with Gustav Kirchoff to study the emission spectra of elements heated in a flame, and they invented an early spectroscope. Henrik Lundegårdh (1888–1969) was born in Stockholm.[18] He obtained his first degree and then his Phil Dr at the University of Stockholm. He studied abroad in Germany and then moved to the University of Lund in 1912. In 1915 he set up a laboratory studying plant physiology. In 1926 he was

[17] Robert Bunsen. http://www.nndb.com/people/900/000095615.

[18] Larkum, A.W.D., 2003. Contribution of Henrik Lunegårdh. *Photosynthesis Research* 76: 105–10.

made head of the Botany Division of the Central Institution for Agricultural Research near Stockholm. His research was on the uptake of salts by plant roots. To help in his research he developed a sensitive and accurate flame photometer with an acetylene-air flame and an aqueous nebuliser to present the solution to the flame as a spray. The commercial flame photometers developed from the late 1940s used coloured filters to select wavelengths. The 1968 BP introduced the use of flame photometry to measure potassium, sodium and calcium. The monograph for Sodium Chloride used flame photometry to limit the level of potassium to no more than 0.1 per cent.

Alan Walsh (1916–1998) was a British physicist, born in Hoddlesdon a village near Darwen in Lancashire.[19] He graduated in physics at Manchester University. After working during World War II at the British Non-Ferrous Metals Research Association he moved to Australia in 1946 to work in the Chemical Physics Section of the Commonwealth Scientific and Industrial Research Organisation. During the 1950s he carried out research on atomic absorption spectroscopy. The instrument which Walsh developed would provide an easy and accurate method to determine levels of more than 65 elements. Walsh was knighted in 1976. An appendix to the 1980 BP entitled Atomic Spectrophotometry: Emission and Absorption was published with details of reagents for determination of barium, calcium, copper, lead, lithium, magnesium, mercury, palladium, potassium, sodium, strontium and zinc. The Appendix on Flame Photometry was then omitted.

Joseph John Thomson[20] (1856–1940) was born in Cheetham Hill, Manchester. He studied at Trinity College Cambridge from 1876 and became a Fellow there in 1880. He became a lecturer in 1883, Professor of Experimental Physics in 1884 and its Master in 1918. Thomson worked on cathode rays by studying the discharge of electricity through gases. His discovery of the electron was announced in April 1897. Working with Francis Aston he built the first mass spectrograph to measure the mass of charged atoms. Writing in 1913 in his book *Rays of Positive Electricity* Thomson encouraged chemists to use the new technique:

> I feel sure that there are many problems in chemistry, which could be solved with far greater ease by this than any other method. The method is surprisingly sensitive – more so than even that of spectrum analysis, requires an infinitesimal amount of material, and does not require this to be purified.

[19] Walsh, A. Biographical Entry. Encyclopaedia of Australian Science. http://www.eoas.info/biogs/P000860b.htm.

[20] Falconer, I., 2004. Thomson, Sir Joseph John (1856–1940). *Oxford Dictionary of National Biography*. Oxford: Oxford University Press.

By the 1940s commercial mass spectrometers became available and were used by industrial research chemists. From the 1950s chemists were able to work out the fragmentation patterns of organic molecules to enable them to determine the structures of unknown molecules. In the 1980s new ionisation techniques enabled MS to be applied to large proteins.

The 1993 BP included the use of a mass spectrometer as a detector after a capillary gas chromatographic column in the limit test for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the monograph for the antiseptic material Hexachlorophane. This dioxin impurity was shown to be fetotoxic, immunosuppressive and carcinogenic in animal studies.[21] It is classified as a human carcinogen by the US Environmental Protection Agency. This method allowed TCDD to be limited to less than two parts per billion. In the 2014 BP mass spectrometry after GLC – GLC-MS – is used to identify the six major glycoforms in the *European Pharmacopoeia* monograph for Interferon Beta-1a Concentrated Solution by comparing them to a reference standard. The 2014 BP uses this same technique to control related substances in the *European Pharmacopoeia* monograph for the aerosol propellant Norflurane and to control Impurity B in the monograph for the antiviral drug Oseltamivir Phosphate – marketed for treatment of influenza by Roche under the trade name Tamiflu. Mass spectroscopy is one of the techniques which can be used to characterise the proteins in Human Factor VIII, Human α-1-proteinase inhibitor and Human Papilloma Virus.

Chandrasekhara Raman (1888–1970) was born in Thiruvanaikaval, Trichinopoly in India.[22] He studied at the Presidency College in Madras and gained his BA in 1904 and his MA in 1907. After working as a civil servant he was appointed the Palit Professor of Physics at the University of Calcutta in 1917. He was awarded the Nobel Prize for Physics in 1930 for his work on scattering of light and the discovery of the Raman effect. Raman spectrometry is included as an appendix in the 2014 BP. It is regarded as complementary to IR spectrometry as it is particularly sensitive to non-polar bonds. Raman spectra can be obtained from solids, liquids and gases. It is listed as one of the available techniques to study polymorphism.

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[21] 1984. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, 'dioxin'). DHSS (NIOSH) Publication No. 84–104. Current Intelligence Bulletin 40. Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/dov/84–104/.

[22] Falconer, I., 2004. Raman, Sir (Chandrasekhara) Venkata (1888–1970). *Oxford Dictionary of National Biography*. Oxford: Oxford University Press.

Chromatography

Mikhail Semonovich Tswett was born in the Italian town of Asti in 1872 to a Russian father.[23] He lived in Lausanne in Switzerland until he was 24. He was a botanist and his PhD from the University of Geneva was on the structure of plant cells. He went to live in Russia to join his father, but had to start his studies afresh to obtain qualifications which would enable him to obtain a post at a Russian university. He obtained his master's degree in 1901 from the University of Kazan and obtained a position at the University of Warsaw, then in Russian occupied Poland. His master's thesis had included studies on the effect of different solvents on chlorophyll and the associated pigments dissolved in ethanol and impregnated on filter paper. He continued his investigations in Warsaw with adsorbent powder packed into a tube onto which a petroleum ether solution of plant pigments was added. By adding solvent to the tube, rings of green and yellow separated and these could be separately eluted from the column. He summarised his results on 8 March 1903 in a lecture to the Biological Section of the Warsaw Society of Natural Sciences. In 1906 Tswett published his results in the journal of the German Botanical Society. In two papers he described his method and coined the terms 'chromatography' and 'chromatogram'. Chromatography is derived from two Greek words – *chroma* for colour and *graphein* to write. Tswett mentioned that although his column chromatography method had been applied to coloured plant pigments it could also be used for other compounds. In 1908 Tswett published his work in a book in Russian entitled in English translation *Chlorophylls in the Plant and Animal World*. Tswett died in June 1919. During the next 30 years his work had little impact until the technique was revived by Edgar Lederer a researcher at the University of Heidelberg who studied carotenoids in egg yolk.

The next major advance was made by Archer Martin (1910–2002) and Richard Synge (1914–1994). Synge was a biochemist, educated at Winchester and Trinity College, Cambridge. Archer Martin was educated at Bedford College and Cambridge and was another biochemist. They collaborated at Cambridge on the separation of amino acid derivatives from wool – Synge was at the time on a scholarship from the International Wool Secretariat in Leeds. They first evaluated a countercurrent apparatus, but this was slow and complex, so they moved to using a column with a chloroform/ethanol mix as mobile phase and a stationary phase of silica gel moistened with water. This was the start of column partition chromatography. Martin and Synge developed and applied this method to the analysis of proteins and peptides such as gramicidin. Martin

[23] Ettre, L.S., 2008. MS Tswett and the Invention of Chromatography. In *The Evolution of Chromatography*, edited by J.V. Hinshaw. London: Imperial College Press.

and Synge were awarded the Nobel Prize in 1952 for their work on partition chromatography.[24, 25]

In 1855 the German chemist Friedlieb Runge published his work on separation of dyes on filter paper. He is considered to be the originator of paper chromatography. In 1944 Martin and Synge extended their work from columns to sheets and thus paper chromatography. Martin moved to the National Institute for Medical Research where he worked with Anthony James. There they developed apparatus using nitrogen as the mobile phase to separate organic acids. This was the beginning of gas liquid chromatography (GLC).

In 1938 two Russian scientists, N.A. Ismailov and M.S. Schreiber, investigated the use of a thin layer of different adsorption media as a stationary phase to separate alcoholic plant extracts.[26] In 1949 J.E. Meinhard and N.F. Hall used microscope slides with an alumina adsorbent layer and a binder to separate inorganic ions. Justus Kirchner and a group at the US Department of Agriculture extended this work and found that silicic acid and starch gave a suitable stationary phase layer with suitable solvents as the mobile phase which travels up the stationary phase separating out the components depending on their affinity. They also investigated different methods for visualising the detection of the chromatographic zones such as spray reagents. In Germany Egon Stahl (1924–1986) developed a method using aluminium oxides and silica gel stationary layer on glass plates and in 1956 published his results in the magazine *Die Pharmazie* in an article entitled 'Thin Layer Chromatography'. Stahl was to be a prolific researcher and in 1962 published a handbook on TLC, *Dünnschicht-Chromatographie, ein Laboratoriumshandbuch*.[27] This was translated into English in 1967. In the 1960s commercially pre-coated plates and tanks for development of the plates were marketed.

Paper chromatography was introduced in the 1963 BP in the Related Foreign Steroids test in the monographs for a number of steroid drugs: cortisone, hydrocortisone, fludrocortisone, dexamethasone, methylprednisolone, prednisolone and prednisone. This was effectively both an identification test and a limit test for related steroid compounds. A solution of the steroid was spotted on the strip of filter paper impregnated with formamide alongside a solution of an authentic specimen of the drug. When the paper was eluted with the mobile phase and then dried, the spot for the test solution and the authentic specimen

[24] Gordon, H., 2004. Synge, Richard Lawrence Millington (1914–1994). *Oxford Dictionary of National Biography*. Oxford: Oxford University Press.

[25] Morris, P.J.T., 2004. Martin, Archer John Porter (1910–2002). *Oxford Dictionary of National Biography*. Oxford: Oxford University Press.

[26] Ettre, L.S., 2008. Chapter 16 in *The Evolution of Chromatography*, edited by J.V. Hinkshaw. London: Imperial College Press.

[27] Stahl, E., 1962. *Dünnschicht – Chromatographie: Ein Laboratoriumshandbuch*. Berlin: Springer.

were equidistant from the top of the paper and had the same intensity and order of magnitude. No secondary spot appeared.

Thin layer chromatography (TLC) replaced paper chromatography for the Related Foreign Steroids in the 1968 BP. The test used a silica gel with calcium sulphate stationary phase made on glass plates as described in Appendix XIII Chromatography. After elution with the mobile phase the plate was dried and sprayed with an alkaline tetrazolium blue solution to visualise the spots. TLC was also introduced more widely as a test for impurities in drug substances such as the test for 4-chloroacetanilide in the Phenacetin monograph, which effectively limited this impurity to less than 0.01 per cent.

The introduction of gas liquid chromatography (GLC) in the 1968 BP was largely as a result of work carried out in the BP Commission's own laboratory. It was introduced both for control of impurities and to estimate the bound solvent in medicinal substances. The 0.2 per cent w/w limit test for Dichloromethane in the monograph for Ampicillin Sodium used GLC. The 1973 BP extended the use of GLC to the estimation of the amount of alcohol in galenical preparations such as Opium Tincture, Belladonna Tincture, Cascara Liquid Extract and Colchicum Liquid Extract. The detector used was a flame ionisation detector.

Csaba Horvath (1930–2004) was a Hungarian chemical engineer who then studied for his PhD at Goethe University in Frankfurt on the topic of GLC. He moved to the United States and whilst at the Yale School of Medicine worked on the further development of liquid chromatography.[28] He coined the acronym HPLC for High Pressure Liquid Chromatography in 1970 as the method then used pumps which worked at up 500 pounds per square inch to generate the flow needed in chromatography columns. However when pumps were used at pressures up to 6,000 pounds per square inch the name was changed to mean High Performance Liquid Chromatography. HPLC was first cited in the 1977 *Addendum* to the 1973 BP in the monographs for Idoxuridine and Idoxuridine Eye Drops. The use of HPLC was extended in the 1980 BP, for example in the monograph for Oestradiol Benzoate Injection, and has gradually become the analytical method of choice for many monographs for both the assay and to control impurities. Dr Geoff Carr, who was a senior analyst and then head of laboratory at the BP Commission Laboratory, adds the following:

> HPLC was first used in the 1977 *Addendum* to the 1973 BP in the monographs for Idoxuridine and Idoxuridine Eye Drops. The introduction of this test created an issue of naming specific commercial HPLC columns since official compendia needed to be wary about showing apparent preference to commercial products. Within BP the use of verbiage along the lines that "HPLC columns containing the stationary phase xyz have been found suitable" was adopted to overcome

[28] Ettre, L.S., 2004. In Memoriam: Csaba Horvath. *American Laboratory* May: 4–6.

this. Other compendial publications still continue to struggle with this issue. The use of HPLC was extended in the 1980 BP, for example in the monograph for Oestradiol Benzoate Injection but in addition a major collaborative exercise was set up with ICI, Pfizer and BP Lab to establish a HPLC procedure for the determination of assay and related substances in Oxytetracycline. This was a very novel approach because it required that we first synthesise our own Strong Cation Exchange (SCX) stationary phase by means of reacting HPLC grade 10μm Silica with Trimethyloctylsilylchloride followed by Chlorosulphonic Acid and then packing the product into our own HPLC columns. The collaborative exercise was successful and the HPLC procedure complete with details of the stationary phase manufacture was published and probably provided an alternative approach to getting round the issue of showing preference to commercial manufacturers of HPLC columns by naming specific column materials.

Determination of Water

Some of the monographs in the 1914 BP included a test for loss on drying. The monograph for Potassium Acetate included a specification that it loses not more than 10 per cent of its weight when dried at 100°C. The monograph stated that it contains not less than 90 per cent of pure potassium acetate. The 1932 BP changed the way the limit is expressed to say that it contains not less than 99 per cent of $C_2H_3O_2K$ calculated with reference to the dried substance. The limit for loss on drying was tightened to not more than 5.0 per cent when dried at 100°C. This method of statement of assay limits in terms of the dried substance is one that would eventually be adopted throughout the BP. The 1948 BP had a separate heading entitled Loss on Drying in the Potassium Acetate monograph. The conditions for drying varied somewhat for different substances; for Potassium Iodide the temperature was 110°C, for Morphine Sulphate the temperature was 120°C.

Joseph Karl Fischer (1901–1978) was born in Pasing, a suburb of Munich. He obtained his PhD at the University of Leipzig in 1925 and then went to work for a company involved with the oil industry. One of the major problems in the oil industry was the presence of water, which can lead to the formation of emulsions. In 1853 the great German chemist Robert Bunsen had found that sulphur dioxide could be converted to sulphuric acid by iodine if water was present. Fischer found that by adding a base such as pyridine to the mixture drove the equilibrium strongly to the right. He proposed using a titration where the presence of iodine was used as the end-point. He published his findings in

1935.[29] The method was added to the BP in the 1951 *Addendum* to the 1948 BP and was used in the monograph for Procaine Benzylpenicillin. In the BP method the titration vessel is fitted with two platinum electrodes. The end-point is defined by the use of a battery connected to a variable resistance of about 200 ohms. The resistance is arranged so that a suitable current passes through the platinum electrodes in series with a micro-ammeter. After each addition of the original Karl Fischer reagent the meter needle is deflected. The end-point is shown by a longer standing deflection. Pyridine is harmful if inhaled, causing dizziness, headaches and nausea, so it was eventually replaced by imidazole in the commercial Karl Fischer reagent. The whole system is now sold as a complete commercial kit.

Standards for Tablets

During the period 1885 to 1932 tablets grew to be an increasingly commercially important dosage form as automated production equipment was used by manufacturers for a wider range of products. Despite this, from 1885 to 1947 the BP only included one tablet – Glyceryl Trinitrate Tablets. The 1948 BP contained 49 tablet monographs, which comprised 21 per cent of the monographs for dosage forms. By 1968 there were 220 tablet monographs comprising nearly 50 per cent of the monographs for dosage forms. In 2013 there were 404 tablet monographs comprising 33 per cent of the 1220 individual monographs for dosage forms.

The list of products that can be prescribed on the NHS in the UK is given in the *Drug Tariff*.[30] In 1941 there were 110 mixtures, 45 pills and 100 tablets listed (including different strengths of the same product). By 1973 379 tablets were listed in the *Drug Tariff*, and in 2011 this number had grown to over 1,300. Thus tablets now comprise the major dosage form in clinical use and it is necessary to consider the development of standards for them as this separate section of this chapter.

At the BP Commission meeting in June 1970 Mr Arthur Fishburn, chair of the *ad hoc* Committee on Tablet Standards, reported that they had started considering the provision of tests for 'solution rate' – what would now be called dissolution tests. The disintegration test only measured the time taken for a tablet or capsule to break up into granules. For a drug to be absorbed from the gastrointestinal tract the drug needed to have gone into solution in the body. In

[29] Fischer, K., 1935. Neues Verfahren sur massanalytischen Bestimmung des Wassergehaltes von Flüssigkeiten und festen Körpern. *Angew. Chem.* 48: 394–6.

[30] Electronic Drug Tariff compiled on behalf of the Department of Health by the NHS Business Services Authority, NHS Prescription Services, NHS England and Wales.

February 1972 the discussion in the Commission on the need for solution rate tests for tablets continued. Some commissioners were against the early adoption of the test for a range of tablets as the only available test, published in the United States Pharmacopeia (USP) was apparently being revised. There was also little experience of the test from UK manufacturers. Both the chairman and Mr Adamson – a retired industry chief analyst – stressed the importance of a test to reduce batch to batch variation and eliminate poor quality tablets.

In 1972 an *Addendum* was published to the 1968 *British Pharmacopoeia*. It included the new monographs for Slow Lithium Carbonate Tablets and Slow Orphenadrine Citrate Tablets. These contained the first very crude dissolution tests to measure release of drug from the tablets. These tests used a modification of the disintegration test apparatus.

On 11 September 1972 the BP Commission discussed a letter in the *Lancet* on the bioavailability of digoxin and a number of other published papers.[31,32,33,34] These showed an increase in potency of Burroughs Wellcome's Lanoxin brand of digoxin tablets, and had focused attention again on the issue of bioavailability. The monograph for Digoxin Tablets had been revised in the 1973 edition to include a test for content uniformity, but there was no requirement which would distinguish tablets with different bioavailability. The USP did not apply a test to Digoxin Tablets. The Commission set up a Digoxin Tablets Panel to advise the Commission on improvements in standards which would reduce the variations in bioavailability resulting from differences in methods of tablet manufacture. Digoxin was the most commonly prescribed cardiac glycoside; it is still used in the treatment of supraventricular arrhythmias and cardiac failure. However the difference between a therapeutic dose and a toxic dose is often narrow. In the 1970s there were over 20 brands of digoxin 0.25 mg. About half the patients were being treated with Burroughs Wellcome's brand Lanoxin, which was the first digoxin tablet on the market. In 1969 the manufacturing process for Lanoxin tablets was changed and this led to a two-fold decrease in bioavailability. From 1970 to 1972 low digoxin plasma levels were reported and cardiologists found that many patients were under-digitalised. The differences were associated with

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[31] Johnson, B.F., Fowle, A.S., Lader, S., Fox, J and Munro-Faure, A.D., 1973. Biological Availability of Digoxin from Lanoxin Produced in the United Kingdom. *Br. Med. J.* 4: 323–6.

[32] Shaw, T.D.R., Raymond, K., Howard, M.R., Hamer, J., 1973. Therapeutic Non-equivalence of Digoxin Tablets in the United Kingdom: Correlation with Dissolution Rate. *Br. Med. J.* 4: 763–6.

[33] Shaw, T.D.R, Howard, M.R. and Hamer, J., 1974. Recent Changes in Biological Availability of Digoxin. Effect of an Alteration in 'Lanoxin' Tablets. *British Heart Journal* 36: 85–9.

[34] Johnson, B.F. and Lader, S., 1974. Bioavailability of Digoxin from Rapidly Dissolving Preparations. *Br. J. clin. Pharmac*. 1: 329–33.

differences in the rate of release of the digoxin into solution as measured by an *in vitro* dissolution test. In 1972 Burroughs Wellcome changed the method of tablet manufacture back again to improve the bioavailability of Lanoxin tablets. In 1972 the Council of the Pharmaceutical Society after consulting the Committee on Safety of Medicines advised pharmacists not to dispense Lanoxin on 'open' prescriptions – ones where the brand was not specified. A number of investigations into the dissolution and bioavailability were then reported on Lanoxin and other brands of digoxin. The problem with digoxin bioavailability was to trigger a wider debate on the need to know the bioavailability of different brands of drugs. A leading article in the *British Medical Journal* on 9 September 1972 headed 'Therapeutic Non-Equivalence'[35] drew attention to bioavailability issues with other drugs such as cortisone, spironolactone, tolbutamide and phenytoin. The BMJ article stated that '*in-vitro* dissolution tests, though not completely predictive, do correspond fairly well with plasma levels and yield information which is probably adequate for most drugs'. Medical advice was sought by the BP Commission on what was the most clinically desirable pattern of release of drug from batches of digoxin tablets.

By March 1973 an *in vitro* solution rate test for Digoxin Tablets had been devised using the rotating mesh basket method originally developed in the United States with a 1 litre of medium in a flat-bottomed flask, with a spectrofluorimetric assay for determining the digoxin released. Two collaborative studies had been carried out to evaluate inter-laboratory variability. A third study would be carried out and if satisfactory the method could be written up and sent to manufacturers for comment. The test could also be given publicity. It could also be extended to Tablets of Prednisolone, Prednisone and Oxytetracycline.

By 1974 the dissolution test for digoxin tablets had been finalised using the rotating basket method. Publication of the test was however delayed to enable the Department of Health to consider the consequences of the test. It was published in January 1975 and brought into effect from 1 October 1975.

The discussion on bioavailability issues continued on both sides of the Atlantic. In 1974 at the request of Senator Edward Kennedy, the US Office of Technology Assessment established a study panel to examine the relationships between chemical and therapeutic equivalence of drug products.[36] The panel was chaired by Robert Berliner, the dean of the Yale University School of Medicine. The panel's report in July 1974 criticised both the US Food and Drug Administration and the USP. It recommended bioavailability studies for certain critical classes of drugs but conceded that *in vitro* dissolution testing was probably the only practical approach in most instances.

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[35] 1972. Therapeutic Non-Equivalence. *Br. Med. J.* 5287: 599–600.

[36] 1974. *Drug Bioequivalence: A Report from the Drug Bioequivalence Study Panel to the Office of Technology Assessment*. Congress of the United States, Washington, DC.

The text of the 1975 *Addendum* to the 1973 BP included the new solution rate test for Digoxin Tablets, which the introduction suggested would be a general procedure and the precursor to the extension of the method to other tablets and capsules. The book was published at the beginning of April 1975.

From 1976 an extensive programme of laboratory work was being carried out, by the author of this book, then working in the BP Commission Laboratory, on the dissolution of pharmacopoeial tablets and capsules. Problems of very long dissolution of many sugar-coated tablets were identified, due to the fact that tablets of water-soluble drugs had to be given a protective coat of shellac before the layers of sugar coating were applied. This shellac coating varied in thickness and was also prone to toughening on ageing. At the April 1977 Commission meeting it was agreed that tetracycline tablet monographs should include an interim dissolution specification to allow the products to be reformulated. The introduction of the official dissolution test was to create as much of a quality revolution for tablets and capsules as the disintegration test had when it was introduced 30 years earlier. It forced manufacturers to replace sugar coating with a much more reproducible film coating made from cellulosic polymers. It also provided analysts with a development and routine quality control tool.

At the November 1977 Commission meeting the work of the BP Dissolution Tests Panel was reviewed. Extensive laboratory work had been done and many of the commercial preparations tested showed very considerable variation in dissolution between different manufacturers. It was agreed that the inclusion of dissolution requirements was another step in the control of oral preparations. In the first place disintegration had been an arbitrarily imposed test and such tests had been responsible for a considerable improvement in the quality of tablets on the market. Concern was expressed by several members of the Commission that manufacturers would challenge any new proposed standard which their products did not meet. In reality the discussions on bioavailability and dissolution in the BP Commission pre-dated by some years any formal licensing requirements in the UK or Europe. A UK guideline on bioequivalence testing was only issued by the Medicines Control Agency (MCA) in the early 1980s and the first European guideline entitled *Investigation of Bioavailability* was not issued until February 1987.[37] In the late 1970s many generic products were still being approved for marketing without any data on blood level studies to show bioequivalence in man compared to the originator's product.

The March 1978 meeting of the Commission returned to the topic of dissolution testing. On 2 March 1978 an *ad hoc* meeting had been held. This had

[37] 1987. *Investigation of Bioavailability*. The Rules governing Medicinal Products in the European Community. Volume III. Guidelines on the quality, safety and efficacy of medicinal products for human use. Brussels: Office for Official Publications of the European Communities.

agreed to divide conventional release products into two categories. Category I products needed to release a substantial proportion of the active ingredient within a reasonable time. Category II products would require a different release rate specific for the particular product, for example for clinical reasons. Critical preparations such as digoxin or the anticoagulants would come into Category II. The Medicines and Doses Committee of the BP Commission was asked to select those tablets for which special dissolution tests were needed. In June 1978 the Commission's policy was published in the *Pharmaceutical Journal*. The article stated that the preliminary selection of dosage forms for the provision of a dissolution test was based on ones where clinical problems might arise if the required dosage was not available or that have characteristics such as low drug solubility that might give rise to difficulties, or ones where there had been reports of issues of bioinequivalence. A list of 41 products was given for which the early development of a dissolution test was felt to be a priority. For the majority of tablet and capsule products a specification of not less than 70 per cent released in 45 minutes would be reasonable. In special cases such as drugs with a low therapeutic index, or short plasma half-life or selective absorption in a limited area of the gastrointestinal tract, the BP Commission would need to be satisfied that there was an adequate correlation with *in vivo* absorption.

At the BP Commission meeting in October 1978 one of the topics was the uniformity of content test for tablets – which controlled the allowed variability of dose in low dose tablets. Some manufacturers had objected to the existing policy which was to apply limits for tablets containing 1 mg or less of the active ingredient, or 1 per cent or less of active ingredient. It was agreed to maintain the policy.

During 1979 attention focussed on the design of the dissolution test equipment. Close liaison between the BP Commission, the USP Convention and the *European Pharmacopoeia* was felt to be essential to adopt a common form of apparatus that was described in sufficient detail to permit identical equipment to be manufactured anywhere in the world. At the September 1979 BP Commission meeting it was noted that the fifth supplement to USP XIX had included a rotating paddle method in addition to the rotating basket. Both methods used a round-bottomed flask instead of the flat-bottomed one specified in the BP. It was felt that the *European Pharmacopoeia* was unlikely to adopt the flat-bottomed flask and it was therefore desirable to change the BP equipment. Both the paddle and basket method would be included in the next revision of the BP. The international adoption of common apparatus would be of benefit to all concerned with quality control of oral solid dosage forms such as tablets and capsules.

In 1983 another round of consultation was organised with the industry on how official tablets should be controlled. The official policy was that tablets of a particular drug and dosage should be similar in appearance irrespective of

their manufacturer. However in reality tablets were in fact often of different shapes, diameters and had different coatings. Should the BP Commission be so prescriptive? No final decision was made.

In September 1984 the change in policy on dissolution – the inclusion of the rotating paddle method and the change in shape of the flask to a round-bottomed flask – was announced.

In 1985 a further consultation took place on coating, shape and diameter of tablets. Requirements in relation to coating were abandoned except in some special cases where this was considered essential. The diameters of tablets would also not be specified in future. This now meant that many generic tablets were officially allowed to be different in appearance to the products of both the originator and other generic manufacturers. This was sometimes a source of confusion to patients who would then complain to the pharmacist that they were being given a different product.

By the 1990s the pharmaceutical industry was using dissolution testing routinely in the development and quality control of tablets and capsules. The Commission announced in 1997 that the test would be included for a much broader range of products. A test would not be needed however if there was no clinical concern for products where the active ingredient was very soluble in dilute hydrochloric acid, for example the beta-blocker Atenolol Tablets.

In 2007 the Supplementary Chapter SC I E on Dissolution of Solid Oral Dosage Forms in the BP 2008 was revised to bring it into line with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Q6A guideline on '*Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products*' on the application of dissolution testing to drug products.[38] The new BP text provided criteria as to whether to include a dissolution test or not in an individual tablet or capsule monograph. The general BP guideline now states that it is expected that all new monographs for conventional-release capsules and tablets will contain a dissolution test except where the solubility of the drug substance is high through the physiological pH range of 1.2 to 6.8, where the dissolution of the dosage form is greater than 80 per cent in 15 minutes at pHs 1.2, 4.0 and 6.8, and where a relationship has been shown between disintegration and dissolution or when disintegration has been shown to be a more discriminatory test.

The BP Commission devoted a considerable amount of time in meetings in the 2000s to discussing uniformity of dosage of products such as uncoated and

[38] 1999. Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. Q6A. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

film coated tablets and hard capsules. This was as a result of the international Pharmacopoeial Discussion Group consideration. A final text of the Uniformity of Dosage Units General Chapter to ICH Guideline Q4B Annex 6 was approved and adopted for adoption in the three ICH regions of the United States, Europe and Japan on 13 November 2013. However the requirements became official in Europe at the earlier date of April 2008 as Chapter 2.9.40 of the *European Pharmacopoeia*. Chapter 2.9.40 represented the original USP version of the test rather than concepts behind the BP Uniformity of Content/Uniformity of Mass. The new text requires a uniformity of mass test to be applied to products containing more than 25 mg of active ingredient or more than 25 per cent by mass of active ingredient. For products containing less than 25 mg/25 per cent a uniformity of content test had to be applied by assaying individual tablets or capsules. David Woolfson, the former BP Commission chairman, comments that this was 'repeatedly on the agenda during most of my time as Chair'. He states that this 'was a good example of the increasing importance of pharmacopoeial decisions taken in Strasbourg, or in the ICH arena'.

In 2008 the BP general monograph on tablets was changed to omit the requirement for tablet shape. This affected 70 monographs which were amended to reflect this change in the BP 2009.

Problems of dissolution and bioavailability of generic drug products still arise. In 2011 the UK Medicines and Healthcare Products Regulatory Agency (MHRA) started a review on the bioavailability and dissolution of levothyroxine. During the preceding five years there had been an increase in the number of reports from healthcare professionals of inconsistency in the efficacy of different makes of Levothyroxine Tablets. In particular some of the adverse drug reaction reports received between December 2011 and February 2012 for Teva's 100 microgram tablet were supported by patient results which showed that the levels of thyroid stimulating hormone (TSH), the marker for thyroid disease, were not in the target range. Certain patient groups, such as pregnant women, those with heart disease, and those being treated for thyroid cancer, might be particularly susceptible to changes in TSH. In February 2012 the marketing authorisation for Teva's 100 microgram tablet was suspended because of concerns about its efficacy and non-equivalence to other levothyroxine tablets.[39] Although the FDA had issued guidance for carrying out bioequivalence and dissolution studies in 2000, and the USP had a test in its monograph, at the time the BP monograph did not include a dissolution test. Investigations showed that using an MHRA devised dissolution test, the extent of dissolution was significantly lower for the

[39] 2012. Teva Levothyroxine 100 Microgram Tablets: Potential Reduced Efficacy – Suspension of Marketing Authorization. *Drug Safety Update* 5(8): March 2012.

Teva tablet than other UK thyroxine tablets.[40] The BP 2014 monograph for Levothyroxine Tablets now contains a dissolution test using the rotating paddle at 100 rpm, with 500 mL of water at 37°C as the dissolution medium. Not less than 75 per cent of the declared content must be released after 45 minutes.

Biological Products

The BP 1932 had introduced biological assays for products covered by the requirements of the Therapeutic Substances Act such as insulin. The BP 1968 continued to include a number of biological assays using microorganisms, animal tissues or whole live animals. These were used for drug substances and preparations whose potency could not be adequately determined using a chemical assay or by a physical method. The principle used in all of these biological assays was a comparison with a standard preparation. The BP 1968 included tests for microbiological potency of 17 antibiotics comprising tetracyclines, colistin, neomycin, novobiocin, paromomycin, polymyxin, streptomycin and viomycin. These tests were carried out on Petri dishes or trays filled with nutrient agar medium and comparing the dose which inhibited the growth of a suitable microorganism with the dose of the standard preparation. This edition also included seven different antitoxins, and a number of vaccines and toxins. These were tested in animals. For example the potency of a sample of botulinum antitoxin was found by comparing the dose necessary to protect a group of mice against the lethal effects of a fixed dose of botulinum toxin in comparison to the dose of a standard preparation which gave the same protection. A number of the hormones such as Corticotrophin, Insulin, Oxytocin and Vasopressin were also assayed biologically. A number of other drugs were also assayed biologically such as Prepared Digitalis, Heparin and Vitamin D. In all of these cases the Standard Preparations were to be obtained from the National Institute for Medical Research at Mill Hill in London.

In the 1970s the responsibility for the provision of biological standards was transferred to the new National Institute for Biological Standards and Control (NIBSC). This was originally sited at Holly Hill, Hampstead, London. The Biological Standards Act of 1975 established the Biological Standard Board which managed NIBSC. In 1987 NIBSC moved from Hampstead to purpose-built facilities at South Mimms in Hertfordshire. NIBSC is also a WHO International Laboratory for Biological Standards. Members of the NIBSC staff have served on the BP Commission and on the various BP committees, and are still involved with the work.

[40] 2013. MHRA Report: Levothyroxine Tablet Products: A Review of Clinical and Quality Considerations. 7 January 2013.

As time went on many of the animal tests and microbiological potency tests were gradually replaced by chemical assays. For example the 1989 *Addendum* to the BP 1988 liquid chromatographic assays replaced the biological assay for Gonadorelin and the oxytocic component of Ergometrine and Oxytocin Injection. Derek Calam, a former BP Commission Chairman, has provided another example from his experience at NIBSC:[41]

> Gentamicin is a complex mixture of amino-sugars linked in triplets and had been licensed although there were concerns about ototoxicity. Its composition was controlled by TLC as best as possible as the sugars have no UV chromophores and could not be analysed with sufficient sensitivity by the upcoming method of liquid chromatography. Although the main components could be separated qualitatively and a rough measure of their relative intensity could be made, control was poor. Examining batches by NMR, it was clear that the signals for the methyl groups on the different components varied in intensity from batch to batch and could be used as a basis for quantitative analysis. A collaborative study was carried out between my laboratory, three manufacturers and an academic group and the results showed that the method was viable and accurate. The BP Antibiotics Committee adopted the method and it was the first use of NMR for pharmacopoeial purposes, I believe in any pharmacopoeia.

Calam also commented on the development of chemical assays for the antibiotics:

> Using samples received under the batch release requirements, a range of antibiotics were studied and in collaboration with other groups and the BP laboratory, a number of liquid chromatography – LC – methods were brought into the BP. The longer term aim was to develop accurate separation methods for control of composition and of impurities so that, eventually, LC could replace microbiological assays. It was possible to relate the results from the chromatographic methods to the results of microbiological assay and so build up sufficient data to show that the values obtained correlated between methods but also that more detailed information was provided by the separation method. A further advantage was the much wider availability of chromatographic equipment compared with the assay facilities required for pouring assay plates, incubators and plate readers, as well as the lower cost per analysis. Not surprisingly LC slowly but steadily replaced microbiological assay except for the aminosugar antibiotics where the lack of a UV chromophore made detection difficult and insensitive. Nevertheless, the availability of UV detectors going down to about 200 nm finally allowed the development of assays and control of the composition of erythromycin and related antibiotics.

[41] 2014. Personal communication from Professor D. Calam.

The pyrogen test for increase in body temperature caused if injections were contaminated with Gram negative bacterial endotoxins had been carried out by injecting a group of rabbits and then monitoring their rectal temperature. In the 1989 *Addendum* to the 1998 BP a start was made in some monographs to replace this test by the Limulus Amoebocyte Lysate (LAL) test which had recently been introduced in the *European Pharmacopoeia*. The LAL test had been approved by the US Food and Drug Administration in 1970. It uses an extract from the blood cells of the horseshoe crab *Limulus polyphemus* which reacts by clotting when mixed with bacterial endotoxin.

As many of the biological materials and antibiotics were introduced into the *Pharmacopoeia* a test for abnormal toxicity was often included in the monograph to check for impurities which might be toxic. However by 1992 it was felt that manufacturing processes were sufficiently well controlled so that such testing was unnecessary. The 1992 *Addendum* to the BP 1988 removed this test from all monographs.

The biological assay for insulin and human insulin had compared the effect on blood glucose of the test product against the Standard Preparation in a group of either rabbits or mice. In the BP 1993 this was replaced by a liquid chromatographic test. The biological assay for vitamin D in cod liver oil consisted of taking 40 young rats just after weaning and then feeding them with a diet deficient in vitamin D to produce rickets in the animals. The animals were X-rayed to check the extent of rickets. The animals were then fed vitamin D using either the test sample or a Standard Preparation to compare the extent to which the rickets had been cured. In the BP 1993 this test was also replaced by a liquid chromatographic test.

On 1 April 2013 NIBSC, which was formerly part of the Health Protection Agency (HPA), officially become a new 'centre' of the Medicines and Healthcare Products Regulatory Agency (MHRA). Dr Atkinson, the secretary and scientific director of the BP Commision, says 'The BP is further strengthened by the merger of the MHRA with the National Institute of Biological Standards and Control'.[42]

[42] 2014. Personal communication from Dr S. Atkinson.

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Illustrations are indicated in **bold** type.