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CONTRACT RESEARCH AND MANUFACTURING SERVICES (CRAMS) IN INDIA

THE BUSINESS, LEGAL, REGULATORY AND TAX ENVIRONMENT IN THE PHARMACEUTICAL AND BIOTECHNOLOGY SECTORS

MILIND ANTANI AND GOWREE GOKHALE

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The business, legal, regulatory and tax environment in the pharmaceutical and biotechnology sectors

Milind Antani and Gowree Gokhale

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List of abbreviations

AOP	Association of Persons
API	active pharmaceutical ingredient
CAGR	compound annual growth rate
CDSCO	Central Drug Standard Control Organization
CMO	contract management organisation
CRO	contract research organisation
DCGI	Drugs Controller General of India
EMEA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research
IEC	institutional ethics committee
ITA	Income Tax Act, 1961
MHRA	Medicines and Healthcare products Regulatory Agency
PE	Permanent Establishment
R&D	research and development
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TP	transfer pricing
WHO	World Health Organization

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1

Introduction

Abstract: Global pharmaceutical companies face major challenges as new product approvals decrease, due to high drug development costs, and existing patents expire. Outsourcing of clinical trials can result in lower costs and more efficient timelines, and India offers significant advantages. Global pharmaceutical companies have either entered into or significantly expanded operations in India in the fields of drug discovery, contract manufacturing and clinical research. India, with a large patient population and genetic pool, can provide both cost savings and speedier trials. Its skilled manpower contributes to the R&D and manufacturing processes. India has emerged as a critical component for drug companies seeking efficiencies of cost and time.

Keywords: drug discovery, contract manufacturing, clinical research, outsourcing, R&D India, cost savings

The significant advantages that India offers to global pharmaceutical companies have led multinational pharmaceutical companies to enter into or significantly expand existing operations in India in the fields of drug discovery, contract manufacturing and clinical research. Over the past two decades India's pharmaceutical and life sciences sector has made huge strides and it is now considered a fast-emerging industry with a global reach. From the development of new chemical entities (NCEs) to the export of active pharmaceutical ingredients (APIs), intermediates and formulations are integral elements of joint development and research collaborations between multinational pharmaceutical companies and Indian companies.

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Global pharmaceutical companies are facing major challenges because new product approvals have decreased, due to the high cost of drug development, and existing patents are expiring. The costs of developing a major drug run into billions of dollars. In 1999 the US Food and Drug Administration (FDA) approved 37 novel treatments; in 2007 only 19 drugs were approved, the lowest annual number in 24 years. Global markets have seen an increase in generics. According to an IMS Health report, drugs worth some US$60 billion will have come off patent by 2011.[1] Lipitor – Pfizer's cholesterol-lowering medication – the world's biggest-selling drug, with an annual revenue of US$13 billion, lost patent protection in June 2011.[2] Through bilateral agreements with major generic drug manufacturers, pharmaceutical companies try to delay the introduction of generics, but most of these agreements provide a reprieve of only about six months before the market is flooded with low-priced generics.[3]

Due to the high cost structure, conducting clinical trials in the United States greatly increases the cost of developing a new drug. In the United States, a Phase I study, which tests the safety of a drug on a small number of patients, costs approximately $15,700 per patient. The average cost per patient for a Phase II trial is $19,300 and a Phase III trial can cost up to $26,000 per patient.[4] The delays that are often associated with clinical trials can cost a company up to US$23 million per day in terms of lost sales in the United States.[5] Drug companies are constantly exploring ways to outsource clinical trials to countries that provide services at lower costs and with more efficient timelines. Further, globally, a significant amount of research and development (R&D) and manufacturing opportunities are shifting from developed markets to developing ones. India, due to its large patient population and genetic pool, can provide global drug companies both cost savings and speedier trials and, with its skilled manpower, is able to contribute to the R&D and manufacturing process. India has emerged as a critical component for drug companies that are seeking greater efficiency in terms of cost and time.

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Notes

1. 'Big Pharma's patent headache', *Business Week*, 6 February 2008, www.businessweek.com.
2. 'Pfizer wins patent extension on cholesterol drug', 3 August 2009, www.nj.com/business/index.ssf/2009/01/pfizer_wins_patent_extension_o.html.
3. Milind Antani, 'Issues and concerns in conducting clinical trials in India', *Pharma Focus Asia*, 14, 2011.
4. 'Phase 3 clinical trial costs exceed $36,000 per patient', 12 October 2006, www.lifesciencesworld.com.
5. 'The Pharmaceutical Industry', *Datamonitor*, March 2008.

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2

Overview of CRAMS

Abstract: The Indian outsourcing industry is renowned for its cost-effective and highly skilled manpower. Outsourcing helps pharmaceutical companies to increase their skills base, control costs and reduce drug development timelines. CRAMS in the pharmaceutical or biotechnology sector include contract research outsourcing (including clinical trials) and contract manufacturing outsourcing. Services include drug development, medical writing, clinical trials except Phase I, clinical data management and manufacturing of APIs and intermediates in various sectors. The contract research industry now includes the outsourcing of products' entire development, including drug packaging and labelling. The fast-growing contract manufacturing sector offers distinct advantages: skilled manpower, competitive salary levels, well-equipped training centres and institutions, a large patient pool, conducive government policies and incentives and a strategic geographic location. Contract manufacturing requires upfront investment in facilities and is capital intensive, and thus requires long-term assured supply contracts. India has significant strengths that have played a vital role in developing contract manufacturing. However, there are some concerns around quality control and supply chain issues. CROs provide various services, including drug discovery, new product development, formulation, pre-clinical trial management planning to Phase IIA and conduct of clinical trials. Stringent research procedures are adopted for testing the safety and efficacy of drugs in humans.

Keywords: clinical research, drug development, skills base, contract research outsourcing, clinical trials, active pharmaceutical ingredients (APIs), patient pool, human resources, contract manufacturing organisation (CMO), intellectual property (IP), contract research organisation (CRO)

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In the last few years India has become a key outsourcing destination for US and European countries, among others. The Indian outsourcing industry is world renowned for its cost-effective and highly skilled manpower, and a dramatic growth in outsourcing to India can be seen in all areas. Following the success of the outsourcing model in the information technology sector, the pharmaceuticals sector has adopted the same model.

The cost of drug development has soared over the past ten years, compelling pharmaceutical and biotechnology companies to look for new and more cost-effective ways of conducting clinical research. Driven by mounting market pressures, companies are increasingly implementing outsourcing strategies so as to drive up revenues through faster drug development. By reducing their in-house facilities and staff and outsourcing more of their R&D and manufacturing operations, pharmaceutical and biotechnology companies are reshaping the drug development services industry. Outsourcing these operations is also helping pharmaceutical companies to broaden their skills base, control costs and reduce drug development timelines. The majority of leading pharmaceutical companies around the world are focusing on India as an outsourcing destination, with a view to bringing down their costs. It is estimated that a US pharmaceutical company can save around 55–60 per cent of its costs by outsourcing R&D and manufacturing to India.

While business process outsourcing may currently be stealing the limelight, it will soon have to make way for contract research and manufacturing services (CRAMS) in the pharmaceutical and biotechnology sectors, two young outsourcing sectors with high growth potential.

2.1 What are contract research and manufacturing services (CRAMS)?

CRAMS broadly encompass those services in the pharmaceutical or biotechnology sector that require extensive R&D and large-scale manufacturing facilities. They include contract research outsourcing (including the conducting of clinical trials) and contract manufacturing outsourcing.

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2.1.1 Contract research outsourcing

Contract research outsourcing covers a wide range of services, including the drug development process, medical writing, pre-clinical trials, conducting Phase II and III clinical trials,[1] clinical trial monitoring and statistical services, commonly known as clinical data management. It also includes pre-clinical testing, quality clinical research, reducing development timelines, creating customised post-approval programmes, providing distinct clinical research sites either owned by the company or attached to institutions and the use of contract laboratories for specialised projects.

2.1.2 Contract manufacturing outsourcing

Contract manufacturing outsourcing includes bio manufacturing and the custom manufacture of pharmaceutical ingredients. The first sub-sector, bio manufacturing, includes the manufacture of protein-based biopharmaceutical products. The second sub-sector involves the custom manufacturing of pharmaceutical ingredients like APIs (commonly known as bulk drugs), fine chemicals, custom chemicals and intermediates. India is ranked second only to the US in terms of the annual number of global Drug Master Filings or DMFs.[2]

2.2 Emergence of CRAMS in India

Contract research began in the late 1940s, with businesses offering pre-clinical toxicology studies on a contract basis. However, it was not until the late 1970s that contract research organisations began to appear and to offer some specialised services in the drug development process, such as medical writing, clinical trial monitoring and statistical services.[3]

By the 1980s, some contract researchers were beginning to provide all of the manufacturing services typically found in a major pharmaceutical company, resulting in the outsourcing of the entire development of products.

The early 1990s saw the emergence of specialised services such as clinical trials management (drug packaging, labelling etc.) and trial-monitoring staff. When organisations started to provide all of these services under one roof, they began to be known as contract service organisations.[4] As mentioned earlier, recent years have seen the emergence of a very fast-growing contract manufacturing sector in India.

The pharmaceutical industry the world over is at present looking to India for clinical development, improved processes for early drug development and the supply of quality ingredients. India offers distinct advantages: skilled manpower, competitive salary levels, well-equipped training centres and institutions, a large patient pool and conducive policies and incentives from government at both the central and state levels. India also has strategic geographic locations and positive environmental and infrastructural factors.

India is an ideal place for CRAMS, due to the factors noted below.

2.2.1 Infrastructure

For contract research outsourcing and contract manufacturing outsourcing, good infrastructure is a prerequisite. Indian pharmaceutical companies have invested in the state-of-the-art technology necessary to meet this standard. Many companies have made their plants compliant with current good manufacturing practice. Companies are continuously in the process of making their manufacturing facilities more compliant with additional international regulatory agencies such as the USFDA, Medicines Control Council (South Africa) etc.[5] India boasts the largest number of USFDA-approved plants outside the United States.

2.2.2 Regulatory environment

India has a good regulatory environment that is fast meeting global standards. A range of legislation supports the CRAMS industry. We will take a detailed look at the regulatory environment in Chapter 3.

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2.2.3 Human resources

2.2.3.1 Patient pool

Because of India's large population, the number of patients is significantly higher. Even the number of patients per doctor is high. A variety of cultures, lifestyles and ethnicities are represented in the population, and the heterogeneous gene pool enriches research.

2.2.3.2 Skilled personnel

India's strong human resource base includes a vast number of English-speaking graduates and researchers, and also one of the largest pools of highly skilled doctors and engineers in the world. Hospitals involved in clinical research are attached to the medical colleges, providing access to skilled medical personnel.

Also, the difference in time zones facilitates 24-hour operations, a crucial factor in the outsourcing business.

2.3 Contract manufacturing organisations (CMOs)

Contract manufacturing is the full or partial manufacturing of a product by an organisation other than the one that owns the rights to sell the product under its own brand name. For example, the company that owns the product may obtain bulk drugs, intermediates or finished products manufactured by a third party. The third party can be a subsidiary of the company or an independent company in India.

Providers of contract manufacturing services normally do not post their brand name on any product and the rights to both the design and the brand name belong to the originating designer. Approximately 60 per cent of the US$2.3 billion Indian CMO market relates to chemical synthesis, followed by formulation and packaging, which constitutes about 40 per cent. The market has grown at a compound annual growth rate (CAGR) of 51 per cent from 2007 to 2010, reflecting its strong potential.[6] Contract manufacturing requires upfront investment in order to build up the necessary facilities and is capital intensive in nature, thus requiring long-term assured supply contracts

in order to recoup investments, or 'take or pay' types of contract. The infrastructure plays a significant role in attracting global players.

2.3.1 Trends in India

Large, domestic branded generic players focus more on marketing and product management, hence they outsource non-core activities such as manufacturing. The manufacturing players in India have proved to be more cost efficient, on account of their higher level of larger capacity utilisation, as well as because of certain incentives provided to them. This also helps them to respond rapidly to events such as new product launches (line extension etc.), surges in demand for existing products and new developments. Many contract manufacturers have also been able to develop new products (line extensions, combinations) proactively. Further, novel drug delivery system applications owned by these contract manufacturers help with the relaunching of existing products, thereby leveraging their value proposition.

2.3.2 Strengths

As already mentioned, India has significant strengths, which have played vital role in developing the contract manufacturing industry. These include:

- a high number of USFDA- and UK MHRA-approved plants;
- cost savings: no capital expenditure for plant and equipment, as Indian companies have already set up infrastructure compliant with global standards;
- sufficient product filing track record: Indian companies have been in the forefront, in terms of filing both Drug Master Filings and Abbreviated New Drug Applications;
- access to expertise: India has a significantly large skilled human resource with specialised knowledge and skills, which also facilitates the use of new technology;
- global presence: India provides manufacturing and access to the market globally;

- low labour cost: being small companies, CROs and CMOs have lower salary structures and benefits;
- flexibility: based on current business trends, work scheduling can be reshuffled easily without affecting work on other products;
- quality infrastructure and established track record of intellectual property rights compliance.

2.3.3 Weaknesses

- Quality control: many times quality becomes an issue, and investigation and resolution of the issues can become time-consuming and expensive.
- Supply chain issues: these are a disadvantage to small companies, which lack adequate supply chains.
- Intellectual property risks: even after signing an appropriate contract, one can face breaches of intellectual property and confidentiality clauses. It is imperative to have tight contracts with safeguards in order to cover existing and future intellectual property.
- Acquisition and management change: if, after a long-term relationship, the CMO is acquired by a competitor of the product company, it may be difficult to continue the arrangement. In some cases, the value system of the new management may not be on the same wavelength as the previous management's. If a company has to change its CMO at this point, it will have to spend time, effort and money in acquiring new licenses in the name of the new CMO because transfer of licenses is not permitted in India.

2.4 Contract research organisations (CROs)

CROs provide services including drug discovery, new product development, formulation, pre-clinical trial management planning up to phase IIA and conduct of clinical trials. Most CROs in India

provide medicinal chemistry research for sponsor companies. There is a steady increase in the number of CROs providing biology research as well.

The global contract research market reached US$25 billion in 2010, growing at a CAGR of 19 per cent from 2007 to 2010. The Indian contract research industry has been growing tremendously during the past few years and reached approximately US$1.5 billion in 2010, a CAGR of 65 per cent from 2007 to 2010, albeit on a small base.[7] Indian providers of pharmaceutical outsourcing have capabilities to provide late-stage discovery (research chemistry) and drug development services. However, they are in the process of building up research biology skills to facilitate early-stage discovery.

In India, CROs provide pharmaceutical companies with significant strategic benefit so as to achieve speedier, more cost-effective drug development at both the pre-clinical and the clinical stages.

CROs play a significant role in helping life sciences companies to execute clinical programmes, run entire functional areas, alleviate capacity constraints and reduce costs. As life sciences companies continue to evolve their R&D operating models, CROs enable greater flexibility. However, beyond the traditional transactional services, some CROs remain constrained in their value-added capabilities. To remain competitive, they may be required to evolve so as to provide life sciences companies with access to leading-edge capabilities and innovative means of accelerating clinical trials. An example of this could involve partnerships with the healthcare provider community to use analytics in order to identify patient cohorts based on genetic characteristics and combining this with health outcomes data from electronic medical record (EMR) systems.[8]

The contract research sector is largely dominated by organisations providing clinical research by conducting clinical trials in India.

2.4.1 Clinical trials in India

According to PAREXEL's *Biopharmaceutical R&D Statistical Source Book 2008/2009*, India ranked number 8 in the world with respect

to the number of clinical investigators conducting FDA-regulated clinical trials in 2007. The number of clinical investigators rose by 29 per cent, to 395 in 2007 and represented 1.8 per cent of all investigators conducting FDA-regulated trials worldwide.

Clinical trials are an integral part of the drug development process. To ensure the safety and efficacy of a drug in humans, regulatory authorities require this to be proved through clinical trials before the drug is approved for use.

Clinical trials are divided into four distinct chronological phases that can be multi-centric, single blind or double blind and placebo controlled. Table 2.1 describes the four phases.

Table 2.1 Clinical trial phases

	Phase I	Phase II	Phase III	Phase IV
Objectives	Determination of metabolic and pharmacological actions, and maximally tolerated dose	Evaluation of the effectiveness of the drug for specific population with the disease and identification of common short-term side-effects and risks	Additional effectiveness information and evaluation of overall risk-benefit ratio in a demographically diverse sample	Monitoring of on-going safety in large populations and identification of additional uses of the agent that may obtain FDA approval
Duration	Up to 1 month	Several months	Several years	On-going (following FDA approval)
Population	20–80	200–300	Hundreds to thousands	Thousands
Sample size	Single dose of the 'drug'	Double-blind study evaluating safety and efficacy of 'drug' vs placebo	Study of drug vs standard treatment	Study of economic benefit of newly approved drug vs standard treatment

Since clinical trials involve research with human volunteers to test the safety and efficacy of the drug in humans, stringent research procedures are adopted. The entire clinical trial process can cost millions of US dollars and take up to 10 years.

2.4.2 The clinical trial scenario in India and emerging trends

India has what the global pharmaceutical sector can benefit from: 1 billion people, 290 medical colleges, over 15,000 hospitals, and 24,000 medical students graduating annually. Thus, India provides an ideal location for clinical trials for pharmaceutical companies working on stringent budgets and requiring larger patient pools. Many clinical trials are expected to be run as part of a global strategy, bringing together patient data across a number of countries.

The key reasons for the India strategy[9] are the large number of patients, leading to quicker enrolment, well-qualified investigators and state-of-the-art institutions. India also offers a significant language advantage. These factors are responsible for speedier and more efficient clinical trials, especially Phase II and Phase III trials that are more cost-efficient.

Notes

1. At present India does not allow the conducting of Phase 0 and Phase I clinical trials of molecules developed outside India.
2. Pratap Ravindran, 'Clinical trial on trial', *The Hindu Business Line*, 1 November 2004.
3. Sudhakar S. Bangera, 'From contract research to contract services', www.expresspharmapulse.com/20020912/research1.shtml.
4. Sudhakar S. Bangera, 'From contract research to contract services', www.expresspharmapulse.com/20020912/research1.shtml.
5. Federation of Indian Chambers of Commerce and Industry, 'Competitiveness of the Indian pharmaceutical industry in the new product patent regime', March 2005.

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6. ICRA Limited, 'CRAMS India: overview and outlook', June 2011.
7. ICRA Limited, 'CRAMS India: overview and outlook', June 2011.
8. Ralph Marcello and Raj Jayashankar, 'CROs and advanced analytics: accelerating R&D through data mining and bioanalytics', *Contract Pharma*, 6 June 2011, http://contractpharma.com/contents/view/39596.
9. US National Institutes of Health, ClinicalTrials.gov, www.clinicaltrials.gov.

3

Legal and regulatory scenario

Abstract: The Central Drug Standard Control Organization is the apex authority regulating India's pharmaceutical and healthcare industry. It is headed by the Drugs Controller General of India and performs various functions at central and state level. The central legislation regulating drug and cosmetics import, manufacture, distribution and sales is the Drug and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945, with various amendments. The Act's main objective is to ensure that available human drugs are safe and efficacious and conform to prescribed quality standards and that cosmetics are safe for use. Amendments to the Act address public concerns about the existing framework for clinical trial research and concerns related to contract manufacturing conducted in India. The Act provides regulations that govern manufacturing of drugs in India, manufacture/import of new drugs and clinical trials. Various guidelines and schedules govern the conduct of clinical trials. The guidelines also require adequate compensation to be paid for participation in drugs research.

Keywords: Central Drug Standard Control Organization (CDSCO), Drugs Controller General of India (DCGI), new drugs, Indian Pharmacopoeia, clinical trials, Schedule Y, licensing, institutional ethics committee, serious adverse event (SAE), suspected unexpected serious adverse reaction (SUSAR), first-in-man studies, Schedule Y1, compensation

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3.1 Drugs legislation

The key legislation covering various regulatory matters related to drug import, manufacture, sale and advertising are:

1. The Drugs and Cosmetics Act of 1940 and Drugs and Cosmetics Rules of 1945
2. The Drugs and Magic Remedies (Objectionable Advertisements) Act of 1954
3. The Pharmacy Act of 1948.

3.2 Regulatory authorities in India

The Central Drugs Standard Control Organization (CDSCO) is the apex authority (under the Ministry of Health and Family Welfare) regulating the pharmaceutical and healthcare industry in India. It is headed by the Drugs Controller General of India (DCGI), which is attached to the office of the Director General of Health Services in the Ministry of Health and Family Welfare. The DCGI is a statutory authority under the Act and has port offices, zonal offices and drug testing laboratories functioning under it.

3.2.1 Functions of the CDSCO

The functions of the CDSCO at the central level are:

- approving new drugs to be introduced into the country
- giving permission to conduct clinical trials
- registering and controlling the quality of imported drugs
- giving final approval for medical devices
- setting standards for drugs, cosmetics, diagnostics and devices
- setting regulatory measures, and making amendments to Acts and Rules
- regulating the market authorisation of new drugs
- regulating clinical research in India

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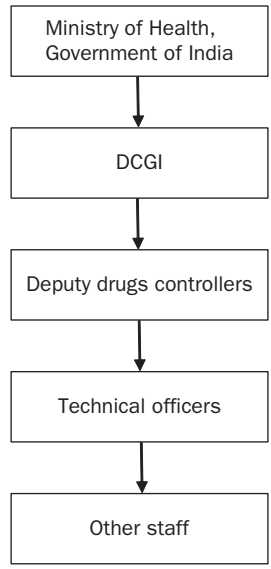

Figure 3.1 Organisational structure of regulatory bodies

- regulating the standard of imported drugs
- updating the Indian Pharmacopoeia
- approving licences as the Central License Approving Authority for the manufacture of large volume parenterals, vaccines and biotechnology products, for the operation of blood banks, and also for such other drugs as may be notified by the government from time to time
- coordinating the activities of the states and advising them on matters relating to uniform administration of the Act and Rules within India.

At state level the functions of the CDSCO are:

- licensing of manufacturing establishments and sales premises
- carrying out inspections of licensed premises to ensure compliance with licence conditions
- drawing samples for testing, and monitoring the quality of drugs and cosmetics within the state
- taking appropriate actions such as suspension/cancellation of licences

- monitoring for the sale of spurious/adulterated drugs
- instituting legal action, wherever needed, as provided in the Act and Rules
- monitoring objectionable advertisements pertaining to drugs.

Table 3.1 Regulatory bodies

Body	Function
DCGI Drug Controller General of India	Regulatory apex body under the government of India that oversees all clinical trials in the country
ICMR Indian Council of Medical Research	Apex body for the formulation, coordination and promotion of biomedical research
GEAC Genetic Engineering Approval Committee	Body of experts in the field of genetic engineering and molecular biology; with DCGI, recommends on clinical trials involving the use of biotech products that are referred to it
DBT Department of Biotechnology	Apex body to oversee the new impetus to develop the field of modern biology and biotechnology in India
AERB Atomic Energy Review Board	Authority that exercises regulatory control over the approval of new types of radiation equipment, and for the registration/commissioning of new radiation equipment, inspection and decommissioning of installations
BARC Baba Atomic Research Centre	Apex body that oversees and approves all radiation-related projects in India. DCGI refers all clinical trials that involve the use of radiopharmaceuticals to BARC for its expert opinion
DCC Drugs Consultative Committee	Provides technical guidance to the CDSCO
CDL Central Drugs Laboratory	National statutory laboratory of the Indian government for quality control of drugs
CLAA Central License Approving Authority	Body within the CDSCO responsible for issuing 'No Objection Certificates' for manufacturing licences
DTAB Drugs Technical Advisory Board	Provides technical guidance to the CDSCO

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3.3 Drugs and Cosmetics Act and Rules

The central legislation regulating the import, manufacture, distribution and sale of drugs and cosmetics in India is the Drug and Cosmetics Act, 1940 ('Act') and the Drugs and Cosmetics Rules, 1945 ('Rules'), with various amendments. The main objective of the Act is to ensure that (1) available human drugs are safe and efficacious; (2) drugs conform to prescribed quality standards; and (3) cosmetics are safe for use. The Act gives statutory authority and responsibility to the DCGI for various approvals, as mentioned earlier.

The Act has been amended several times to address public concerns related to the existing framework surrounding clinical trial research, as well as related to the conduct of contract manufacturing in India.

3.3.1 Manufacturing a drug in India

No drug can be manufactured in India without first obtaining a licence. A licence is mandatory for each location where drugs are to be manufactured, and also for every drug to be manufactured at each location. The licence has to be renewed periodically. The Act also specifies certain conditions for the grant or renewal of a licence. A licence (called a loan licence) to manufacture can be also obtained if the product is manufactured in a factory owned by another party. The licence to manufacture drugs needs to be obtained from the state FDA of the state in which the manufacturing facility is proposed to be located.

Under the Drugs Act, 'manufacturing' includes any process (or part of a process) for making, altering, ornamenting, finishing, packaging, labelling, breaking up or otherwise treating or adapting any drug with a view to its sale or distribution. However, 'manufacturing' does not include dispensing or packing at the retail sale level.

The Drugs Act also makes it mandatory to obtain an import licence for any ingredient of a drug that needs to be imported for the manufacturing of a drug in India.

3.3.2 Manufacture/import of new drugs

The Act has defined the term 'New Drug'[1] in special provisions which apply to the manufacture or import of new drugs into India. Part XA of the Drugs Rules deals with the import or manufacture of new drugs for clinical trials or marketing.

The Indian government announced amendments to the Rules in 2002 to streamline procedures for the manufacture and import of new drugs. According to these rules, institutions will be allowed to conduct clinical trials, whether for clinical investigation or for experiment, for a new drug only after obtaining the permission of the DCGI. Before this amendment, permission was mandatory only if the drug was sought to be marketed in India.

3.4 Clinical trials

In the past, regulations governing clinical trials in India were criticised for their lack of clarity and their focus on generic drugs. Universal regulatory frameworks such as those published by the USFDA did not exist in India a decade ago. Pressure from the global pharmaceutical sector prompted a significant shift towards regulations that promote innovation and compliance with international standards. Recent ethical guidelines and Good Clinical Practice (GCP) guidelines are compliant with international standards and recognised by the FDA. The regulatory environment continues to improve compliance with worldwide standards as well as to significantly reduce the unnecessary red tape involved in the regulatory processes of the past.

3.4.1 Key legislation on clinical trials in India

The regulations specifically affecting the conduct of clinical trials in India are:

1. The Drugs and Cosmetics Rules of 1945 and Schedule Y and Schedule Y1
2. The CDSCO's Good Clinical Practice Guidelines

3. The Ethical Guidelines for Biomedical Research on Human Subjects issued by the Indian Council of Medical Research
4. The Indian Council of Medical Research Guidelines, 2000
5. The Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002
6. Hospitals and institutions typically have their own internal codes and regulations.

3.4.2 Various guidelines

In 2000, the Central Ethics Committee on Human Research of the Indian Council of Medical Research (ICMR) issued the Ethical Guidelines for Biomedical Research on Human Subjects ('Guidelines'). The Guidelines require that all proposals on biomedical research involving human subjects be cleared by an institutional ethics committee (IEC). The basic responsibility of the IEC is to 'ensure a competent review of all ethical aspects of the project proposals received and to execute the same free from any bias and influence that could affect their objectivity'.

The Guidelines provide for the requirement of Informed Consent of Subjects and the responsibility of investigators to communicate the following:

i. the aims and methods of the research;
ii. the expected duration of the subject participation;
iii. the benefits that might reasonably be expected as an outcome of research to the subject or to others;
iv. any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment to which she/he is being subjected;
v. any foreseeable risk or discomfort to the subject resulting from participation in the study;
vi. right to prevent use of his/her biological sample (DNA, cell-line, etc.) at any time during the conduct of the research;
vii. the extent to which confidentiality of records can be maintained, i.e., the limits to which the investigator will be able

to safeguard confidentiality and the anticipated consequences of breach of confidentiality;
viii. free treatment for research-related injury by the investigator/institution;
ix. compensation of subjects for disability or death resulting from such injury;
x. freedom of individual/family to participate and to withdraw from research any time without penalty or loss of benefits which the subject would otherwise be entitled to;
xi. the identity of the research teams and contact persons with address and phone numbers;
xii. foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research, and if the material is likely to be used for secondary purposes or will be shared with others, clear mention of the same;
xiii. risk of discovery of biologically sensitive information;
xiv. publication, if any, including photographs and pedigree charts.

The Guidelines also require adequate compensation for participation in the research. Such compensation 'should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in research against their better judgment'. The Guidelines provide for the protection of certain 'special groups' such as pregnant women and children. For example, pregnant or nursing women are not allowed to participate in trials unless the research carries no more than minimal risk to the foetus or nursing infant and the object of such research is to obtain new knowledge about the foetus, pregnancy or lactation.

In 2001, a central expert committee was formed by the CDSCO to develop Indian GCP guidelines in alliance with the latest WHO, ICH, FDA and MHRA guidelines. In 2002, the CDSCO issued the 'Good Clinical Practices' guidelines for clinical research in India. The GCP guidelines provide an ethical and safety quality standard for the designing, conducting and recording of clinical trials that involve the participation of human subjects. The Indian GCP

guidelines are essentially similar to the ICH GCP guidelines. If a sponsor is conducting international trials in India, the sponsor must adhere to both the ICH GCP and the Indian GCP guidelines.

It is interesting to note that until the guidelines mentioned above were included in Schedule Y, which stipulates the various norms and regulations for the conducting of clinical trials in India, these guidelines did not have the force of law to enforce the same.

The Rules were revised in 2005 and the current rules, the Drugs and Cosmetics (IInd Amendment) Rules, 2005, were released on 20 January 2005. The revised Schedule Y updated the regulations such that they became compatible with internationally accepted definitions and procedures. The 2005 Amendment to Schedule Y was one of the most important legislative changes affecting clinical trials in India. The Amendment to Schedule Y, which is now compliant with ICH guidelines, provides that a company can now include India in multi-centre trials in all phases. In turn, the company will attain faster and more efficient data when conducting clinical trials in India.

3.4.2.1 Schedule Y

Schedule Y provides guidelines for the import, manufacture and process for obtaining market approval for a new drug for sale or for clinical trials in India. Schedule Y also stipulates the data and documentation required to initiate clinical trials and provides several templates, including an informed consent document. It lays out the details of the application process and the process for obtaining permission to conduct clinical trials. Also listed are the responsibilities of the sponsor, the investigators and the IEC.

3.4.2.2 Schedule Y requirements

I. Application Requirements for Submission to DCGI
   a. Form 44
   b. Documents pertaining to chemical and pharmaceutical information, animal pharmacology, toxicology data and clinical pharmacology data

c. Trial related documents
   i. Investigator's Brochure
   ii. Trial Protocol
   iii. Case Report Form
   iv. Informed Consent Form
   v. Patient Information Sheet
   vi. Investigator's Undertaking
   vii. Special documents that may apply (i.e. children, pregnant women, nursing women, elderly patients, patients with renal or other organ system failure, and those on specific concomitant medication(s)).
d. Regulatory Status of trial in other countries
e. Filing Fee

II. Required Approvals
   a. DCGI written approval of Schedule Y Application
   b. IEC written approval of Schedule Y Application

III. Requirements after Trial has started
   a. Amendments to Protocol to DCGI
   b. Serious Adverse Events notification to DCGI and other countries
   c. Progress reports to DCGI every 6 months
   d. Summary report for discontinued projects within 3 months.

3.4.3 Other requirements

Before a clinical trial can be conducted in India, written permission from the DCGI and an IEC must be obtained. The IEC must consist of seven members, including a medical scientist, a clinician, a statistician, a legal expert, a social scientist and a common person from the community. The Schedule Y application must be accompanied by a filing fee. Initial Phase I studies can only be approved for drugs developed in India. Repeat Phase I studies for

other drugs developed outside India can be approved. There is a high risk to the human subjects involved in Phase I study wherein a new drug is administered to human subjects for the first time. As mentioned earlier, these studies are aimed at evaluating the safety and tolerability of the new drug and to understand if the drug has fatal effects on human subjects. The government is concerned about this fact and hence has not allowed Phase I trials for molecules discovered outside India to be conducted in India because severe adverse reaction may not be managed properly.

3.5 Regulatory procedure

The DCGI, as of December 2006, has implemented a two-track system for the regulatory approval of clinical trials: (1) clinical trials that have already gained approval by the European Medicines Agency (EMEA) or regulatory bodies in the United States, United Kingdom, Switzerland, Australia, Japan, South Africa, Europe or Canada (Category A) are likely to be approved within 2 to 4 weeks and (2) all other trials that have not been recognised by a regulatory agency (Category B) must undergo the normal review process (expert committee approval) and may take 12 weeks for approval. After an application is considered under Category B, it cannot be shifted to Category A, even if the applicant produces approval from a Category A country.

At most sites, ethical committees can be approached in parallel to the DCGI submission.

3.5.1. Importation of materials for clinical trials in India

The Director General of Foreign Trade (DGFT) grants licences to import and/or export blood samples/investigational products or by-products. These licences are called T-licences (Trial Licence) and are valid for multiple shipments for one year. The T-Licence and Schedule Y applications may be submitted together, so the licence is issued simultaneously with the application approval. Delays with the DGFT are inevitable if partial or inaccurate documentation is

Table 3.2 Reporting requirements for SAEs/SUSARs at various stages

Stage	Reporting
At the time of filing application with DCGI for approval for conducting clinical trial	Documents include – • Investigator's Brochure (IB) • Regulatory status of the drug in other countries • Latest version of protocol
SUSARs reported during period from filing of application until time of approval	SUSARs occurring during this period at other global trial sites should be communicated to DCGI and IEC as and when such events occur
Before clinical phase of trial commences	GCP Guidelines – Sponsor to Investigator – • Up-to-date IB • Protocol Documents to IEC at time of initiation of site – • IB (including submission of global SUSAR reports) • Signed protocol with amendments • Case Record Form (CRF) • Information given to trial subject • Advertisement for subject recruitment • Financial aspects of the trial • Insurance statement (where required) • Investigator's agreement with Sponsor • Investigator's undertaking • All relevant documents evidencing qualifications of investigator and co-investigator/sub-investigator Documents to be submitted to DCGI at time of initiation of the site – • Protocol
During clinical conduct of trial	Data to be submitted to IEC – • Updated IB • Any revision to the Protocol • Communication to IEC of unexpected SAE occurring during clinical trial and other safety information Data to be submitted to DCGI – • Protocol amendments • Communication of unexpected SAE occurring during clinical trial, which, irrespective of causal relationship to investigational product, should be communicated promptly (within 14 calendar days) by Sponsor to DCGI

submitted. Detailed and close attention must be paid to the labelling of Investigational Medicinal Products. A separate application is required for shipping biological samples collected during the trial out of India (No Objection Certificate). This application can also be submitted simultaneously with that for the clinical trial.

3.5.2 Other clinical trial requirements

All changes to the trial protocol (Protocol Amendments) should be communicated to the DCGI and IEC within 30 days of implementation and all serious adverse events (SAEs) must be communicated to the DCGI and all participating study investigators within 14 days. SAE notification must also be given to the regulatory agencies in other countries where the study is being conducted; proof of such submission should be provided to the DCGI. Progress reports must be submitted to the DCGI every 6 months and a summary report should be submitted within 3 months if the study is discontinued.

3.6 Recent regulatory developments

Due to unfortunate events associated with clinical trials, there has been pressure from the public for CROs and sponsors to provide more transparency, accountability and accessibility to not only the clinical trials but also the resulting data. The World Health Organization (WHO) has launched an international initiative to develop an all-encompassing registry to track trial data from all clinical trials taking place in the world. Existing trial registries such as ACTR, ClinicalTrials.gov and ISRCTN need to be centralised in order to provide accurate information for trials taking place in multiple countries.

3.6.1 Clinical Trial Registry-India (www.ctri.in)

In joint collaboration, the Department of Science and Technology, WHO and ICMR's National Institute of Medical Statistics have

launched efforts to create the Clinical Trial Registry-India (CTRI). The CTRI, operated from Delhi, provides an online platform for the registration of all clinical trials taking place in India. Any researcher planning to conduct a trial involving human participants is advised to register the trial with CTRI before the first patient is enrolled. Registration is currently voluntary, but the International Committee of Medical Journal Editors has declared that its journals will not publish the results of any clinical trials not included on an authorised register at the time of inception.

3.6.2 First-in-man studies for drugs discovered in India

A continuing primary constraint is the inability to perform first-in-man studies for drugs discovered outside of India. Many do not see this as a real concern, as first-in-man studies can be done rapidly and at a reasonable cost in Western countries. More recently, there have been discussions in the Indian government on the removal this burden and updating of Schedule Y so as to be more consistent with US and ICH guidelines. Currently, early-stage clinical trials of compounds developed by foreign companies are not allowed in India. Along with efforts to provide and improve transparency and reliability of the drug approval process, the CDSCO is considering allowing foreign pharmaceutical companies to do early-stage clinical trials on humans, called Phase 0. Phase 0 trials are designed to speed up the development of promising drugs by establishing whether the drug has an effect in human subjects that is based on expectations based on pre-clinical animal studies.

3.6.3 Proposed new Schedule Y1

The Ministry of Health and Family Welfare is planning to incorporate a new 'Schedule Y1' into the Drugs and Cosmetic Rules, 1945 to specify all rules regarding clinical trials. The Ministry will soon be amending the Drugs and Cosmetics Rules, 1945 by inserting an added schedule into the existing Schedule Y (which deals with the

requirements and guidelines for permission to undertake clinical trials in India) as well as a new Rule 122DAB. The proposed amendments, which have already been approved by the Drug Technical Advisory Board and the Drugs Control Committee, and now await notification, are intended to be implemented in view of India's rapid growth in the pharmaceutical sector and its being one of the primary clinical trial markets, attracting multinationals globally who have set their sights on India for the next few years at the least.

The proposed new 'Schedule Y1' will contain rules relating to clinical trials, including regulations for the registration of clinical trials and CROs, penalty provisions for violations, registration of IECs and on-site audits of trials.

Until now, the regulations dealing with clinical trials have not specifically covered penalty-related provisions in instances where clinical trials were not being conducted in accordance with the required regulations, nor have there been adequate provisions dealing with the compensation of clinical study subjects in the event of an injury arising to a particular study subject. However, with the new 'Schedule Y1', it is intended to impose a penalty of 10 years' imprisonment for violating clinical trial norms. Moreover, the mandatory conduct of audits of clinical trials is also proposed, which may come as a timely relief for most multinational companies who enter into arrangements with CROs and in cases where they find it cumbersome to monitor and ensure that appropriate safeguards are in place, including adherence to quality norms, during the trials.

Other proposals include the compulsory registration of all trials in the Clinical Trials Registry and the mandatory recording of fingerprints of all volunteers in Phase III trials in order to avoid double participation in various trials taking place in India. Another proposal is for audit inspections of CROs by a team consisting of a drug inspector, a pharmacologist and a clinical trials expert.

3.6.4 eGovernance 2013

The government of India is planning to introduce an eGovernance project for all clinical trials by 2013. The programme will enable

companies from any part of the world to file online applications seeking approval for clinical trials from the DCGI. The information and application would be reviewed by the DCGI office and generate queries. Approvals would, in turn, be provided online. The government has also stated that it intends to document adverse reactions and multiple enrolments by the same patient. If these proposals are implemented, India will be the first and only country in the world to have an online mechanism for clinical trial applications.[2]

3.6.5 National Pharmacovigilance Programme

The government of India, with the World Bank, has initiated the National Pharmacovigilance Programme. The CDSCO is coordinating the countrywide pharmacovigilance programme under the aegis of the Directorate General of Health Services, Ministry of Health and Family Welfare, New Delhi. With the number of new drugs being regularly approved for marketing in India, there is a need for a vigorous pharmacovigilance system in the country to protect the population from the potential harms that may be caused by some of these new drugs. Besides, with the patent regime coming into force from 2005, it is widely believed that India will become the global hub for new drug trials. These situations make it pertinent for the Indian central drugs regulatory authority to have a strong pharmacovigilance system in the country.

3.6.6 Compensation

The statutes governing clinical trial activity in India currently do contain some provisions for the granting of compensation in cases of research-related injury. For instance:

- The Ethical Guidelines for Biomedical Research on Human Participants issued by the Indian Council of Medical Research provides that 'each research shall include an in-built mechanism

for the compensation for the human participants either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive aftercare, including treatment during and after the research or experiment, in respect of any effect that the conduct of research or experimentation may have on the human participant and to ensure that immediate recompense and rehabilitative measures are taken in respect of all affected, if and when necessary'.

- Schedule Y of the Drugs and Cosmetics Rules, 1945 provides that an essential element of a research participant's informed consent document is compensation and/or treatment(s) available to the subject in the event of a trial-related injury.

However, to date there have been no comprehensive guidelines for the enforcement of such provisions.

The office of the DCGI has recently issued draft guidelines on the process for reporting serious adverse reactions, as well as on compensation provided by sponsor companies in cases where the human subject suffers from any damage as a result of adverse reaction during clinical trials.

3.7 Information on updates

Information on new developments in the legal and regulatory environment can be obtained from the following websites:

Central Drugs Standard Control Organization, www.cdsco.nic.in
Indian Council of Medical Research, www.icmr.nic.in

Notes

1. For the purpose of this part, 'New Drug' shall mean and include –

   (a) A drug, as defined in the Drugs and Cosmetics Act, 1940 including bulk drug substance which has not been used in the country to any significant extent under the conditions prescribed, recommended or

suggested in the labeling thereof and has not been recognized as effective and safe by the licensing authority mentioned under Rule 21 for the proposed claims.

(b) Provided that the limited use, if any, has been with the permission of the Licensing Authority.

(c) A new drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.

(d) A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage, dosage form (including sustained release dosage form) and route of administration. (See items (b) and (c) of Appendix VI to Schedule Y).

Explanation: For the purpose of this Rule – all vaccines shall be new drugs unless certified otherwise by the Licensing Authority under Rule 21;

(i) a new drug shall continue to be considered as new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier.

2. 'India: Online Process for Clinical Trials by 2013', www.ehealthonline.org (5 November 2008).

4

Issues and concerns

Abstract: Although regulations relating to clinical trials have evolved greatly to match global standards, many issues still remain. The extreme shortage of regulatory experts is a major concern. Sponsors should be aware of differences in the Indian GCP version of ICH-GCP, and of the roles and responsibilities of foreign sponsors conducting clinical trials in India. Lack of pre-Investigational New Drug meetings with the regulatory reviewers and deficiencies in the functioning of ethics committees and CROs are other concerns. The participation of human subjects in clinical trials exposes all stakeholders involved in the trial to liability. Improper disclosure, conflict of interest, violation of good clinical practice and injuries resulting from the test drug can expose the sponsor company to the risk of liability. Sponsors/CROs are required to undertake to provide complete medical care and compensation for injury to the subjects in clinical trials. It is mandatory for manufacturers to obtain a licence to manufacture or loan licence from the authorities and to comply with certain conditions. Manufacturing units must undergo periodic inspection by the authorities.

Keywords: regulatory concerns, good clinical practice (GCP), ethics committee, informed consent, approval process, Indian Council of Medical Research (ICMR), Department of Biotechnology, pre-Investigational New Drug (pre-IND), Schedule Y1, stakeholder liabilities, human subjects, injuries, Central Drug Authority Bill, Schedule M

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4.1 Clinical research

4.1.1 Regulatory concerns

Although the regulations relating to clinical trials in India have been evolving considerably to match global standards, many issues still remain and have an impact on the industry. There are certain areas in the regulations that need to be clarified. Hence, authorities often need to be consulted on several issues, or the industry practices need to be followed.

The extreme shortage of regulatory experts is a major concern in India. Unlike the USFDA and EMEA, the DCGI does not release guidance documents providing the current interpretation of the regulations.

It is important for the sponsors to be aware of differences in the Indian GCP version of the ICH-GCP, including the Indian specifications for the composition of the IEC, informed consent procedures, compensation for participation, and also the roles and responsibilities of foreign sponsors conducting clinical trials in India.

4.1.2 Approval process

As mentioned earlier, approvals for clinical trials are granted by the DCGI. The approval process usually takes 4 to 5 months. However, this timeline has recently gone beyond 8 months in some cases. Unlike in the United States – where a sponsor can proceed with a clinical trial 30 days after submission of an Investigational New Drug (IND) application if the FDA has not commented – in India, the sponsor or its agent in India must receive written approval from the DCGI to proceed with a clinical trial. For global trials, a delay in getting DCGI approval could mean Indian sites lagging behind global sites, thereby delaying the whole study. The shortage of skilled staff leads to delays in getting approval from the DCGI. However the DCGI has been making every effort to expedite the approval process.

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Additional approval from other agencies such as the ICMR, the Genetic Engineering Approval Committee, and the Department of Biotechnology is necessary if the study drug is categorised as a biologic or a genetically engineered product, and can take up to 6 months or even longer. It is possible to make a simultaneous submission to the IEC.

Another major concern is the lack of pre-IND meetings with regulatory reviewers. But, the DCGI is very aware of these issues and concerns and is working towards resolving them.

4.1.3 Deficiencies in the functioning of IECs and CROs

There are many CROs that carry out trials on behalf of sponsors, but not all have adequate infrastructure and knowledge. It is therefore advisable to carry out due diligence on a CRO before appointing it.

The inadequate representation of personnel on IECs is another concern with certain organisations in India that carry out clinical research. This may lead to unfair opinion in the IEC and bias in favour of the clinical study. Some institutions have an IEC but regular committee meetings do not take place, or they lack Standard Operating Procedures or lack representation according to the ICMR guidelines.

The proposed new Schedule Y1 has mandated the registration of CROs with the authorities, and only these registered CROs will be allowed to conduct clinical trials. The DCGI has been conducting training programmes regularly for members of IECs across the country to improve the functioning of IECs, in collaboration with the WHO, the ICMR and many committed research professionals.

4.1.4 Clinical trial liabilities

Considering the participation of human subjects in clinical trials, all of the stakeholders involved in conducting the trial are exposed to liability. Generally, the targets for litigation are the investigators and

the institution involved. Improper disclosure, conflict of interest, violation of good clinical practice, injuries occurring as a result of the test drug could all expose the sponsor company to the risk of liability. Liabilities usually arise as a result of breach of informed consent rules or adverse reactions caused by the drugs or the negligence of the institution or investigator. As per the existing regulations, it is the responsibility of the sponsor to provide compensation for any physical or mental injury arising from a clinical trial or to provide adequate insurance coverage for any such injury. The responsibilities for payment of compensation for such injuries are covered by an indemnity clause in the agreement that stakeholders enter into.

Recently the DCGI has instructed sponsors and CROs to include an undertaking in the Informed Consent Form that the sponsor or CRO will provide complete medical care as well as compensation in cases of injury to the subjects in a clinical trial.

A comprehensive piece of legislation called the Central Drug Authority (CDA) Bill has been proposed by the government of India, which envisages a 5 years' term of imprisonment and a fine of Rs 20 lacs (Rs 2 million) for those found violating the norms of clinical trials.

4.2 Contract manufacturing

As mentioned above, it is mandatory for the manufacturer to obtain a licence to manufacture or a loan licence from authorities. The company needs to comply with certain conditions, such as having competent staff, Schedule M of the Drugs and Cosmetics Rules, storage and laboratory norms. This often leads to a delay in the approval process. Apart from complying with these norms, the manufacturing unit has to undergo periodic inspection by the authorities.

Under the provisions of the Drugs Act, the licensee is required to inform the licensing authority in writing in the event of any change in the constitution of the firm operating under the licence. Under the conditions of the licence, in such a situation the current licence shall be deemed valid for a maximum period of 3 months from the date

on which the change takes place. In the meantime, the licensee is required to obtain a fresh licence from the licensing authority in the name of the firm with the changed constitution. This provision can pose certain problems in a situation such as merger or acquisition of licensee or a change in the location of the licensee.

The contract manufacturing process in India also poses certain concerns in relation to tax issues such as transfer pricing, Association of Persons, service tax etc. and the protection of intellectual property. These concerns are discussed in the two following chapters.

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5

Tax environment and related issues

Abstract: Taxation of income in India is governed by the provisions of the Income Tax Act, 1961, as amended annually by the Finance Acts. Recently, the tax authorities have adopted an aggressive approach to transactions where any form of exemption from taxation is sought. Their approach is even more hostile when the transaction has an offshore element. Offshore transactions should be structured in such a manner that legitimate tax exemptions are not challenged. The government has taken various policy initiatives in order to strengthen scientific research and development in various sectors, including the awarding of fiscal incentives in the pharmaceutical sector. Outsourcing arrangements must be carefully structured so as to mitigate the risk of the Indian CRO/CMO being regarded as the Permanent Establishment of the foreign enterprise or the issue of taxation as an Association of Persons. Another area of concern in CRAMS business is transfer pricing issues. Apart from these concerns, the companies need to be aware of indirect tax issues involved in these transactions.

Keywords: Income Tax Act (ITA), tax incentives, Permanent Establishment (PE), tax treaties, Association of Persons (AOP), Double Taxation Avoidance Agreement (DTAA), Transfer Pricing (TP) Regulations, arm's length price, Value Added Tax (VAT), Special Economic Zones (SEZ)

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5.1 Direct taxes

5.1.1 General overview

Taxation of income in India is governed by the provisions of the Income Tax Act, 1961 (ITA) as amended annually by the Finance Acts. Under the ITA, residents are subject to tax in India on their worldwide income, whereas non-residents are taxed only on Indian source income, i.e. income that accrues or arises in India, is deemed to accrue or arise in India or which is received or is deemed to be received in India. Section 9 of the ITA deems certain income of non-residents to be Indian source income. Under section 9(1), 'capital gains' are considered to have their source in India and are taxable in India if they arise directly or indirectly, through the transfer of a capital asset situated in India. Similarly, the 'business income' of a non-resident is taxable in India only if it accrues or arises, directly or indirectly, through or from any business connection in India. The Indian tax rates applicable to non-residents can be up to 40 per cent (all tax rates provided herein are exclusive of surcharge and cess discussed below) on taxable business income and capital gains.

Section 90(2) of the ITA is a beneficial provision which states that, where the taxpayer is situated in a country with which India has a double tax avoidance agreement ('Indian Tax Treaty'), the provisions of the ITA apply only to the extent that they are more beneficial to the taxpayer. Rules under Indian Tax Treaties are generally more beneficial to the taxpayer than those under domestic law (ITA) and hence it is typically advantageous for a non-resident taxpayer to structure his investments or business through a jurisdiction that has signed an Indian Tax Treaty.

In recent years the Indian tax authorities have adopted an aggressive approach to transactions where any form of exemption from taxation is sought by the taxpayer. Their approach is even more hostile when the transaction in question has an offshore element. Hence, it is has become critical to ensure that offshore transactions are structured in such a manner that legitimate tax exemptions are not challenged by the tax department.

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Before we look at specific tax issues concerning contract research and manufacturing, set out below is a snapshot of the taxation regime in India. All tax rates mentioned here are exclusive of surcharge on tax (for companies with total income exceeding Rs 10 million), which is presently set at 5 per cent for domestic companies and 2 per cent for foreign companies, and an education cess on tax, which is presently set at 3 per cent.

5.1.1.1 Taxes applicable to companies

Under the ITA, the corporate income tax rate is 30 per cent for an Indian company and 40 per cent for a foreign company (where such income is taxable in India). Further, shareholders are exempt from income tax on dividends paid by Indian companies, irrespective of their residential status. However, the company distributing the dividends is required to pay a dividend distribution tax of 15 per cent.

5.1.1.2 Minimum Alternate Tax

If the tax payable by any company, including a foreign company taxable in India, is less than 18.5 per cent of its book profits, it will be required to pay Minimum Alternate Tax under the ITA, which will be deemed to be 18.5 per cent of such book profits. The carry-over and set-off is allowed only up to 10 assessment years immediately succeeding the assessment year in which such tax credit becomes allowable and is governed by the following basic principles:

1. The amount of tax credit that is allowed shall be the difference of the Minimum Alternate Tax paid and the amount of tax payable by the taxpayer on his total income as per the other provisions of the ITA.
2. Set-off in a future assessment year in respect of brought-forward tax credit is allowed only to the extent of the difference between the tax payable by the taxpayer on his total income and the tax that would have been payable under the Minimum Alternate Tax provisions.

5.1.1.3 Interest

Interest on foreign-currency denominated loans received from India by a non-resident is generally taxable at a rate of 20 per cent as per the provisions of the ITA (although it may be reduced to 10 or 15 per cent under some Indian Tax Treaties) and is required to be withheld at source by the resident payer. Further, interest is a tax-deductible expense for the Indian payer company, provided that the applicable tax has been withheld before making the payments to the non-resident.

5.1.1.4 Royalties/Fees for Technical Services

Payments of royalties and Fees for Technical Services (FTS) currently attract a withholding tax at the rate of 10.56 per cent as per the provisions of the ITA (on a gross income basis; this rate may be reduced to 10 per cent under some Indian Tax Treaties). Further, where royalties or FTS are paid to a foreign company and are effectively connected to a Permanent Establishment (PE) of the foreign company in India, then such payments will be taxed as business profits on a 'net income' basis.

5.1.1.5 Capital gains

Under the ITA, capital gains earned on the transfer of capital assets are classified into short-term capital gains and long-term capital gains, depending on the period of holding. Shares in a company, securities listed on a recognised Indian stock exchange, if held for more than 12 months, are treated as long-term capital assets, and if held for 12 months or less are treated as short-term capital gains. These gains are taxed as follows:

- Long-term capital gains arising on the transfer of listed equity shares (including units of an equity-oriented mutual fund) on a recognised stock exchange in India will be exempt from tax in India.
- Short-term capital gains arising on the transfer of listed equity shares (including units of an equity-oriented mutual fund) on a recognised stock exchange in India will be taxed at the rate of 15 per cent.

- Capital gains realised on the sale of listed equity shares not executed on a recognised stock exchange in India will be taxed at the rate of 10 per cent for long-term gains and as normal income in the case of short-term gains.
- Capital gains realised on the sale of unlisted Indian securities will be taxed at the rate of 20 per cent for long-term gains and as normal income in the case of short-term gains.

The exemption of long-term capital gains and reduction of the rate for short-term capital gains on the sale/transfer of the equity shares on a recognised stock exchange in India is allowed only where the applicable Securities Transaction Tax has been paid on the transaction.

5.1.2 Incentives under the ITA

The Indian government has taken various policy initiatives in order to strengthen scientific research and development in various sectors, including the pharmaceutical sector. The term 'scientific research' has been defined in the ITA to include *activities for the extension of knowledge in the fields of natural or applied science*. Scientific research can be carried out either in-house or by contributing to outside agencies engaged in scientific research.

Typically, in the pharmaceutical industry, fiscal incentives are awarded to research and development units for the development of new drug molecules, clinical research, new drug delivery systems, new research and development set-ups and infrastructure provision.

5.1.2.1 In-house research and development

Companies engaged in the businesses of biotechnology or the manufacture or production of any drugs, pharmaceuticals, chemicals etc. and who have incurred any expenditure on scientific research (not being expenditure on land or buildings) or on in-house research and development facilities as approved by the Department of Scientific and Industrial Research, are allowed a deduction of 200 per cent of

any such expenditure. Expenditure on scientific research includes that incurred on clinical drug trials, obtaining approval from any regulatory authority under any central, state or provincial Act and filing an application for a patent under the Patents Act, 1970.

It should be borne in mind here that no company will be entitled to the above-mentioned deduction unless it enters into an agreement with the Department of Scientific and Industrial Research for cooperation in such a research and development facility and for audit of the accounts maintained for that research and development facility.

Currently, this deduction is available for expenses incurred prior to 31 March 2012.

5.1.2.2 Contributions made to other institutions for scientific research

The ITA provides for a deduction of 175 per cent of sums paid to any scientific research association (having as its object the undertaking of scientific research) or to any university, college or other institution, for the purpose of scientific research approved by the concerned authority.

5.1.2.3 Capital expenditure

Under Section 35(1)(iv) read with Section 35(2) of the ITA, the whole of any expenditure on scientific research (other than expenditure on the acquisition of any land) being capital in nature and incurred after 31 March 1967 is allowed as a deduction. Further, under Explanation 1 to Section 35(2) of the ITA, the aggregate capital expenditure on scientific research incurred 3 years immediately prior to the commencement of business is allowed as a deduction in the year in which the business is commenced.

5.1.2.4 Incentives provided to venture capital funds investing in the pharmaceutical sector

In order to provide an impetus to venture capital investment in the pharmaceutical sector, the ITA has granted certain tax benefits to

venture capital funds registered with the Securities and Exchange Board of India that invest into certain pharmaceutical businesses. Under Section 10(23FB) of the ITA, income of a venture capital fund which arises as a result of investments into companies engaged in, *inter alia*, 'bio-technology' and 'research and development of new chemical entities in the pharmaceuticals sector' is exempt from tax and such income is taxable only in the hands of the investors of the venture capital fund at the time of distribution of the income.

5.1.3 Potential Permanent Establishment issues in contract research and manufacturing

Where a foreign enterprise proposes to outsource research and manufacturing functions to an Indian CRO/CMO, the outsourcing arrangement will have to be carefully structured in order to mitigate the risk of the Indian CRO/CMO being regarded as the Permanent Establishment (PE) of the foreign enterprise. The risk is significantly greater where significant manufacturing functions are outsourced by the foreign enterprise to an Indian CMO. The issue of the creation of an Indian PE of the foreign enterprise is a significant one, given that, if such a PE is created, the business income (attributable to the PE) of the foreign enterprise, which might otherwise not be taxed in India, would be subject to tax at the rate of 40 per cent.

Under the ITA, the business income of a non-resident is taxable in India (at the rate of 40 per cent) if it accrues or arises, directly or indirectly, through or from any 'business connection' in India. Similarly, under the Indian Tax Treaties, typically, the business income of a non-resident is taxable only to the extent that it is attributable to a PE of such non-resident in India. The concept of PE under typical Indian Tax Treaties is expressed as an exhaustive list of factors, as opposed to the 'business connection' rule contained in the ITA, which has no exhaustive definition in the ITA and which has in the past been afforded a wide interpretation by Indian courts. Therefore, there may be situations where a non-resident is considered to have a business connection in India, but no PE. As mentioned earlier, since it is open for the non-resident taxpayer to choose to be

treated under the more beneficial regime, a non-resident may rely on the PE rule under the applicable Indian Tax Treaty rather than the business connection rule in the ITA.

The term Permanent Establishment has been succinctly defined by the Andhra Pradesh High Court in the case of *CIT* v. *Visakhapatnam Port Trust*, as follows:

> In our opinion, the words permanent establishment postulate the existence of a substantial element of an enduring or permanent nature of a foreign enterprise in another country which can be attributed to a fixed place of business in that country. It should be of such a nature that it would amount to a virtual projection of the foreign enterprise of one country into the soil of another country.

The Indian Tax Treaties typically lay down certain criteria to determine whether a foreign enterprise earning business income from India would be construed to have a PE in India. Some of these tests are discussed below, especially in the context of contract research and manufacturing.

5.1.3.1 Fixed place of business PE

A foreign enterprise is deemed to have a PE in India if the business of the foreign enterprise is, wholly or partly, carried on through a fixed place of business in India.

The principle of fixed place of business PE is particularly relevant in the context of contract research and manufacturing. As demonstrated below, unless such arrangements are structured carefully, there may be circumstances which may lead to the inference that the business of the foreign enterprise, which outsources the research and manufacturing functions to an Indian CRO/CMO, is being carried on through a fixed place of business in India.

In a typical contract research and manufacturing model, it is common for the foreign enterprise to frequently send personnel to the offices of the Indian CRO/CMO to provide training services. Often, the foreign enterprise also sends its personnel to the offices of the Indian CRO/CMO to supervise and inspect the activities carried

on by the Indian CRO/CMO, in order to ensure that such activities adhere to the prescribed standards. In both these instances, if these personnel, being employees of the foreign enterprise, have some premises (often even a desk or an office is regarded as premises) allotted to them within the Indian CRO/CMO for a reasonably long period of time, such premises, though not owned or rented by the foreign enterprise, are likely to be considered a 'fixed place of the foreign enterprise'. In such a scenario, it may be claimed by the Indian tax authorities that the foreign enterprise is carrying on its business through a fixed place, and that hence a PE of the foreign entity exists in India. Therefore, in any arrangement to outsource research and manufacturing to an Indian CRO/CMO, it is critical to ensure that the outsourcing arrangement is structured in a manner that mitigates the risk of the foreign entity having a PE in India.

5.1.3.2 Service PE

Further, under some Indian Tax Treaties, a foreign enterprise may be considered to have a PE in India due to the presence of its personnel in India, who render services beyond a specified time period or to a related enterprise. For instance, under the India–US Tax Treaty, a PE is said to be constituted where there is:

(l) the furnishing of services, other than included services as defined in article 12 (royalties and fees for included services), within a Contracting State by an enterprise through employees or other personnel, but only if:

  (i) activities of that nature continue within that State for a period or periods aggregating to more than 90 days within any twelve-month period; or

  (ii) the services are performed within that State for a related enterprise (within the meaning of paragraph 1 of article 9 (associated enterprises)).

In the example discussed earlier, if the training and inspection personnel sent by the foreign enterprise to the offices of the Indian

CRO/CMO are deemed to be 'furnishing services' beyond the prescribed limit of 90 days, it is likely that the tax authorities may argue that the presence of such personnel constitutes a PE of the foreign enterprise in India.

5.1.3.3 Agency PE

Indian Tax Treaties typically contain a provision whereby an Indian entity may be treated as a PE of a foreign enterprise if the Indian entity, *acting on behalf of the foreign enterprise, has and habitually exercises an authority to conclude contracts on behalf of the foreign enterprise*. Moreover, some Indian Tax Treaties, such as the India–US tax treaty, also contain an additional provision whereby an Indian entity may be regarded as a PE of the foreign enterprise if the Indian entity maintains a stock of goods from which it regularly delivers such goods on behalf of the foreign enterprise and contributes to the sale of such goods. An agent of independent nature is considered as an exception to the Agency PE rule.

In the context of contract manufacturing, it may be contemplated in the arrangement that the Indian CMO will maintain and deliver the final pharmaceutical product on behalf of the foreign enterprise. In such cases, if the contract is not structured cautiously, the Indian CMO may be regarded as a PE of the foreign enterprise under the Agency PE clause in the applicable Indian Tax Treaty. The Indian CRO/CMO may also run the risk of being regarded as the PE of the foreign enterprise where the Indian entity, acting on behalf of the foreign enterprise, has and habitually exercises an authority to conclude contracts on behalf of the foreign enterprise. Although such rights are not ordinarily granted by the foreign enterprise to the Indian CRO/CMO, care should be taken to ensure that the Indian CRO/CMO does not have the right to even represent the foreign entity in any negotiations, since, in the past, the exercise of such a right has been held to constitute a PE of the foreign entity in India.

In cases of outsourcing by a foreign enterprise to its Indian subsidiary, a question arises as to whether there is added PE risk for the foreign enterprise as a result of the parent–subsidiary relationship of the two entities. The answer to this lies in the Indian Tax Treaties. The principle that is embodied in typical Indian Tax Treaties is that

the existence of a subsidiary company does not, by itself, constitute that subsidiary company a PE of its parent company. This follows from the principle that, for the purpose of taxation, such a subsidiary company constitutes an independent legal entity. Thus, where a foreign enterprise outsources its research and manufacturing functions to an Indian CRO/CMO, the fact that the Indian CRO/CMO is the subsidiary of the foreign enterprise should not, by itself, constitute that Indian CRO/CMO to be a PE of the foreign enterprise.

As is clear from the discussion above, the issue as to whether any activity of a foreign entity in India results in a PE of that foreign entity in India depends on the facts and circumstances of each case. In the context of contract research and manufacturing, the answer lies in the manner in which the outsourcing arrangement is structured and the activity of the Indian CRO/CMO is managed and operated.

5.1.4 Issue of taxation as an Association of Persons

Depending on the manner in which it is structured, a contract research and manufacturing arrangement could run the risk of being taxed under the ITA as a separately taxable unit called an Association of Persons (AOP). This is a significant issue for the foreign enterprise that outsources these functions, given that, if such an arrangement is treated as an AOP, the profits of the foreign enterprise attributable to the AOP, which otherwise would not have been subjected to tax in India (in the absence of a PE of the foreign enterprise in India), would be taxable at the maximum marginal rate of 40 per cent.

Although there is no definition of an AOP under the ITA, there have been a number of cases in which this issue has been discussed. In the case of *Commissioner of Income Tax* v. *Indira Balkrishna* ([1960] 39 ITR 546 (SC)), the Supreme Court has explained the concept of an AOP as follows:

> an association of persons must be one in which two or more persons join in a common purpose or a common action, and as the words occur in a section which imposes a tax on income, the association must be one the object of which is to produce income, profits or gains.

Further, in the case of *Deccan Wine and General Stores* ([1977] 106 ITR 111 (AP)), the Andhra Pradesh High Court further examined this concept and observed that

> it is, therefore, clear that an association of persons does not mean any and every combination of persons. It is only when they associate themselves in an income-producing activity that they become an association of persons. They must combine to engage in such an activity; the engagement must be pursuant to the combined will of the persons constituting the association; there must be a meeting of the minds, so to speak. In a nutshell, there must be a common design to produce income. If there is no common design, there is no association. Common interest is not enough. Production of income is not enough.

Although there is lack of clarity in Indian law on the concept of an AOP, broadly, the essential conditions for constituting an AOP may be said to be:

- two or more persons
- voluntary combinations
- a common purpose or common action with object to produce profit or gains
- combination in joint enterprise
- some kind of scheme for common management.

The risk of a contract research and manufacturing arrangement being regarded as an AOP is particularly great in cases where the Indian CRO/CMO co-develops the drug with its foreign partner based on a revenue-sharing model. Such special arrangements, if not structured appropriately, could lend weight to the characterisation of the arrangement as an AOP, namely, *two persons joining in a common purpose or a common action the object of which is to produce income, profits or gains*. Thus, in order to avoid such characterisation, it becomes important to demonstrate clearly in the contract that the intention is not to carry out any business in common and that the Indian CRO/CMO will execute only a part of

the job (i.e. research and manufacturing), according to its technical skill and capability. To the extent possible, the contract should convey that the work and income arising from the foreign enterprise's contribution is quite distinct and independent of the Indian CRO/CMO's work and income. Hence, it must be ensured that the arrangement is structured in such a manner as to mitigate any risk of its being regarded as a single assessable unit and liable to tax as an AOP.

5.1.5 Structuring investment into India – use of intermediate jurisdictions

Foreign entities that are considering the incorporation of subsidiaries in India for outsourcing research and manufacturing functions can achieve tax efficiency by using a tax-neutral intermediate jurisdiction that has signed an Indian Tax Treaty ('Treaty Jurisdiction'), rather than directly investing in the Indian company. The foreign entity can achieve tax efficiency by incorporating a company (or any other entity that is eligible for the benefits of the relevant Indian Tax Treaty) in the Treaty Jurisdiction that would, in turn, invest into the underlying Indian company.

The choice of an appropriate Treaty Jurisdiction, apart from tax neutrality and a good treaty network, will depend on factors such as political stability, ease of administration, availability of reliable administrators, favourable exchange controls and legal system, certainty in the tax and legal framework and ease of winding-up operations.

Indian Tax Treaties aim to prevent double taxation of income and capital gains for a person or entity resident in another jurisdiction. For instance, under the India Mauritius Double Taxation Avoidance Agreement (DTAA), capital gains earned on the sale of Indian securities by a Mauritius company would be taxable only in Mauritius. Further, currently the Mauritius domestic tax laws provide an exemption on most categories of capital gains. By investing through such a jurisdiction, a foreign investor need only pay capital gains tax in its home jurisdiction. Further, in selecting an appropriate

Treaty Jurisdiction, it is important for a foreign investor to select a jurisdiction that gives it the specific benefits it requires. For instance, when investing in debt and extracting returns in the form of interest, Cyprus proves to be better placed than Mauritius, even though the latter is widely used by investors making investments into India.

Box 5.1 Popular treaty jurisdictions

Mauritius

↑ Settled jurisdiction for investment into India
↑ Capital gains tax exemption
↓ No tax benefit for interest income

Cyprus

↑ Capital gains tax exemption
↑ Interest taxed at 10 per cent
↓ Reports of treaty undergoing renegotiation

Singapore

↑ Reputed and preferred financial services sector
↑ Limitation of benefits clause
↓ Capital gains tax exemption linked to Mauritius DTAA
↓ Income characterisation issues

5.1.6 Indian transfer pricing issues in contract research and manufacturing services

Where entities are looking to outsource research and manufacturing functions to an associated enterprise, such as in cases of captive outsourcing, the fees payable to the service provider should take into account transfer pricing issues.

In India, Transfer Pricing Regulations (TP Regulations) were introduced on 1 April 2001. The Indian Income Tax Act, 1961 lays down provisions that deal with the computation of income arising from 'international transactions' between 'associated enterprises'.

The basic rule enshrined in the TP Regulations is that any income arising from an 'international transaction' shall be computed having regard to the arm's length price (discussed below). The TP Regulations define 'associated enterprise' to include any enterprise that participates directly or indirectly or through one or more intermediaries in the management or control of capital of another enterprise. Enterprises may also be regarded as 'associated' as a result of circumstances such as interdependence by virtue of borrowings, guarantees, licensing of trademarks, purchase, sales or where enterprises have 'mutual interest' as may be prescribed by the revenue authorities. Here, 'enterprise' is defined broadly and covers any entity (including a PE) that is or proposes to be engaged in any activity relating to the provision of goods/services of any kind, investment activity, dealing in securities and extending loans. The term 'international transaction' has been defined as a transaction between two or more associated enterprises, either or both of which are non-residents. As mentioned earlier, the basic principle is that any income arising from such an 'international transaction' shall be computed having regard to the 'arm's length price'.

5.1.6.1 Arm's length price

Arm's length price is the price that is applied or proposed to be applied in a transaction between persons other than associated enterprises, in uncontrolled conditions. The Organisation for Economic Co-operation and Development Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations, 2010 ('Guidelines') provide that the application of the arm's length principle is generally based on a comparison of all the relevant conditions in a controlled transaction with the conditions in an uncontrolled transaction. Under the Guidelines, comparability is achieved when there are no differences in the conditions that could materially affect the price or when reasonably accurate adjustments can be made to eliminate the effects of any such differences. The analysis of the controlled transactions with uncontrolled transactions is the very basis of ascertaining whether the controlled transactions adhere to the arm's length standard.

The arm's length price in relation to an international transaction is to be determined by any of the following methods, depending on which is the most appropriate, given the business of the enterprises:

- comparable uncontrolled price method
- resale price method
- cost plus method
- profit split method
- transactional net margin method
- such other method that may be prescribed by the Central Board of Direct Taxes (to date, no other method that may be considered appropriate in determining the arm's length price has been prescribed).

The pharmaceutical industry in India has time and again faced issues with respect to arriving at a comparable arm's length price for the purpose of transfer pricing. The industry faced a significant setback early in 2011, when the Mumbai Income Tax Appellate Tribunal ('Tax Tribunal'), hearing an appeal by Serdia Pharmaceuticals India Private Limited ('Serdia') *[Serdia Pharmaceuticals (India) Private Limited* v. *ACIT, ITA Nos: 2469/Mum/07 and 2531/Mum/08]*, held that the arm's length price for importing active pharmaceutical ingredients (APIs) from related enterprises should be determined on the basis of the price at which locally manufactured generic APIs are sold in the domestic market. Serdia, a pharmaceutical company, imported APIs from its related entities in France and Egypt for the purpose of manufacturing certain drugs. In order to arrive at the correct arm's length price of the APIs that were imported into India, the taxpayer had adopted the Transactional Net Margin Method (TNMM). However, the Income Tax Department contended that the APIs purchased were at prices that were higher than those paid for similar APIs by other companies in India and that the Comparable Uncontrolled Price (CUP) was the most appropriate method to be adopted. On the basis of domestically available data, the tax department claimed that the arm's length price for the APIs should have been significantly less than that at which Serdia had imported these APIs. The Tax Tribunal ruled in favour of the tax department

and held that the tax department was justified in applying the CUP method without specifying the reasons for rejection of the TNMM method. The Tax Tribunal did not accept Serdia's justification of the high import price, namely, that the APIs were manufactured on equipment complying with standards set by the WHO, the British Good Manufacturing Practices (GMP) and as per HSE or health, safety and environment standards. The Tax Tribunal observed that the high quality-standards employed in the manufacturing process conferred merely a certain degree of comfort pertaining to the minimum level of impurities and this did not necessarily affect the APIs' comparability with the same APIs manufactured by generic drug companies.

The Tax Tribunal's ruling in the Serdia case has had an adverse impact on pharmaceutical multinationals that do business in India. It has been observed that, post the Serdia ruling, the tax department has been aggressively pursuing multinational pharmaceutical companies that are procuring APIs from their respective parent companies.

Another challenge faced by Indian pharmaceutical companies with respect to transfer pricing is that the TP Regulations do not specifically deal with intangibles, or provide a basis for computing the arm's length price, while dealing with the same. As opposed to transactions involving tangibles, where a pricing situation in a controlled transaction can be compared with that of an uncontrolled transaction (provided that all other conditions are similar or identical), in the case of intangibles/intellectual property it is very difficult to identify comparables, given the unique nature of the intellectual property involved. Hence, it becomes difficult to find a comparable on the basis of which the arm's length price may be ascertained.

The Indian contract research and manufacturing industry has also had its fair share of problems with the tax department as far as transfer pricing is concerned. This is once again attributable to the lack of comparables for arriving at an appropriate arm's length price. The databases that provide comparable information are lacking in so far as they fail to provide information relating to companies engaged in pure contract research activities. Typically, the information offered by these databases relates to companies that

work on different models, such as co-development of a drug by the Indian CMO in partnership with its foreign associate, based on a revenue-sharing arrangement. Hence it becomes extremely difficult for Indian CROs/CMOs to arrive at a suitable arm's length price. As a result, the Indian tax department has time and again created problems for Indian CROs/CMOs by insisting on a significantly higher mark-up.

It is important to note that the TP Regulations also require persons entering into international transactions to maintain prescribed documents and information, and to obtain and furnish to the revenue authorities an accountant's report containing prescribed details regarding the international transactions. Stringent penalties have been prescribed for non-compliance with the procedural requirements and for understatement of profits.

5.2 Indirect taxes

India has a well-developed tax structure with clearly demarcated authority between central and state government and local bodies. The Indian central government levies taxes on income (except tax on agricultural income, which the state government can levy), customs duties, central excise and service tax. Value Added Tax (sales tax in states where VAT is not yet in force), stamp duty, land revenue and tax on professions are levied by the state governments.

Although the cost of labour and production in India is significantly lower than in other countries, the ultimate price of the goods is on the high side on account of a multi-layer and multi-stage levy of indirect taxes. As a result, the growth of industry in India, including the pharmaceutical industry, has been stunted. Further, the greater concern is that the appreciation in the cost of goods that results from the levy of such taxes is indirectly passed on to the end customer, namely the common man, who bears the burden, especially in the case of essential products such as pharmaceuticals. Because of the resulting impact on the post-taxation price of goods, efforts are being made to replace the existing indirect tax system with a unified goods and services tax (GST) system.

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5.2.1 Service tax

Service tax was introduced vide Chapter V of the Finance Act, 1994 and further widened in scope by subsequent Finance Acts. Currently, service tax is levied at the rate of 10 per cent (excluding an education cess of 3 per cent) on gross basis on specified taxable services. From 1 April 2011 service tax is payable on accruals, and not on the realised value of services. Some of the taxable services are management consulting services, consultancy or technical services provided by a consulting engineer, business auxiliary services, intellectual property services etc.

In addition to the aforesaid services, scientific or technical consultancy services fall within the category of taxable services. 'Scientific or technical consultancy' means any advice, consultancy or scientific or technical assistance rendered (directly or indirectly) by a scientist or a technologist, or by any science or technology institution or organisation.

Further, service provided by a technical testing and analysis agency is also subject to service tax in India. 'Technical testing and analysis' means any service in relation to physical, chemical, biological or any other scientific testing, or analysis of information technology software or any immovable property, but does not include any testing or analysis service provided in relation to human beings or animals. The Finance Act clarifies that while technical testing and analysis includes testing and analysis undertaken for the purpose of clinical testing of drugs and formulations, it does not include testing or analysis for the purpose of determination of the nature of a diseased condition, identification of a disease or prevention of any disease or disorder in human beings or animals.

Export of services is not subject to service tax in India, while in cases of imported services, the recipient is liable to pay service tax. In order to qualify as an export under the Export of Service Rules 2005, *inter alia* the service must be rendered from India but consumed outside India, and the consideration must be paid in convertible foreign exchange. Additional conditions are imposed, depending upon the type of service provided.

5.2.2 Customs duty

Customs duties are levied whenever there is trafficking of goods through an Indian customs barrier, i.e. they are levied both for the export and import of goods. Export duties are competitively fixed so as to give advantage to the exporters. Consequently, a large share of customs revenue is contributed by import duty. Customs duty primarily has a 'Basic Customs Duty' for all goods imported into India and the rates of duty for classes of goods are mentioned in the Customs Tariff Act, 1975 (the 'Tariff Act'), which is based on the internationally accepted Harmonized System of Nomenclature (HSN). The general rules of interpretation with respect to tariffs are mentioned in the Tariff Act. The rates are applied to the transaction value of goods (for transactions between unrelated parties) as provided under the Customs Act, 1962 (the 'Customs Act') or by notification in the official gazette. A further duty, Countervailing Duty (CVD), is imposed to countervail the appreciation of end price resulting from the excise duty imposed on similar goods produced indigenously. To bring the price of imported goods to the level of locally produced goods that have already suffered a duty for manufacture in India (excise duty), CVD is imposed at the same rate as excise duty. In addition to the above, there are also Additional Customs Duties in lieu of state and local taxes (ACD) which are also imposed as a countervailing duty against sales tax and VAT imposed by states. The ACD is currently levied at the rate of 4 per cent.

Further, the central government, if satisfied that circumstances exist that render it necessary to take immediate action to provide for the protection of the interests of any industry, arising from a sudden upsurge in the import of goods of a particular class or classes, may provide for a Safeguard Duty. Safeguard Duty is levied on such goods as a temporary measure, and the intention of the same is the protection of a particular industry from the sudden rise in imports. In the Indian pharmaceutical industry, given that a large number of companies are involved in the import and subsequent resale of unpackaged pharmaceutical products, such imports are subject to a levy of a special duty termed the Special Additional Duty (SAD). An exemption has been provided for pre-packaged goods where the sale

price has been declared on the package. The SAD paid can be refunded only if it is proved that state-level VAT is paid on the subsequent sale of the imported products. The issue often faced by companies is that the process of obtaining refunds of SAD is tedious and time consuming, and the time limit for filing the refund is stipulated as one year, which often leads to a failure in obtaining rightful refunds.

Under Section 9A of the Tariff Act, the central government can impose an Antidumping Duty on imported articles if they are exported to India at a value less than the normal value of the same article in other jurisdictions. This duty is not to exceed the margin of dumping with respect to the article concerned. The law in India with respect to anti-dumping is based on the 'Agreement on Anti-Dumping' pursuant to Article VI of the General Agreement on Tariffs and Trade, 1994.

5.2.3 Sales Tax and Value Added Tax

Central Sales Tax (CST) is imposed on the sale of goods in the course of inter-state trade or commerce. Sales of goods are deemed to take place in the course of inter-state trade if they result in the movement of goods from one state to another, or if such sales are effected by the transfer of documents of title to the goods during their movement from one state to another. No CST is levied on direct imports or exports or on purchases or sales effected in the course of importing or exporting. The process of phasing out CST commenced with a reduction in the CST rate from 4 per cent to 2 per cent on 1 April 2008.

Value Added Tax (VAT) is levied on the sale of goods within a particular state at the two main VAT rates of 4 per cent and 12.5 per cent. VAT is a state-specific levy and most states in India have introduced specific legislation for VAT based on the model VAT legislation circulated by the Empowered Committee of State Finance Ministers. Further, under the VAT regime, a system of tax credits on input goods procured by the dealer is also available, to avoid the cascading effect of taxes that prevailed under the erstwhile sales tax regime.

5.2.4 CENVAT

CENVAT is an excise duty that is levied on all goods that are produced or manufactured in India, marketable, movable and covered by the excise legislation. The peak duty rate was reduced from 16 per cent to 14 per cent by the Finance Act, 2008 and was further reduced to 8 per cent, although there are other rates ranging upwards, or based on an *ad valorem*/quantity rate.

In order to avoid the cascading of excise duty and double taxation, the CENVAT scheme has been framed under the Central Excise Act and the CENVAT Credit Rules. Under the CENVAT Credit Rules, a manufacturer of excisable goods can avail themselves of credit for duty paid on certain inputs and capital goods, barring certain inputs used in the specified manufacture of certain products. The credit can be utilised towards the duty payable on removal of the final product. It must also be noted that the CENVAT scheme also takes into account credits with respect to any service tax paid by the manufacturer on input services received.

In the pharmaceutical industry the rate of excise duty on inputs has always been higher than the rate of excise duty applicable to the finished products. While the generic excise duty rate on the inputs (APIs) is currently at 10.3 per cent, the generic excise duty rate on finished formulations is 4.12 per cent. The net result is that the CENVAT credit accumulates in the books of the drug manufacturer, who is unable to use it efficiently. Manufacturers catering for the domestic market have borne the burden of this issue, since they can neither set off the entire CENVAT credit nor claim a refund of the same, unlike their counterparts who export pharmaceutical products and are eligible for refunding of the unused CENVAT credit. One can only hope that in the future the Indian government will either align the excise duty rates of APIs (inputs) with those of the finished formulations or provide a refund mechanism for the unused CENVAT credit.

Another issue commonly faced by pharmaceutical companies is the low abatement percentage for pharmaceutical products. The assessable value for the purpose of levying excise duty on pharmaceutical products is calculated by providing a certain

abatement from the Maximum Retail Price (MRP) of the product. At present, an abatement of 35 per cent of MRP is permitted for pharmaceutical products. The pharmaceutical industry has claimed that the abatement is not sufficient, given that the industry faces trade margins, R&D costs and other costs specifically associated with the pharmaceutical industry.

5.2.5 Research and development cess

All payments made towards the import of technology are subject to a cess of 5 per cent under the Research and Development Cess Act, 1986. Technology includes any special or technical knowledge or any special service required for any purpose whatsoever by an industrial concern under any foreign collaboration, and includes designs, drawings, publications and technical personnel.

5.3 Synopsis of benefits available to units set up in Special Economic Zones

The following benefits are available to units located in Special Economic Zones ('SEZ units') in India:

- During the financial year beginning 1 April 2005, SEZ units will get the following exemptions:
  - 100 per cent exemption of profits and gains from business for the first 5 years
  - 50 per cent exemption on profits and gains from business for the next 5 years
  - 50 per cent exemption to the extent that such amounts are re-invested in the SEZ Special Reserve Account.
- Exemption from capital gains arising on transfer of capital assets in the case of shifting of industrial undertaking from urban areas to any SEZ, provided that, 1 year before, or 3 years after the transfer (i) machinery/plant was purchased for the business of

the industrial undertaking in the SEZ, (ii) building or land was acquired or building was constructed in the SEZ, (iii) the original asset was shifted and the establishment was transferred to the SEZ and (iv) the assessee incurred such other expenses as are notified by the central government.

- 100 per cent customs duty exemption on the import of goods or services into the SEZ. However, any goods removed from the SEZ into a domestic tariff area will be subject to customs duty.
- 100 per cent excise duty exemption on goods brought from a domestic tariff area into the SEZ.
- 100 per cent service tax exemption.
- 100 per cent exemption from Securities Transaction Tax.
- Exemption from the levy of taxes on the sale or purchase of goods other than newspapers under the Central Sales Tax Act, 1956 if such goods are meant to carry on the authorised operations by the developer or entrepreneur.

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6

Service agreements

Abstract: Once the outsourcing company has selected the CMO/CRO, it is extremely critical to enter into a detailed agreement. The outsourcing contract forms the core of a successful outsourcing relationship and must capture the unique business strategies and concerns and the commercial understanding of the parties. As regards liability arising out of the trial, relevant clauses must be inserted for allocation of responsibilities among the parties and are a requirement for obtaining insurance. Apart from clauses on indemnification, clauses related to the obligations of all parties involved, use of investigational drugs, supply chain, change of control, intellectual property, confidentiality, roles and responsibilities must be included in the agreement. It is very important that all the clauses in the agreement are discussed and negotiated in detail to avoid conflict in future or to provide clarity in cases of dispute.

Keywords: milestones, liability, change of control, intellectual property (IP), termination, dispute resolution mechanisms, service fees, insurance, alternate dispute resolution, foreign awards and judgments

Once the outsourcing company (customer) has completed the process of selecting the CMO or CRO, it is absolutely critical to enter into a detailed agreement. Since an outsourcing contract forms the core of a successful outsourcing relationship, it should be drafted meticulously and must capture the unique business strategies and concerns, as well as the commercial understanding of the parties.

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In relation to clinical trials, the sponsor enters into the master agreement/services agreement with the CRO, and in turn the CRO enters into the clinical trial agreement with the institution and/or investigators. Depending upon the arrangement and degree of ease between the parties, the sponsor is also made a party to the clinical trial agreement. As regards liability arising out of the trial, relevant clauses have to be inserted for the allocation of responsibility among the parties and are a requirement for obtaining insurance. Apart from clauses on indemnification, clauses related to the obligation of all the parties involved, the use of investigational drugs, the supply chain, change of control, intellectual property, confidentiality and roles and responsibilities must be included in the agreement.

6.1 Contract research/contract manufacturing agreements

These agreements must document the scope of services to be rendered, the responsibilities of the parties, performance specifications, accountability and measurement standards, a pricing structure for the services, a schedule of deliverables and other conditions concerning employment, confidentiality, termination, dispute resolution mechanisms and governing law. The main agreement may also contain schedules or exhibits that specify some of the terms and conditions in detail.

Incomplete documentation of mutual rights and obligations can result in disputes.

The following are some of the key issues that have to be addressed in the agreement.

6.1.1 Scope of services

In relation to the scope of services, the following should be captured in the agreement:

- details of the services to be rendered and the resources to be used for providing the services;
- how the parties should deal with any widening of the scope of services.

While the documentation of the scope of services and other related details may not appear to require the same rigour as is customarily applied to the more obvious 'legal' provisions in the terms and conditions, the exhibits set out numerous important obligations. Complete and accurate content in the exhibits is integral to the successful operation of the relationship between the parties. Placing sufficient focus on the exhibits early, and consistently throughout the transaction cycle, will allow the parties time to negotiate and document appropriate terms and ensure the consistency of the exhibits with the terms and conditions of the agreement.

6.1.2 Milestones

One of the most important reasons for outsourcing is to capitalise on the expertise and higher quality of services offered by the service provider in a timely manner. Thus, some of the most important areas that an agreement should address are milestones and service levels, such as specifying the details of the milestones, deliverables, performance to be measured and methods for measuring service levels. The parameters for service measurements will depend on the services that are being outsourced.

The agreement should cover the requirement of periodic reporting, the content of the report and audit rights.

6.1.3 Service fees

The fees may be a lump sum amount or may depend on various factors such as the achievement of milestones.

When determining the fees payable to the service provider, especially in cases of captive outsourcing, the transfer pricing issues discussed in Chapter 5 should be borne in mind.

6.1.4 Managing the service provider

Even if a company outsources its manufacturing or research process, it will want to maintain some degree of control over the service provider; for example, to ensure stability and consistency in the management of the project, the customer should have the right of prior approval of the appointment, removal and replacement of the senior members of the team. This is because the senior members will have gained a comprehensive understanding of the client's needs and any replacements will require some time to achieve the same degree of familiarity. Further, it is very important to manage the team effectively, as the team personnel will have access to confidential information.

For better coordination between the customer and the vendor, each should appoint one contact person and all communications between the parties should always be routed through such contacts.

The customer may impose training requirements on the agents working on the outsourced operations, seek reports on performance levels and require the service provider to have the latest technology and infrastructure. The customer may also prohibit the service provider from subcontracting/assigning its services to a third party without the client's consent.

The customer will impose the above restrictions in order to maintain some control over the outsourced operations. While such measures will provide a degree of comfort to the customer, the amount of control exercised should not become an administrative burden or amount to 'managing' the service provider.

6.2 Intellectual property (IP)

In any outsourcing agreement there could be several IP issues involved, such as the licensing or assignment of copyrights, trademarks and patents etc. Issues concerning IP will largely depend on whether the IP is licensed by the service provider or the customer, or developed by the service provider.

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6.2.1 IP owned/licensed by the service provider

If the CMO or CRO owns or has the right to use IP that is required to provide the services, the customer should examine the licence agreement or seek a representation and warranty stating that there is a valid right to use such IP for the required purposes. If the service provider does not adhere to the terms and conditions of the licence, the licence could be terminated. This could have an adverse effect on the services being offered to the customer. Thus, the customer will normally impose an obligation on the service provider to do all that is necessary to maintain the validity of the licence.

If the service provider claims ownership of particular IP, the customer will require a representation and warranty that the IP does not violate the intellectual property of any third party. If the IP violates any third party's rights, the service provider will be under an obligation to use similar IP that is non-infringing or to obtain a licence from the IP's owner, without any cost to the customer. The customer will also seek an indemnification against any suit that may be brought against it, due to the infringing of IP.

The service provider may also own other types of IP, such as patented inventions that it uses to perform the services under the outsourcing agreement. In such a case, the service provider should be obliged to ensure that it continues to own the IP during the term of the agreement.

6.2.2 IP owned/licensed by the customer

The customer may provide the vendor with operations manuals, systems documentation and IP in order to perform the outsourced services. The service provider may have a licence to use such IP, or the customer may receive such a licence and provide a sub-licence to the service provider.

In addition, while providing services to the customer, the service provider will have access to confidential information, trade secrets and other IP of the customer. Such information will continue to

remain the IP of the customer. Sometimes a customer may need to license certain patented inventions that it uses for its business processes to the service provider. In such a case, the contract should regulate the manner in which the service provider uses the patented invention.

If the IP is owned or licensed by the customer, a limited licence is granted to the service provider to enable it to provide the services. The customer should ensure that the service provider does not use the IP for any other purpose or customer, or sub-license it to any third party. The service provider should seek an indemnification from the customer against any suit that may be brought against the service provider, due to the infringing of IP.

6.2.3 Developed IP

Intellectual property may be developed by the service provider while it is providing services to the customer. The agreement should clearly state the ownership of such IP. Such IP will normally vest with the customer and an obligation will be imposed on the service provider to assign such IP to the customer. The agreement will have to specify that the customer is not under any obligation to make any additional payments for the assignment of such IP. Alternatively, the parties can be co-owners of the IP and they can share the revenues received from the licensing of such IP to a third party. The agreements of the service provider with its employees, consultants and sub-contractors should also be examined to ensure that the IP to be created by them has been appropriately assigned to the service provider.

6.3 Other issues

6.3.1 Avoid vagueness

The agreement should include clear definitions of the terms used in the agreement. Each aspect should be detailed and terms and conditions should not be left to be decided in the future. For

example, parties often leave certain aspects to be 'mutually decided' in the future. In the event that the relationship between the parties sours, any such mutual agreement will be difficult to reach. Issues that are likely to have a long-term impact should not be left open.

6.3.2 Non-compete provisions

The customer will typically insist upon a non-compete clause. The parties will have to negotiate a fair and enforceable non-compete clause. The vendor may in return insist upon an exclusivity clause. It will also be important to expand the scope of non-compete provisions to employees who may be working on the same molecules or intermediates or APIs for other companies.

6.3.3 Non-solicitation

The customer may often seek to employ high-skilled employees of the vendor's, and therefore the vendor should include a non-solicitation clause.

6.3.4 Tax matters

The build-operate-transfer (BOT) transaction has to be structured in such a manner that even after the transfer of operations the tax benefits are retained and, for that purpose, relevant clauses have to be added in the agreement.

6.3.5 Transfer pricing and PE issues

The captive contracts and BOT agreements have to take into account transfer pricing and PE issues, and the relevant clauses must be inserted into the agreement.

6.3.6 Human resource (HR) issues

In the case of BOT agreements, where the Indian entity agrees to transition its R&D or manufacturing unit to the outsourcing partner at a later date, HR issues should be tackled carefully, because the vendor's employees are required to be transferred to the customer at a later date. For this reason, the vendor's employee contracts have to be carefully drafted.

6.3.7 Limitation of liability

The vendor should negotiate a limitation of liability provision in the contract, whereby the vendor's liability can be limited only to the extent of the fees being paid by the customer or to the extent that the loss or damage is on account of a default on the vendor's part.

6.3.8 Liquidated damages

The customer can also negotiate a liquidated damages clause whereby the vendor is liable to pay to the customer monies in the form of damages, in the event that there is a deficiency/delay in providing services and such deficiency/delay is attributable to a default on the vendor's part.

6.3.9 Technology and infrastructure

The customer should also ensure that the vendor has the latest technology and infrastructure, in order for the services to be rendered in the most efficient manner.

6.3.10 Prohibition or limitation on vendor to subcontract/assign the contract services

In order to ensure control over the manner in which the services are provided, restrictions could be implemented, prohibiting the vendor

from subcontracting or assigning its services to a third party without the customer's consent.

6.3.11 Insurance

The vendor will require the client to maintain certain specified insurance cover. Often the vendor will have obtained Employer's Liability Insurance, Worker's Compensation Insurance, Comprehensive General Liability Insurance etc., in which case the client should examine the policies and, if necessary, require the vendor to obtain additional cover for specified liabilities. Vendors are often reluctant to obtain client-specific insurance cover. Upon entering into the contract, the client is named in the policies as the beneficiary.

6.4 Term and termination

This is one of the most important clauses in the outsourcing agreement, as the business plans of both the parties can be adversely affected by an early termination of the agreement. The customer will be apprehensive about granting the service provider the right to terminate the agreement, as termination will necessitate a search for another service provider. Similarly, the service provider will have engaged employees and agents and invested in infrastructure based on the expected revenues from the customer. However, both parties will also like to have an exit option if the relationship turns out not to be favourable.

6.4.1 Automatic renewal

As discussed earlier, outsourcing agreements are usually for a long period of time and have high rates of renewal. The agreement usually specifies the term of the agreement and provides for automatic renewal, unless the parties expressly terminate the agreement.

6.4.2 Termination for default

The agreement should grant an aggrieved party the right to terminate the agreement if the other party commits a material default or there is a material breach of its representations and warranties. Such material default on the part of the service provider would include: continued failure to comply with service levels; a change of control of the service provider; and a violation of exclusivity obligations. Material default by the customer would be continued non-payment of service fees.

6.4.3 Termination for convenience

The parties may also have a right to terminate the agreement even if there is no default by the other party. Such termination will usually require the payment of an early termination fee and sufficient notice to the other party.

6.4.4 Transition

If the relationship between the parties comes to an end, either due to termination or due to expiry, the parties may provide for a transition phase during which the service provider will continue to provide services for a specified period of time. In this phase, the service provider may be required to train certain persons designated by the customer, to provide documentation of the processes, and to perform other acts that are required for a smooth transition. The customer will insist on having the right to purchase the assets and infrastructure that are being used to provide the services and will also have the right to employ the persons on the team that was providing such services.

6.4.5 Effect of termination

The agreement should also specify the effects of termination on various aspects such as payment of outstanding fees, escrow, IP and confidential information, and current work orders.

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6.5 Governing law and jurisdiction

Parties will typically prefer to have the agreement governed by the laws of, and be subject to, the courts in their respective home countries. As a compromise, they may agree to have the agreement governed by the laws of a foreign country that has no nexus with the parties or the agreement. Normally, the courts will give effect to the intention of the parties as expressed in the agreement entered into by them, except when there are strong reasons to justify disregard of the contractual agreement of the parties.[1] When choice of law is *bona fide*, legal and not against public policy, such choice is generally upheld by the Indian courts. Whether or not the law chosen has some connection with the transaction is one of the important issues considered by the courts while deciding the *bona fide* intention of the parties.

6.6 Alternate dispute resolution (ADR)

Parties resort to alternate dispute resolution (ADR) mechanisms such as arbitration rather than resorting to the traditional legal systems, due to the high cost and time required for resolving disputes. Arbitration is usually held in accordance with the Rules of the International Chamber of Commerce or the London Court of International Arbitration, for international commercial arbitration. More recently, parties subject themselves to arbitration in the Singapore International Arbitration Centre.

6.6.1 Enforcement of foreign awards and judgments

If there is a dispute between the parties that is subject to arbitration or litigation, the award or decree must be enforced against the losing party. Such enforcement can occur within or outside of India.

6.6.1.1 Enforcement of foreign awards in India

India is a signatory to the New York Convention on the Recognition and Enforcement of Foreign Arbitral Awards, 1968 (NYC). Thus, if a party receives a binding award with respect to a commercial dispute

from another country that is a signatory to the NYC and is recognised as a reciprocating country by India, the award would be enforceable in India. However, the courts in India may refuse to enforce a foreign award under certain conditions such as incapacity of the parties, noncompliance with the agreed arbitration procedure, non-adherence to the principles of natural justice, among others. Enforcement may also be refused if the subject matter of the award cannot be settled upon by arbitration under the laws of India or if the award's enforcement would be contrary to the public policy of India.

6.6.1.2 Enforcement of foreign judgments in India

A foreign judgment may be enforced by filing a suit upon judgment under Section 13 of the Code of Civil Procedure, 1908 (CPC); or by proceedings executed under Section 44A of the CPC, provided that the judgment is rendered by a court in a 'reciprocating territory'. A 'reciprocating territory' is one that is deemed by the government of India to be a 'reciprocating territory' under Section 44A of the CPC. For instance, the United Kingdom has been deemed by the government of India to be a 'reciprocating territory', while the United States has not been considered as such.

However, a foreign judgment cannot be enforced in India under certain circumstances, such as when the judgment has not been pronounced by a court of competent jurisdiction, the decision is not on the merits of the case, the principles of natural justice have been violated or the judgment violates public policy.

6.6.1.3 Enforcement of awards and judgments outside India

To determine the modalities for the enforcement of an Indian award or judgment in a foreign jurisdiction, it is necessary to examine the procedural laws of the foreign country in question.

Note

1. *Modi Entertainment Network and Anr*. vs. *Respondent: W.S.G. Cricket PTE. Ltd*. decided by Supreme Court of India on 21 January 2003 (AIR 2003 SC 1177).

7

Negotiating a contract

Abstract: The foundation of any outsourcing relationship is set out in the outsourcing contract. It should be negotiated carefully – so as to ensure the long-term success of the arrangement. It is advisable to set up a negotiation team to deal with all aspects of the contract. The team should document all discussions pertaining to the transaction. A balanced approach will lead to a better understanding of the other party's interests, ultimately creating a harmonious long-term relationship. It is important to segregate issues into the areas of 'Key Issues', 'Operational Issues', and 'Internal Issues'.

Keywords: negotiation team, negotiation scale, negotiation process, non-binding, issues management

The foundation of any outsourcing relationship is laid out in an outsourcing contract. Therefore, it should be negotiated carefully – keeping in mind business, operational and legal risks – to ensure the long-term success of the outsourcing arrangement.

7.1 Separate negotiation team

The outsourcing vendor and the customer should set up a negotiation team consisting of representatives who deal with all aspects of the contract, such as operations, management, finance and legal issues. The negotiation team should document all discussions pertaining to the transaction, to ensure that no stone is left unturned and that the

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team is on common ground with respect to the general approach towards the negotiation.

7.2 Approach

The approach towards negotiations should always be a balanced one. On a negotiation scale of '0 to 100' (where '0' represents an adverse term in the agreement and '100' represents a favourable term), the goal should be to ensure that the entire negotiation process falls in the '35 to 65' band (Figure 7.1). A balanced approach will lead to a better understanding of the other party's interests and will result in successfully closing the deal, ultimately creating a harmonious long-term relationship.

7.3 Negotiation process

Figure 7.2 represents a typical negotiation process. It is prudent to begin any negotiation with the term sheet, which is the condensed version of the agreement. It records the initial understanding of the parties on certain basic issues. This approach helps parties to compartmentalise issues and concepts, to sort out macro-level terms (including business terms) and to assess their capabilities and expectations. The term sheet could be binding or non-binding, should have at least binding confidentiality and no-shop clauses, and a termination clause and the effects of termination. Detailed agreements should be signed within a specific period of time. Pending negotiation of the final contract, if the service provider is likely to commence work, it will be prudent to at least have a term sheet in place setting forth the commercial understanding of the parties.

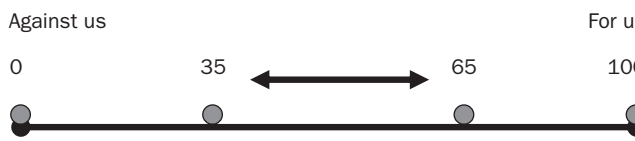

Figure 7.1 Negotiation scale

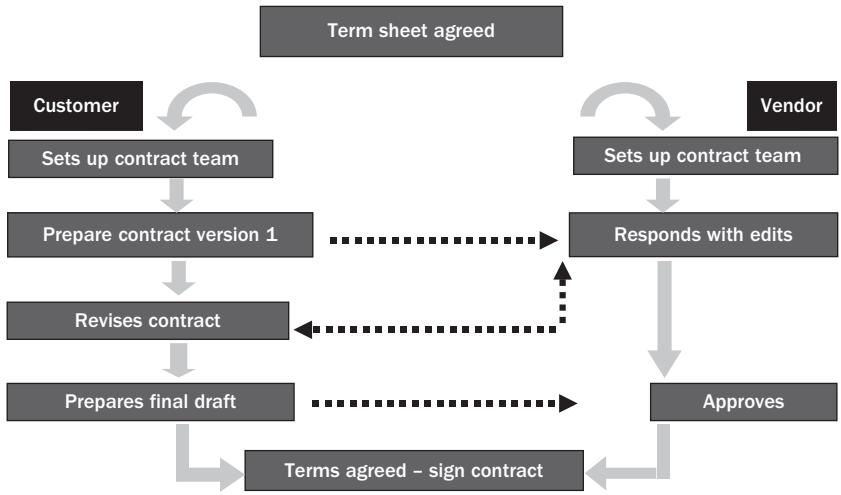

Figure 7.2 Contract negotiation process

7.4 Issues management

The team should segregate the issues into 'Key issues', 'Operational issues' and 'Internal issues', so that each type of issue is dealt with at the appropriate levels in the organisation (Figure 7.3).

Further, each issue should be categorised under:

- non-negotiables
- give-aways
- don't-cares.

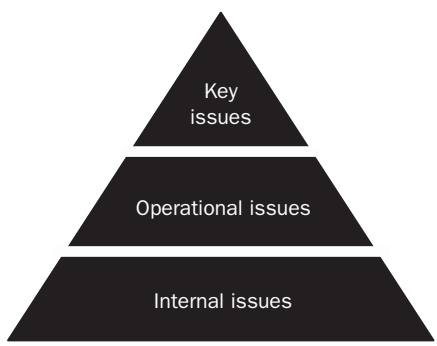

Figure 7.3 Separation of issues

This approach helps each party to assess its bargaining power and also assists the party in setting up an effective negotiation strategy. This categorisation should be done on the basis of impact vs probability theory, as illustrated in Figure 7.4.

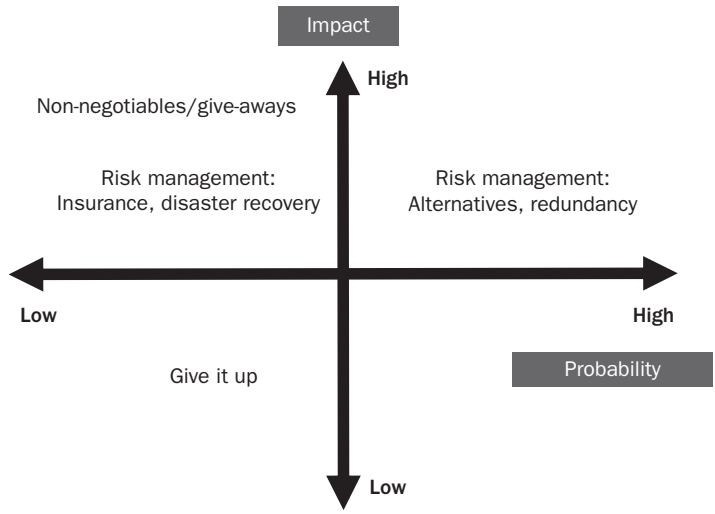

Figure 7.4 Impact vs probability theory

8

Outlook and conclusion

The global CRAMS market is expected to grow further, to approximately US$85 billion by 2012. Many companies will lose patent protection for their block-busters in the next few years. This has compelled them to look to alternatives, such as entering into the generic field and cost efficiencies. As a result of this, the outsourcing of activities like the manufacturing of intermediates and APIs to low-cost destinations such as India is gaining momentum amongst pharmaceutical multinationals as they focus on their core R&D and brand-building business.

The Indian CRAMS market is estimated to reach US$7.6 billion by 2012. With a high and increasing number of USFDA approved plants in India, cost advantage and skilled manpower, contract manufacturing is likely to dominate the CRAMS space. Added to this, the number of clinical trials being conducted in India has recently been declining, for a variety of reasons, regulatory delays being one of the important ones. Indian companies have been acquiring better technologies and developing technical expertise in certain niche segments.

Many companies in India are likely to become sole providers of services such as drug development, research, clinical trials and manufacturing outsourcing services to pharmaceuticals companies in the long term.

Overall, the outlook for Indian CRAMS appears healthy, supported by contract manufacturing outsourcing for APIs and an increasing presence in high-end contract research business.

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Appendix 1: Some important players in contract manufacturing in India

The following brief descriptions of Indian CMOs have been compiled from information that is available in the public domain.

Divi's Lab

- One of the largest CRAMS players – custom synthesis of active ingredients for innovator companies, other speciality chemicals like peptides and nutraceuticals. CRAMS contributes 50% of the turnover, while the remainder comes from manufacture of generic APIs.
- USFDA approved facility with 38 DMF filings and 10 Certificates of Suitability with European directorate.
- Relatively high product concentration with top product accounting for 18% of sales and top 5 products accounting for 55% of sales.
- Established relationship with innovator companies; top 5 companies accounting for 49% of revenues.
- Exports constitute 91% of revenues, thereby exposing it to foreign exchange fluctuations.

Dishman Pharma

- Research-driven company with expertise in chemical synthesis, manufacturing of APIs, API intermediates, quaternary compounds

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(Quats) and fine chemicals. Approximately 70% of turnover comes from CRAMS.
- Acquisition of Carbogen-Amcis (2006) has enabled the company to be present across the value chain of CRAMS and to strengthen its position.
- Entrenched relationship with pharmaceuticals multinationals, with Solvay as the top customer contributing more than 15% of revenues.
- USFDA approved manufacturing facilities.
- Exports constitute 90% of revenues; the majority to Europe.

Jubilant Life Sciences Limited

- Largest Indian CRAMS player with a presence across the value chain from drug discovery research service to development and custom manufacturing (APIs, pyridines, sterile and non-sterile products and radiology).
- Acquired Draxis Health Inc. in 2008, a Canada-based contract manufacturing and radio pharmaceutical company, for US$255 million; in June 2007 acquired Hollister Stier, having contract manufacturing of sterile injectables. Acquisition to allow higher presence in regulated markets and on-shore presence.
- Divested low margin Agri & Performance Polymers from FY 2011 business into a separate company to enhance business focus on life sciences.
- USFDA approved manufacturing locations in India as well as North America, with DMFs filed across various regulated markets.

Piramal Healthcare

- Presence in CRAMS business with assets in India and abroad. Capacity scale-up in the past with Aveica (UK) acquisition and Pfizer's Morpeth facility (UK).

- Divested domestic formulations business to Abbott for total consideration of US$3.8 billion; intend to scale up contract manufacturing business through organic and inorganic route.
- Focused CRAMS player with presence across the value chain from drug discovery research service to development and custom manufacturing.
- Recently acquired Ahmadabad-based discovery services business which offers synthetic chemistry, medicinal chemistry and computational chemistry; acquisition to complement CRAMS business.

Biocon Limited

- Integrated biotechnology company with a presence across the value chain – R&D, manufacturing and building strengths in marketing.
- CRAMs presence through its subsidiaries (Syngene International Limited, Clinigene International Limited), offering contract research and clinical trials services, besides Biocon offering contract manufacturing services for select innovator products (deal with Optimer).
- Research services business focus on discovery research in the areas of molecular biology, custom synthesis and chemistry FTEs in pre-clinical phase, besides offering clinical trial services; research services has partnerships with large global pharmaceutical companies, with the company having set up a dedicated facility for Bristol-Myers Squibb.

Appendix 2: Contract research organisations in India

Domestic

1.	Accutest Research Laboratories	www.accutestindia.com
2.	Ace Biomed Pvt Ltd	www.acebiomed.com
3.	Actimus Biosciences	www.actimusbio.com
4.	Apothecaries Ltd.	www.apothecaries.net
5.	Asian Clinical Trials Pvt Ltd.	www.act-india.com
6.	Aurigene Discovery Technologies	www.aurigene.com
7.	Avra Laboratories	www.avralab.com
8.	Bioserve Biotechnologies (I) Pvt Ltd	www.bioserve.com
9.	Chembiotek Research International	www.chembiotek.com
10.	C B Patel Research Center	www.cbprc.svkm.ac.in
11.	Clinigene International (BioCon)	www.biocon.com
12.	Clininvent Research	www.clininvent.com
13.	ClinTec International India	www.clintec.com
14.	Clintrac International Pvt. Ltd	www.clintracintl.org
15.	D & O CRO	www.dnogroup.com
16.	Dr Reddy's Laboratories Limited	www.drreddys.com
17.	Eli Lilly and Company (India) Pvt. Ltd	www.lillyindia.co.in
18.	GVK Biosciences Pvt Ltd	www.gvkbio.com
19.	iGate Clinical Research International	www.igatecorp.com/icri/
20.	INTOX Pvt Ltd	www.intoxlab.com
21.	Jubilant Clinsys	www.jubl.com
22.	Kendle India	www.kendle.com

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23.	Lambda Therapeutic Research Ltd	www.lambda-cro.com
24.	Lotus Labs	www.lotuslabs.com
25.	Manipal Acunova	www.acunovalife.com
26.	Mayfair Clinical Education and Research Center	www.mayfaircro.com
27.	Metropolis Clinical Laboratories	www.metropolisindia.com
28.	Micro Therapeutic Research Labs Pvt. Ltd.	www.microtheraps.com
29.	Neeman Medical International (Asia)	www.neeman-medical.com
30.	Omnicare Clinical Research India	www.omnicarecr.com
31.	PPD Pharmaceutical Development India	www.ppdi.com
32.	QUINTILES TECHNOLOGIES (INDIA) PVT. LTD.	www.quintiles.com
33.	Ranbaxy Laboratories Limited	www.ranbaxy.com
34.	REAMETRIX INDIA	www.reametrix.com
35.	Reliance Clinical Research Services	www.relclin.com
36.	ROCHE SCIENTIFIC COMPANY (I) PVT. LTD.	www.roche.com
37.	Sanofi-Aventis (Aventis Pharma Ltd)	www.aventispharmaindia.com
38.	Sipra Labs Pvt Ltd	www.sipralabs.com
39.	SIRO Clinpharm Pvt. Ltd.	www.siroclinpharm.com
40.	Sitec Labs	www.siteclabs.com
41.	SRL Ranbaxy Ltd.	www.srl.in
42.	Sterling Synergy Systems	www.sterling-synergy.com
43.	Suven Life Sciences Limited	www.suven.com
44.	Synchron Research Services	www.synchronresearch.com
45.	Torrent Pharmaceuticals Limited	www.torrentpharma.com
46.	Triesta Sciences	www.triesta.com
47.	Veeda Clinical Research	www.veedacr.com
48.	Vimta Labs	www.vimta.com
49.	Wellquest	www.nicholaspiramal.com
50.	Dr Lal PathLabs Pvt Ltd	www.lalpathlabs.com

Source: pharmabiz.com

Apart from Indian CROs, many international CROs have a presence in India.

Appendix 3: Schedule M

Relevant sections of Schedule M are reproduced below.

[*See* Rules 71, 74, 76 and 78]
GOOD MANUFACTURING PRACTICES AND REQUIREMENTS OF PREMISES, PLANT AND EQUIPMENT FOR PHARMACEUTICAL PRODUCTS

Note: – To achieve the objectives listed below, each licensee shall evolve appropriate methodology, systems and procedures which shall be documented and maintained for inspection and reference; and the manufacturing premises shall be used exclusively for production of drugs and no other manufacturing activity shall be undertaken therein.

PART 1
GOOD MANUFACTURING PRACTICES FOR PREMISES AND MATERIALS

1. GENERAL REQUIREMENTS

1.1. *Location and surroundings*.- The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environmental including open sewage, drain, public lavatory or any factory which product disagreeable or obnoxious odour, fumes, excessive soot, dust, smoke, chemical or biological emissions.

1.2. *Building and premises*.- The building(s) used for the factory shall be designed, constructed, adapted and maintained to suit the

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manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948).

The premises used for manufacturing, processing, warehousing, packaging labeling and testing purposes shall be –

• Omitted by G.O.I. Notification No. G.S.R. 462(E) dt.22.06.1982.
•• Ins.by G.O.I. Notification No G.S.R. 864(E) dt.11.12.2001.- applicable to manufacturers licensed to manufacture drugs, for the period upto 31.12.2003.

(i) compatible with other drug manufacturing operations that may be carried out in the same or adjacent area/section;

(ii) adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to:

  (a) avoid the risk of mix-up between different categories of drugs or with raw materials, intermediates and in-process material;
  (b) avoid the possibilities of contamination and cross-contamination by providing suitable mechanism;

(iii) designed / constructed / maintained to prevent entry of insects, pests, birds, vermins, and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection;

(iv) air-conditioned, where prescribed for the operations and dosage froms under production. The production and dispensing areas shall be well lighted, effectively ventilated, with air control facilities and may have proper Air Handling Units (wherever applicable) to maintain conditions including temperature and, wherever necessary, humidity, as defined for the relevant product. These conditions shall be appropriate to the category of drugs and nature of the operation. These shall also be suitable to the comforts of the personnel working with protective clothing, products handled, operations undertaken within them in relation to the external environment. These areas shall be regularly monitored for compliance with required specifications;

(v) Provided with drainage system, as specified for the various categories of products, which shall be of adequate size and so designed as to prevent back flow and/or prevent insets and rodents entering the premises. Open channels shall be avoided in manufacturing areas and, where provided, these shall be shallow to facilitate cleaning and disinfection;

(vi) The walls and floors of the areas where manufacture of drugs is carried out shall be free from cracks and open joints to avoid accumulation of dust. These shall be smooth, washable, covered and shall permit easy and effective cleaning and dis-infection. The interior surfaces shall not shed particles. A periodical record of cleaning and painting of the premises shall be maintained.

1.3 *Water System* – There shall be validated system for treatment of water drawn from own or any other source to render it potable in accordance with standards specified by the Bureau of Indian Standards or Local Municipality, as the case may be, so as to produce Purified Water conforming to Pharmacopoeial specification. Purified Water so produced shall only be used for all operations except washing and cleaning operations where potable water may be used. Water shall be stored in tanks, which do not adversely affect quality of water and ensure freedom from microbiological growth. The tank shall be cleaned periodically and records maintained by the licensee in this behalf.

1.4. *Disposal of waste* -

(i) The disposal of sewage and effluents (solid, liquid and gas) from the manufactory shall be in conformity with the requirements of Environment Pollution Control Board.

(ii) All bio-medical waste shall be destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 1996.

(iii) Additional precautions shall be taken for the storage and disposal of rejected drugs. Records shall be maintained for all disposal of waste.

(iv) Provisions shall be made for the proper and safe storage of waste materials awaiting disposal. Hazardous, toxic substances and flammable materials shall be stored in suitably designed and

segregated, enclosed areas in conformity with Central and State Legislations.

2. *Warehousing Area.* -

2.1 Adequate areas shall be designed to allow sufficient and orderly warehousing of various categories of materials and products like starting and packaging materials, intermediates, bulk and finished products, products in quarantine, released, rejected, returned or recalled, machine and equipment spare parts and change items.

2.2 Warehousing areas shall be designed and adapted to ensure good storage conditions. They shall be clean, dry and maintained with acceptable temperature limits, where special storage conditions are required (e.g. temperature, humidity), these shall be provided, monitored and recorded. Storage areas shall have appropriate house-keeping and rodent, pests and vermin control procedures and records maintained. Proper racks, bins and platforms shall be provided for the storage of materials.

2.3 Receiving and dispatch bays shall protect materials and products from adverse weather conditions.

2.4. Where quarantine status is ensured by warehousing in separate earmarked areas in the same warehouse or store, these areas shall be clearly demarcated. Any system replacing the physical quarantine, shall give equivalent assurance of segregation. Access to these areas shall be restricted to authorized persons.

2.5. There shall be a separate sampling area in the warehousing area for active raw materials and excipients. If sampling is performed in any other area, it shall be conducted in such a way as to prevent contamination, cross-contamination and mix-up.

2.6. Segregation shall be provided for the storage of rejected, recalled or returned materials or products. Such areas, materials or products shall be suitably marked and secured. Access to these areas and materials shall be restricted.

2.7. Highly hazardous, poisonous and explosive materials such as narcotics, psychotropic drugs and substances presenting potential risks of abuse, fire or explosion shall be stored in safe and secure

areas. Adequate fire protection measures shall be provided in conformity with the rules of the concerned civic authority.

2.8. Printed packaging materials shall be stored in safe, separate and secure areas.

2.9. Separate dispensing areas for β (Beta) lactum, Sex Hormones and Cytotoxic substances or any such special categories of product shall be provided with proper supply of filtered air and suitable measures for dust control to avoid contamination. Such areas shall be under differential pressure.

2.10. Sampling and dispensing of sterile materials shall be conducted under aseptic conditions conforming to Grade A, which can also be performed in a dedicated area within the manufacturing facility.

2.11. Regular checks shall be made to ensure adequate steps are taken against spillage, breakage and leakage of containers.

2.12. Rodent treatments (Pest control) should be done regularly and at least once in a year and record maintained.

3. *Production area* -

3.1. The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations.

3.2. In order to avoid the risk of corss-contamination, separate dedicated and self-contained facilities shall be made available for the production of sensitive pharmaceutical products like penicillin or biological preparations with live microorganisms. Separate dedicated facilities shall be provided for the manufacture of contamination causing and potent products such as Beta-Lactum, sex hormones and cytotoxic substances.

3.3. Working and in-process space shall be adequate to permit orderly and logical positioning of equipment and materials and movement of personnel to avoid cross-contamination and to minimize risk of omission or wrong application of any manufacturing and control measures.

3.4. Pipe-work, electrical fittings, ventilation openings and similar services lines shall be designed, fixed and constructed to avoid

creation of recesses. Services lines shall preferably be identified by colours and the nature of the supply and direction of the flow shall be marked/indicated.

4. *Ancillary Areas* -

4.1 Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas.

4.2 Facilities for changing, storing clothes and for washing and toilet purposes shall be easily accessible and adequate for the number of users. Toilets, separate for males and females, shall not be directly connected with production or storage areas. There shall be written instructions for cleaning and disinfection of such areas.

4.3 Maintenance workshops shall be separate and away from production areas. Whenever spares, changed parts and tools are stored in the production area, these shall be kept in dedicated rooms or lockers. Tools and spare parts for use in sterile areas shall be disinfected before these are carried inside the production areas.

4.4. Areas housing animals shall be isolated from other areas. The other requirements regarding animal houses shall be those as prescribed in Rule 150-C(3) of the Drugs and Cosmetics Rules, 1945 which shall be adopted for production purposes.

5. Quality Control Area-

5.1. Quality Control Laboratories shall be independent of the production areas. Separate areas shall be provided each for physico-chemical, biological, microbiological or radio-isotope analysis. Separate instrument room with adequate area shall be provided for sensitive and sophisticated instruments employed for analysis.

5.2 Quality Control Laboratories shall be designed appropriately for the operations to be carried out in them. Adequate space shall be provided to avoid mix-ups and cross-contamination. Sufficient and suitable storage space shall be provided for test samples, retained samples, reference standards, reagents and records.

5.3. The design of the laboratory shall take into account the suitability of construction materials and ventilation. Separate air

handling units and other requirements shall be provided for biological, microbiological and radioisotopes testing areas. The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purpose.

5.4. Quality Control Laboratory shall be divided into separate sections i.e. for chemical, microbiological and wherever required, biological testing. These shall have adequate area for basis installation and for ancillary purposes. The microbiology section shall have arrangements such as airlocks and laminar air flow work station, wherever considered necessary.

6. *Personnel-*

6.1. The manufacture shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant dosage and / or active pharmaceutical products.

6.2 The head of the Quality Control Laboratory shall be independent of the manufacturing unit. The testing shall be conducted under the direct supervision of competent technical staff who shall be whole time employees of the licensee.

6.3. Personnel for Quality Assurance and Quality Control operations shall be suitably qualified and experienced.

6.4. Written duties of technical and Quality Control personnel shall be laid and following strictly.

6.5. Number of personnel employed shall be adequate and in direct proportion to the workload.

6.6. The licensee shall ensure in accordance with a written instruction that all personnel in production area or into Quality Control Laboratories shall receive training appropriate to the duties and responsibility assigned to them. They shall be provided with regular in-service training.

7. *Health, clothing and sanitation of workers -*

7.1 The personnel handling Beta-lactum antibiotics shall be tested for Penicillin sensitivity before employment and those handling sex hormones, cytotoxic substances and other potent drugs shall be

periodically examined for adverse effects. These personnel should be moved out of these sections (except in dedicated facilities), by rotation, as a health safeguard.

7.2 Prior to employment, all personnel, shall undergo medical examination including eye examination, and shall be free from Tuberculosis, skin and other communicable or contagious diseases. Thereafter, they should be medically examined periodically, at least once a year. Records shall be maintained thereof. The licensee shall provide the services of a qualified physician for assessing the health status of personnel involved in different activities.

7.3 All persons prior to and during employment shall be trained in practices which ensure personnel hygiene. A high level of personal hygiene shall be observed by all those engaged in the manufacturing processes. Instructions to this effect shall be displayed in change rooms and other strategic locations.

7.4 No person showing, at any time, apparent illness or open lesions which may adversely affect the quality of products, shall be allowed to handle starting materials, packing materials, in-process materials, and drug products until his condition is no longer judged to be a risk.

7.5 All employees shall be instructed to report about their illness or abnormal health condition to their immediate supervisor so that appropriate action can be taken.

7.6 Direct contact shall be avoided between the unprotected hands of personnel and raw materials, intermediate or finished, unpacked products.

7.7 All personnel shall wear clean body coverings appropriate to their duties. Before entry into the manufacturing area, there shall be change rooms separate for each sex with adequate facilities for personal cleanliness such as wash basin with running water, clean towels, hand dryers, soaps, disinfectants, etc. The change room shall be provided with cabinets for the storage of personal belongings of the personnel.

7.8 Smoking, eating, drinking, chewing or keeping plants, food, drink and personal medicines shall not be permitted in production,

laboratory, storage and other areas where they might adversely influence the product quality.

8. *Manufacturing Operations and Controls* -

8.1 All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing Authority. Each critical step in the process relating to the selection, weighing and measuring of raw material addition during various stages shall be performed by trained personnel under the direct personal supervision of approved technical staff.

The contents of all vessels and containers used in manufacture and storage during the various manufacturing stages shall be conspicuously labeled with the name of the product, batch number, batch size and stage of manufacture. Each label should be initialled and dated by the auhorised technical staff.

Products not prepared under aseptic conditions are required to be free from pathogens like *Salmonella, Escherichia coli, Pyocyanea, etc.*

8.2. *Precautions against mix-up and cross-contamination-*

8.2.1. The licensee shall prevent mix-up and cross-contamination of drug material and drug product (from environmental dust) by proper air-handling system, pressure differential, segregation, status labeling and cleaning. Proper records and Standard Operating Procedures thereof shall be maintained.

8.2.2 The licensee shall ensure processing of sensitive drugs like Beta-Lactum antibiotics, sex hormones and cytotoxic substances in segregated areas or isolated production areas within the building with independent air-handling unit and proper pressure differential. The effective segregation of these areas shall be demonstrated with adequate records of maintenance and services.

8.2.3 To prevent mix-ups during production stages, materials under process shall be conspicuously labeled to demonstrate their status. All equipment used for production shall be labeled with their current status.

8.2.4 Packaging lines shall be independent and adequately segregated. It shall be ensured that all left-overs of the previous

packaging operations, including labels, cartons and caps are cleared before the closing hour.

8.2.5 Before packaging operations are begun, steps shall be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials and spillages. The line clearance shall be performed according to an approximate check-list and recorded.

8.2.6 The correct details of any printing (for example of batch numbers or expiry dates) done separately or in the course of the packaging shall be rechecked at regular intervals. All printing and overprinting shall be authorized in writing.

8.2.7 The manufacturing environment shall be maintained at the required levels of temperature, humidity and cleanliness.

8.2.8 Authorised persons shall ensure change-over into specific uniforms before undertaking any manufacturing operations including packaging.

8.2.9 There shall be segregated enclosed areas, secured for recalled or rejected material and for such materials which are to be reprocessed or recovered.

9. *Sanitation in the Manufacturing Premises*. -

9.1 The manufacturing premises shall be cleaned and maintained in an orderly manner, so that it is free from accumulated waste, dust, debris and other similar material. A validated cleaning procedure shall be maintained.

9.2 The manufacturing areas shall not be used for storage of materials, except for the material being processed. It shall not be used as a general throughfare.

9.3 A routine sanitation program shall be drawn up and observed, which shall be properly recorded and which shall indicate-

(a) specific areas to be cleaned and cleaning intervals;

(b) cleaning procedure to be followed, including equipment and materials to be used for cleaning; and

(c) personnel assigned to and responsible for the cleaning operation.

9.4 The adequacy of the working and in-process storage space shall permit the orderly and logical positioning of equipment and materials so as to minimize the risk of mix-up between different pharmaceutical products or their components to avoid cross contamination, and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

9.5 Production areas shall be well lit, particularly where visual on-line controls are carried out.

10. *Raw Materials.* -

10.1 The licensee shall keep an inventory of all raw materials to be used at any stage of manufacture of drugs and maintain records as per Schedule U.

10.2 All incoming materials shall be quarantined immediately after receipt or processing. All materials shall be stored under appropriate conditions and in an orderly fashion to permit batch segregation and stock rotation by a 'first in/first expiry' – 'first-out' principle. All incoming materials shall be checked to ensure that the consignment corresponds to the order placed.

10.3 All incoming materials shall be purchased from approved sources under valid purchase vouchers. Wherever possible, raw materials should be purchased directly from the producers.

10.4 Authorized staff appointed by the licensee in this behalf, which may include personnel from the Quality Control Department, shall examine each consignment on receipt and shall check each container for integrity of package and seal. Damaged containers shall be identified, recorded and segregated.

10.5 If a single delivery of material is made up of different batches, each batch shall be considered as a separate batch for sampling, testing and release.

10.6 Raw materials in the storage area shall be appropriately labeled. Labels shall be clearly marked with the following information:

(a) designated name of the product and the internal code reference, where applicable, and analytical reference number;

(b) manufacturer's name, address and batch number;

(c) the status of the contents (e.g. quarantine, under test, released, approved, rejected); and

(d) the manufacturing date, expiry date and re-test date.

10.7 There shall be adequate separate areas for materials "under test", "approved" and "rejected" with arrangements and equipment to allow dry, clean and orderly placement of stored materials and products, wherever necessary, under controlled temperature and humidity.

10.8 Containers from which samples have been drawn shall be identified.

10.9 Only raw materials which have been released by the Quality Control Department and which are within their shelf-life shall be used. It shall be ensured that shelf life of formulation product shall not exceed with that of active raw materials used.

10.10 It shall be ensured that all the containers of raw materials are placed on the raised platforms/racks and not placed directly on the floor.

11. *Equipment* -

11.1 Equipment shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of the equipment shall aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general any adverse effect on the quality of products. Each equipment shall be provided with a logbook, wherever necessary.

11.2 Balances and other measuring equipment of an appropriate range, accuracy and precision shall be available in the raw material stores, production and in process control operations and these shall

be calibrated and checked on a scheduled basis in accordance with Standard Operating Procedures and records maintained.

11.3 The parts of the production equipment that come into contact with the product shall not be reactive, additive or adsorptive to an extent that would affect the quality of the product.

11.4 To avoid accidental contamination, wherever possible, non-toxic/edible grade lubricants shall be used and the equipment shall be maintained in a way that lubricants do not contaminate the products being produced.

11.5 Defective equipment shall be removed from production and Quality Control areas or appropriately labeled.

12. *Documentation and Records* – Documentation is an essential part of the Quality assurance system and, as such, shall be related to all aspects Good Manufacturing Practices (GMP). Its aim is to define the specifications for all materials, method of manufacture and control, to ensure that all personnel concerned with manufacture know the information necessary to decide whether or not to release a bath of drug for sale and to provide an audit trail that shall permit investigation of the history of any suspected defective batch.

12.1 Documents designed, prepared, reviewed and controlled, wherever applicable, shall comply with these rules.

12.2 Documents shall be approved, signed and dated by appropriate and authorized persons.

12.3 Documents shall specify the title, nature and purpose. They shall be laid out in an orderly fashion and be easy to check. Reproduced documents shall be clear and legible. Documents shall be regularly reviewed and kept up to date. Any alteration made in the entry of a document shall be signed and dated.

12.4 The records shall be made or completed at the time of each operation in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated Standard Operating Procedures (SOP) shall be retained for at least one year after the expiry date of the finished product.

12.5 Data may be recorded by electronic data processing systems or other reliable means, but Master Formulae and detailed operating procedures relating to the system in use shall also be available in a hard copy to facilitate checking of the accuracy of the records. Wherever documentation is handled by electronic data processing methods, authorized persons shall enter modify data in the computer. There shall be record of changed and deletions. Access shall be restricted by 'passwords' or other means and the result of entry of critical data shall be independently checked. Batch records electronically stored shall be protected by a suitable back-up. During the period of retention, all relevant data shall be readily available.

13. *Labels and other Printed Materials.* – Labels are absolutely necessary for identification of the drugs and their use. The Printing shall be done in bright colours and in a legible manner. The label shall carry all the prescribed details about the product.

13.1 All containers and equipment shall bear appropriate labels. Different colour coded tablets shall be used to indicate the status of a product (for example under test, approved, passed, rejected).

13.2 To avoid chance mix-up of printed packaging materials, product leaflets, relating to different products, shall be stored separately.

13.3 Prior to release, all labels for containers, cartons and boxes and all circulars, inserts and leaflets shall be examined by the Quality Control Department of the licensee.

13.4 Prior to packaging and labeling of a given batch of a drug, it shall be ensured by the licensee that samples are drawn from the bulk and duly tested, approved and released by the quality control personnel.

13.5 Records of receipt of all labeling and packaging materials shall be maintained for each shipment received indicating receipt, control reference numbers and whether accepted or rejected. Unused coded and damaged labels and packaging materials shall be destroyed and recorded.

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13.6 The label or accompanying document of reference standards and reference culture shall indicate concentration, lot number, potency, date on which containers was first opened and storage conditions, where appropriate.

14. *Quality Assurance* – This is a wide-ranging concept concerning all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that products are of the quality required for their intended use.

14.1 The system of quality assurance appropriate to the manufacture of pharmaceutical products shall ensure that:-

(a) the pharmaceutical products are designed and developed in a way that takes account of the requirement of Good Manufacturing Practices (herein referred as GMP) and other associated codes such as those of Good Laboratory Practices (hereinafter referred as GLP) and Good Clinical Practices (herein after referred as GCP);

(b) adequate arrangements are made for manufacture, supply and use of the correct starting and packaging materials.

(c) adequate controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out.

(d) the finished product is correctly processed and checked in accordance with established procedures;

(e) the pharmaceutical products are not released for sale or supplied before authorized persons have certified that each production batch as been produced and controlled in accordance with the requirements of the label claim and any other provisions relevant to production, control and release of pharmaceutical products.

15. *Self Inspection and Quality audit* – It may be useful to constitute a self-inspection team supplemented with a quality audit procedure for assessment of all or part of a system with the specific purpose of improving it.

15.1 To evaluate the manufacturer's compliance with GMP in all aspects of production and quality control, concept of self-inspection shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who can audit objectively the implementation of methodology and procedures evolved. The procedure for self-inspection shall be documented indicating self-inspection results; evaluation, conclusions and recommended corrective actions with effective follow up program. The recommendations for corrective action shall be adopted.

15.2 The program shall be designed to detect shortcomings in the implementation of Good Manufacturing Practice and to recommend the necessary corrective actions. Self-inspections shall be performed routinely and on specific occasions, like when product recalls or repeated rejections occur or when an inspection by the licensing authorities is announced. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of Good Manufacturing Practice objectively; all recommendations for corrective action shall be implemented.

15.3 Written instructions for self-inspection shall be drawn up which shall include the following:-

(a) Personnel
(b) Premises including personnel facilities.
(c) Maintenance of buildings and equipment
(d) Storage of starting materials and finished products
(e) Equipment
(f) Production and in-process controls
(g) Quality control
(h) Documentation
(i) Sanitation and hygiene
(j) Validation and revalidation programmes
(k) Calibration of instruments or measurement systems.
(l) Recall procedures
(m) Complaints management
(n) Labels control
(o) Results of previous self-inspections and any corrective steps taken

16. *Quality Control System* – Quality control shall be concerned with sampling, specifications, testing, documentation, release procedures which ensure that the necessary and relevant tests are actually carried and that the materials are not released for use, nor products released for sale or supply until their quality has been judged to be satisfactory. It is not confined to laboratory operations but shall be involved in all decisions concerning the quality of the product. It shall be ensured that all quality control arrangements are effectively and reliably carried out the department as a whole shall have other duties such as to establish evaluate, validate and implement all Quality Control Procedures and methods.

16.1 Every manufacturing establishment shall establish its own quality control laboratory manner by qualified and experience staff.

16.2 The area of the quality control laboratory may be divided into Chemical, Instrumentation, Microbiological and Biological testing.

16.3 Adequate area having the required storage conditions shall be provided for keeping reference samples. The quality control department shall evaluate, maintain and store reference samples.

16.4 Standard operating procedures shall be available for sampling, inspecting and testing of raw materials, intermediate bulk finished products and packing materials and, wherever necessary, for monitoring environmental conditions.

16.5 There shall be authorized and dated specifications for all materials, products, reagents and solvents including test of identity, content, purity and quality. These shall include specifications for water, solvents and reagents used in analysis.

16.6 No batch of the product shall be released for sale or supply until it has been certified by the authorized person(s) that it is in accordance with the requirements of the standards laid down.

16.7 Reference/retained samples from each batch of the products manufactured shall be maintained in quantity which is at least twice

the quantity of the drug required to conduct all the tests, except sterility and pyrogen/Bacterial Endotoxin Test performed on the active material and the product manufactured. The retained product shall be kept in its final pack or simulated pack for a period of three months after the date of expiry.

16.8 Assessment of records pertaining to finished products shall include all relevant factors, including the production conditions, the results of in process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack. Assessment records should be signed by the in-charge of production and countersigned by the authorised quality control personnel before a product is released for sale or distribution.

16.9 Quality control personnel shall have access to production areas for sampling and investigation, as appropriate.

16.10 The quality control department shall conduct stability studies of the products to ensure and assign their shell life at the prescribed conditions of storage. All records of such studies shall be maintained.

16.11 The in-charge of Quality Assurance shall investigate all product complaints and records thereof shall be maintained.

16.12 All instruments shall be calibrated and testing procedures validated before these are adopted for routine testing. Periodical calibration of instrument and validation of procedures shall be carried out.

16.13 Each specification for raw materials, intermediates, final products, and packing materials shall be approved and maintained by the Quality Control Department. Periodic revisions of the specifications shall be carried out wherever changes are necessary.

16.14 Pharmacopoeiae, reference standards, working standards, references, spectra, other reference materials and technical books, as required, shall be available in the Quality Control Laboratory of the licensee.

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17. *Specification*

17.1 *For raw materials and packaging materials.* – They shall include-

a) the designated name and internal code reference;
b) reference, if any, to a pharmacopoeial monograph;
c) qualitative and quantitative requirements with acceptance limits;
d) name and address of manufacturer or supplier and original manufacturer of the material;
e) specimen of printed material;
f) directions for sampling and testing or reference to procedures;
g) storage conditions; and
h) maximum period of storage before re-testing.

17.2 For product containers and closures. –

17.2.1 all containers and closures intended for use shall comply with the pharmacopoeial requirements. Suitable validated test methods, sample sizes, specifications, cleaning procedure and sterilization procedure, wherever indicated, shall be strictly followed to ensure that these are not reactive, additive, absorptive, or leach to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used.

17.2.2 whenever bottles are being used, the written schedule of cleaning shall be laid down and followed. Where bottles are not dried after washing, they should be rinsed with de-ionised water or distilled water, as the case may be.

17.3. *For in-process and bulk products.* – Specifications for in-process material, intermediate and bulk products shall be available. The specifications should be authenticated.

17.4 *For finished products.* – Appropriate specifications for finished products shall include: -

a) the designated name of the product and the code reference;
b) the formula or a reference to the formula and the pharmacopoeial reference;
c) directions for sampling and testing or a reference to procedures;

d) a description of the dosage form and package details;

e) the qualitative and quantitative requirements, with the acceptance limits for release;

f) the storage conditions and precautions, where applicable, and

g) the shelf-life.

17.5 *For preparation of containers and closures*. – The requirements mentioned in the Schedule do not include requirements of machinery, equipments and premises required for preparation of containers and closures for different dosage forms and categories of drugs. The suitability and adequacy of the machinery, equipment and premises shall be examined taking into consideration the requirements of each licensee in this respect.

18. *Master Formula Records*.

There shall be Master Formula records relating to all manufacturing procedures for each product and batch size to be manufactured. These shall be prepared and endorsed by the competent technical staff i.e. head of production and quality control. The master Formula shall include: -

(a) the name of the product together with product reference code relating to its specifications;

(b) the patent or proprietary name of the product along with the generic name, a description of the dosage form, strength, composition of the product and batch size;

(c) name, quantity, and reference number of all the starting materials to be used. Mention shall be made of any substance that may 'disappear' in the courts of processing.

(d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

(e) a statement of the processing location and the principal equipment to be used.

(f) the methods, or reference to the methods, to be used for preparing the critical equipments including cleaning, assembling, calibrating, sterilizing.

(g) detailed stepwise processing instructions and the time taken for each step;

(h) the instructions for in-process control with their limits;

(i) the requirements for storage conditions of the products, including the container, labeling and special storage conditions where applicable;

(j) any special precautions to be observed; and

(k) packing details and specimen labels.

19. *Packing Records* -

There shall be authorised packaging instructions for each product, pack size and type. These shall include or have a reference to the following: -

(a) name of the product;

(b) description of the dosage form, strength and composition;

(c) the pack size expressed in terms of the number of doses, weight or volume of the product in the final container;

(d) complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types with the code of reference number relating to the specifications of each packaging material.

(e) reproduction of the relevant printed packaging materials and specimens indicating where batch number and expiry date of the product have been applied;

(f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before the operations begin.

(g) description of the packaging operation, including any significant subsidiary operations and equipment to be used;

(h) details of in-process controls with instructions for sampling and acceptance; and

(i) upon completion of the packing and labeling operation, a reconciliation shall be made between number of labeling and packaging units issued, number of units labeled, packed and

excess returned or destroyed. Any significant or unusual discrepancy in the numbers shall be carefully investigated before releasing the final batch.

20. *Batch Packaging Records.*

20.1 A batch packaging record shall be kept for each batch or part batch processed. It shall be based on the relevant parts of the packaging instructions, and the method of preparation of such records shall be designed to avoid transcription errors.

20.2 Before any packaging operation begins, check shall be made and recorded that the equipment and the work stations are clear of the previous products, documents or materials not required for the planned packaging operations, and that the equipment is clean and suitable for use.

21. *Batch Processing Records*

21.1 There shall be Batch Processing Record for each product. It shall be based on the relevant parts of the currently approved Master Formula. The method of preparation of such records included in the Master Formula shall be designed to avoid transcription errors.

21.2 Before any processing begins, check shall be performed and recorded to ensure that the equipment and work station are clear of previous products, documents or materials not required for the planned process are removed and the equipment is clean and suitable for use.

21.3 During processing, the following information shall be recorded at the time each action is taken and the record shall be dated and signed by the person responsible for the processing operations:-

(a) the name of the product
(b) the number of the batch being manufactured,
(c) dates and time of commencement, of significant intermediate stages and of completion of production,
(d) initials of the operator of different significant steps of production and where appropriate, of the person who checked each of these operations,
(e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed,

(f) any relevant processing operation or event and major equipment used,

(g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained,

(h) the amount of product obtained after different and critical stages of manufacture (yield),

(i) comments or explanations for significant deviations from the expected yield limits shall be given.

(j) notes on special problems including details, with signed authorization, for any deviation from the Master Formula.

(k) addition of any recovered or reprocessed material with reference to recovery or reprocessing stages.

22. *Standard Operating Procedures (SOPs) and Records, regarding -*

22.1 Receipt of materials:

22.1.1 there shall be written Standard Operating Procedures and records for the receipt of each delivery of raw, primary and printed packaging material.

22.1.2 the records of the receipts shall include;

(a) the name of the material on the delivery note and the number of containers;

(b) the date of receipt;

(c) the manufacturer's and/or supplier's name;

(d) the manufacturer's batch or reference number;

(e) the total quantity, and number of containers, quantity in each container received;

(f) the control reference number assigned after receipt;

(g) any other relevant comment or information.

22.1.3 There shall be written standard operating procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

22.1.4 There shall be Standard Operating Procedures available for each instrument and equipment and these shall be placed in close proximity to the related instrument and equipment.

22.2 *Sampling: -*

22.2.1 There shall be written Standard Operating Procedures for sampling which include the person(s) authorized to take the samples.

22.2.2 The sampling instruction shall include:

(a) The method of sampling and the sampling plan,

(b) The equipment to be used,

(c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality,

(d) The quantity of samples to be taken,

(e) instructions for any required sub-division or poling of the samples,

(f) The types of sample containers to be used,

(g) any specific precautions to be observed, especially in regard to sampling of sterile and hazardous materials.

22.3. *Batch Numbering -*

22.3.1 There shall be Standard Operating Procedures describing the details of the batch (lot) numbering set up with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

22.3.2 Batch numbering Standard Operating Procedures applied to a processing stage and to the respective packaging stage shall be same or traceable to demonstrate that they belong to one homogenous mix.

22.3.3 Batch number allocation shall be immediately recorded in a logbook or by electronic data processing system. The record shall include date of allocation, product identity and size of batch.

22.4. *Testing:*

22.4.1 There shall be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed shall be recorded.

22.5 *Records of Analysis* -

22.5.1 The records shall include the following data:

(a) name of the material or product and the dosage form

(b) batch number and, where appropriate the manufacturer and/ or supplier,

(c) reference to the relevant specifications and testing procedures,

(d) test results, including observations and calculations, and reference to any specifications (limits),

(e) dates of testing,

(f) initials of the persons who performed the testing,

(g) initials of the persons who verified the testing and the detailed calculations,

(h) A statement of release or rejection, and

(i) signature and date of the designated responsible person.

22.5.2 There shall be written standard operating procedures and the associated records of actions taken for:

(a) equipment assembly and validation

(b) analytical apparatus and calibration,

(c) maintenance, cleaning and sanitation;

(d) personnel matters including qualification, training, clothing, hygiene

(e) environmental monitoring;

(f) pest control;

(g) complaints;

(h) recalls made; and

(i) returns received.

23. *Reference Samples* -

23.1 Each lot of every active ingredient, in a quality sufficient to carryout all the tests, except sterility and pyrogens / Bacterial Endotoxin Test, shall be retained for a period of 3 months after the date of expiry of the last batch produced from that active ingredient.

23.2. Samples of finished formulations shall be stored in the same or simulated containers in which the drug has been actually marketed.

24. *Reprocessing and Recoveries* -

24.1. Where reprocessing is necessary, written procedures shall be established and approved by the Quality Assurance Department that shall specify the conditions and limitations of repeating chemical reactions. Such reprocessing shall be validated.

24.2. If the product batch has to be reprocessed, the procedure shall be authorized and recorded. An investigation shall be carried out into the causes necessitating re-processing and appropriate corrective measures shall be taken for prevention of recurrence. Re-processed batch shall be subjected to stability evaluation.

24.3. Recovery of the product residue may be carried out, if permitted, in the master production and control records by incorporating it in subsequent batches of the product.

25. *Distribution records:*

25.1. Prior to distribution or dispatch of given batch of a drug, it shall be ensure that the batch has been duly tested, approved and released by the quality control personnel. Pre-dispatch inspection shall be performed on each consignment on a random basis to ensure that only the correct goods are dispatched. Detailed instructions for warehousing and stocking of Large Volume Parenterals, if stocked, shall be in existence and shall be complied with after the batch is released for distribution. Periodic audits of warehousing

practices followed at distribution centers shall be carried out and records thereof shall be maintained. Standard Operating Procedures shall be developed for warehousing of products.

25.2. Records for distribution shall be maintained in a manner such that finished batch of a drug can be traced to the retain level to facilitate prompt and complete recall of the batch, if and when necessary.

26. *Validation and process validation* -

26.1. Validation studies shall be an essential part of Good Manufacturing Practices and shall be conducted as per the pre-defined protocols. These shall include validation of processing, testing and cleaning procedures.

26.2. A written report summarizing recorded results and conclusions shall be prepared, documented and maintained.

26.3. Processes and procedures shall be established on the basis of validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Critical processes shall be validated, prospectively for retrospectively.

26.4. When any new Master Formula or method of preparation is adopted, steps shall be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified shall be demonstrated to yield a product consistently of the required quality.

26.5. Significant changes to the manufacturing process, including any changes in equipment or materials that may affect product quality and/or the reproducibility of the process, shall be validated.

27. *Product Recalls* -

27.1 A prompt and effective product recall system of defective products shall be devised for timely information of all concerned stockists, wholesalers, suppliers, upto the retail

level within the shortest period. The licensee may make use of both print and electronic media in this regard.

27.2. There shall be an established written procedure in the form of Standard Operating Procedure for effective recall of products distributed by the licensee. Recall operations shall be capable of being initiated promptly so as to effectively reach at the level of each distribution channel.

27.3 The distribution records shall be readily made available to the persons designated for recalls.

27.4 The designated person shall record a final report issued, including reconciliation between the delivered and the recovered quantities of the products.

27.5 The effectiveness of the arrangements for recalls shall be evaluated from time to time.

27.6 The recalled products shall be stored separately in a secured segregated area pending final decision on them.

28. *Complaints and Adverse Reactions*

28.1 All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated/evaluated by the designated personnel of the company and records of investigation and remedial action taken thereof shall be maintained.

28.2. Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority.

28.3 There shall be written procedure describing the action to be taken, recall to be made of the defective product.

29. *Site Master File* -The licensee shall prepare a succinct document in the form of Site Master File containing specific and

factual Good Manufacturing Practices about the production and/or control of pharmaceutical manufacturing preparations carried out at the licensed premises. It shall contain the following: -

29.1 *General information* -

(a) brief information of the firm;

(b) pharmaceutical manufacturing activities as permitted by the licensing authority;

(c) other manufacturing activities, if any, carried out on the premises;

(d) type of product licensed for manufacture with flow charts mentioning procedure and process flow;

(e) number of employees engaged in the production, quality control, storage and distribution;

(f) use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;

(g) short description of the Quality Management System of the firm; and

(h) products details registered with foreign countries.

29.2 *Personnel* -

(a) organisational chart showing the arrangement for quality assurance including production and quality control;

(b) qualification, experience and responsibilities of key personnel;

(c) outline for arrangements for basic and in-service training and how the records are maintained;

(d) health requirements for personnel engaged in production; and

(e) personal hygiene requirements, including clothing.

29.3 *Premises* -

(a) simple plan or description of manufacturing areas drawn to scale;

(b) nature of construction and fixtures/fittings;

(c) brief description of ventilation systems. More details should be given for critical areas with potential risk of airborne contamination (schematic drawing of systems). Classification of the rooms used for the manufacture of sterile products should be mentioned;

(d) special areas for the handling of the highly toxic, hazardous and sensitizing materials;

(e) brief description of water system (schematic drawings of systems), including sanitation; and

(f) description of planned preventive maintenance programs for premises and of the recording system.

29.4 *Equipment* -

(a) brief description of major equipment used in production and Quality Control Laboratories (a list of equipment required);

(b) description of planned preventive maintenance programs for equipment and of the recording system; and

(c) qualification and calibration including the recording systems and arrangements for computerized systems validation.

29.5 *Sanitation* -

(a) availability of written specifications and procedures for cleaning manufacturing areas and equipment.

29.6 *Documentation* -

(a) arrangements for the preparation, revision and distribution of;

(b) necessary documentation for the manufacture;

(c) any other documentation related to product quality that is not mentioned elsewhere (e.g. microbiological controls about air and water).

29.7 *Production* -

(a) brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters;

(b) arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage;

(c) arrangements for the handling of rejected materials and products; and

(d) brief description of general policy for process validation.

29.8 *Quality Control* -

(a) description of the quality control system and of the activities of the Quality Control Department. Procedures for the release of the finished products.

29.9 *Loan licence manufacture and licensee* -

(a) description of the way in which compliance of Good Manufacturing Practices by the loan licensee shall be assessed.

29.10 *Distribution, complaints and product recall* -

(a) arrangements and recording system for distribution; and

(b) arrangements for handling of complaints and product recalls.

29.11 *Self inspection* -

(a) short description of the self inspection system indicating whether an outside, independent and experienced external export was involved in evaluating the manufacturer's compliance with Good manufacturing Practices in all aspects of production.

29.12 *Export of drugs* -

(a) products exported to different countries; and

(b) complaints and product recall, if any.

Appendix 4: Schedule Y

SCHEDULE Y
[See rules 122A, 122B, 122D, 122DA, 122DAA and 122E]

REQUIREMENTS AND GUIDELINES FOR PERMISSION TO IMPORT AND/OR MANUFACTURE OF NEW DRUGS FOR SALE OR TO UNDERTAKE CLINICAL TRIALS

1. Application for permission.- (1) Application for permission to import or manufacture new drugs for sale or to undertake clinical trials shall be made in Form 44 accompanied with following data in acccordance with the appendices, namely:-

(i) chemical and pharmaceutical information as prescribed in item 2 of Appendix I;

(ii) animal pharmacology data as prescribed in item 3 of Appendix I and Appendix IV;

(a) specific pharmacological actions as prescribed in item 3.2 of Appendix I, and demonstrating, therapeutic potential for humans shalls be described according to the animal models and species used. Wherever possible, dose-response relationships and ED 50s shall be submitted. Special studies conducted to elucidate mode of action shall also be described (Appendix IV);

(b) general pharmacological actions as prescribed in item 3.3 of Appendix I and item 1.2 of Appendix IV;

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(c) pharmacokinetic data related to the absorption, distribution, metabolism and excretion of the test substance as prescribed in item 3.5 of Appendix I. Wherever possible, the drug effects shall be corelated to the plasma drug concentrations;

(iii) animal toxicology data as prescribed in item 4 of Appendix I and Appendix III;

(iv) human Clinical Pharmacology Data as prescribed in items 5,6 and 7 of Appendix I and as stated below:-

(a) for new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as required under items 1, 2, 3, 4, 5 (data, if any, from other countries) , and 9 of Appendix I;

(b) for new drug substances discovered in countries other than India, Phase I data as required under items 1, 2, 3, 4, 5 (data from other countries) and 9 of Appendix I should be submitted along with the application. After submission of Phase I data generated outside India to the Licensing Authority, permission may be granted to repeat Phase I trials and/or to conduct Phase II trials and subsequently Phase III trials concurrently with other global trials for that drug. Phase III trials are required to be conducted in India before permission to market the drug in India is granted;

(c) the data required will depend upon the purpose of the new drug application . The number of study subjects and sites to be involved in the conduct of clinical trial will depend upon the nature and objective of the study. Permission to carry out these trials shall generally be given in stages, considering the data emerging from earlier Phase(s);

(d) application for permission to initiate specific phase of clinical trial should also accompany Investigator's brochure, proposed protocol (Appendix X), case record form, study subject's informed consent document(s) (Appendix V), investigator's undertaking (Appendix VII) and ethics committee clearance, if available, (Appendix VIII);

(e) reports of clinical studies submitted under items 5-8 of Appendix I should be in consonance with the format prescribed in Appendix II of this Schedule. The study report shall be certified by the Principal Investigator or, if no Principal Investigator is designated, then by each of the Investigators participating in the study. The certification should acknowledge the contents of the report, the accurate presentation of the study as undertaken, and express agreement with the conclusions. Each page should be numbered;

(v) regulatory status in other countries as prescribed in item 9.2 of Appendix I, including Information in respect of restrictions imposed, if any, on the use of the drug in other countries, e.g. dosage limits, exclusion of certain age groups, warning about adverse drug reactions,.etc. (item 9.2 of Appendix I). Likewise, if the drug has been withdrawn in any country by the manufacturer or by regulatory authorities, such information should also be furnished along with the reasons and their relevance, if any, to India. This information must continue to be submitted by the sponsor to the Licensing Authority during the course of marketing of the drug in India;

(vi) the full prescribing information should be submitted as part of the new drug application for marketing as prescribed in item 10 of Appendix I. The prescribing information (package insert) shall comprise the following sections: generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.) ; contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions. All package inserts, promotional literature and patient education material subsequently produced are required to be consistent with the contents of the approved full prescribing information. The drafts of label and carton texts should comply with provisions

of rules 96 and 97. After submission and approval by the Licensing Authority, no changes in the package insert shall be effected without such changes being approved by the Licensing Authority; and

(vii) complete testing protocol/s for quality control testing together with a complete impurity profile and release specifications for the product as prescribed in item 11 of Appendix I should be submitted as part of new drug application for marketing. Samples of the pure drug substance and finished product are to be submitted when desired by the regulatory authority.

(2) If the study drug is intended to be imported for the purposes of examination, test or analysis, the application for import of small quantities of drugs for such purpose should also be made in Form 12.

(3) For drugs indicated in life threatening/serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.

2. CLINICAL TRIAL

(1) Approval for clinical trial

(i) Clinical trial on a new drug shall be initiated only after the permission has been granted by the Licensing Authority under rule 21 (b), and the approval obtained from the respective ethics committee(s). The Licensing Authority as defined shall be informed of the approval of the respective institutional ethics comittee(s) as prescribed in Appendix VIII, and the trial initiated at each respective site only after obtaining such an approval for that site. The trial site(s) may accept the approval granted to the protocol by the ethics committee of another trial site or the approval granted by an independent ethics committee (constituted as per Appendix VIII), provided that the approving ethics committee(s) is/are willing to accept their responsibilities for the

study at such trial site(s) and the trial site(s) is/are willing to accept such an arrangement and that the protocol version is same at all trial sites.

(ii) All trial Investigator(s) should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol. A qualified physician (or dentist, when appropriate) who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions. Laboratories used for generating data for clinical trials should be compliant with Good Laboratory Practices. If services of a laboratory or a facilities outside the country are to be availed, its/their name(s), address(s) and specific services to be used should be stated in the protocol to avail Licensing Authority's permission to send clinical trial related samples to such laboratory(ies) and/or facility(ies). In all cases, information about laboratory(ies)/facilities to be used for the trial, if other than those at the investigation site(s), should be furnished to the Licensing Authority prior to initiation of trial at such site(s).

(iii) Protocol amendments if become necessary before initiation or during the course of a clinical trial, all such amendments should be notified to the Licensing Authority in writing along with the approval by the ethics committee which has granted the approval for the study. No deviations from or changes to the protocol should be implemented without prior written approval of the ethics committee and the Licensing Authority except when it is necessary to eliminate immediate hazards to the trial Subject(s) or when change(s) involve(s) only logistic or administrative aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the Licensing Authority. Administrative and/or logistic changes in the protocol should be notified to the Licensing Authority within 30 days.

(2) **Responsibilities of Sponsor.-**

(i) The clinical trial Sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice (GCP) Guidelines issued by the Central Drugs Standard Control Organization, Directorate General of Health Services, Government of India as well as with all applicable statutory provisions. Standard operating procedures should be documented to ensure compliance with GCP and applicable regulations.

(ii) Sponsors are required to submit a status report on the clinical trial to the Licensing Authority at the prescribed periodicity.

(iii) in case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within 3 months. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions (Appendix XI), if any, and the reason for discontinuation of the study or non-pursuit of the new drug application;

(iv) Any unexpected serious adverse event (SAE) (as defined in GCP Guidelines) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study (see Appendix XI).

(3) **Responsibilities of the Investigator(s).-** The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per the undertaking given in Appendix VII. Standard operating procedures are required to be documented by the investigators for the tasks performed by them. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided to the participant for any adverse events. Investigator(s) shall report all serious and unexpected adverse events to the Sponsor within 24 hours and to the Ethics Committee that accorded approval to the study protocol within 7 working days of their occurance.

(4) Informed Consent.-

(i) In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject. The Subject's consent must be obtained in writing using an 'Informed Consent Form'. Both the patient information sheet as well as the Informed Consent Form should have been approved by the ethics committee and furnished to the Licensing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Licensing Authority before such changes are implemented.

(ii) Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative (a legally acceptable representative is a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India). If the Subject or his/her legally acceptable representative is unable to read/write – an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

(iii) A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the Informed Consent Form for study Subjects is given in Appendix V.

(5) Responsibilities of the Ethics Committee.-

(i) It is the responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard the rights, safety and well being of all trial subjects. The ethics committee should exercise particular care to protect the rights, safety and well being of all vulnerable subjects participating in the study, e.g., members of a group with hierarchical structure (e.g. prisoners, armed forces personnel, staff and students of medical,

nursing and pharmacy academic institutions), patients with incurable diseases, umemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally giving consent. Ethics committee(s) should get document 'standard operating procedures' and should maintain a record of its proceedings.

(ii) Ethics Committee(s) should make, at appropriate intervals, an ongoing review of the trials for which they review the protocol(s). Such a review may be based on the periodic study progress reports furnished by the investigators and/or monitoring and internal audit reports furnished by the Sponsor and/or by visiting the study sites.

(ii) In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the Investigator as well as to the Licensing Authority.

(6) Human Pharmacology (Phase I).-

(i) The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into human(s). Studies in this Phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients. Phase I trials should preferably be carried out by Investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the Subjects.

(ii) Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives:-

(a) Maximum tolerated dose: To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.

(b) Pharmacokinetics, i.e., characterization of a drug's absorption, distribution, metabolism and excretion. Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

(c) Pharmacodynamics: Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic/pharmacodynamic studies) may be conducted in healthy volunteer Subjects or in patients with the target disease. If there are appropriate validated indicators of activity and potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.

(d) Early Measurement of Drug Activity: Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later Phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

(7) **Therapeutic exploratory trials (Phase II).-**

(i) The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this Phase is to determine the dose(s) and regimen for Phase III trials. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I.

(ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild

versus severe disease) for further studies in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

(ii) If the application is for conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and the patients as well as the justification for undertaking such trials in India shall be provided to the Licensing Authority.

(8) **Therapeutic confirmatory trials (Phase III).-**

(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefit(s). Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drug(s).

(ii) For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).

(iii) For new drugs approved outside India, Phase III studies need to be carried out primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

(iv) If the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of

sites and patients as well as the justification for undertaking such trials in India should be provided to the Licensing Authority along with the application.

(9) **Post Marketing Trials (Phase IV).-** Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g. mortality/morbidity studies, epidemiological studies etc.

3. Studies in special populations:

Information supporting the use of the drug in children, pregnant women, nursing women, elderly patients, patients with renal or other organ systems failure, and those on specific concomitant medication is required to be submitted if relevant to the clinical profile of the drug and its anticipated usage pattern. Any claim sought to be made for the drug product that is not based on data submitted under preceding items of this Schedule should be supported by studies included under this item of the Schedule (Appendix I, item 8.3).

(1) **Geriatrics.-** Geriatric patients should be included in Phase III clinical trials (and in Phase II trials, at the Sponsor's option) in meaningful numbers, if-

(a) the disease intended to be treated is characteristically a disease of aging; or

(b) the population to be treated is known to include substantial numbers of geriatric patients; or

(c) when there is specific reason to expect that conditions common in the elderly are likely to be encountered; or

(d) when the new drug is likely to alter the geriatric patient's response (with regard to safety or efficacy) compared with that of the non-geriatric patient.

(2) Paediatrics.-

(i) The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.

(ii) If the new drug is for diseases predominantly or exclusively affecting paediatric patients, clinical trial data should be generated in the paediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk.

(iii) If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options, paediatric population should be included in the clinical trials early, following assessment of initial safety data and reasonable evidence of potential benefit. In circumstances where this is not possible, lack of data should be justified in detail.

(iv) If the new drug has a potential for use in paediatric patients – paediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post marketing surveliance in adults if a safety concern exists. In cases where there is limited paediatric data at the time of submission of application – more data in paediatric patients would be expected after marketing authorisation for use in children is granted.

(v) The paediatric studies should include-

(a) clinical trials,

(b) relative bioequivalence comparisons of the paediatric formulation with the adult formulation performed in adults, and

(c) definitive pharmacokinetic studies for dose selection across the age ranges of paediatric patients in whom the drug is likely to be used. These studies should be conducted in the paediatric patient population with the disease under study.

(vi) If the new drug is a major therapeutic advance for the paediatric population – the studies should begin early in the drug development, and this data should be submitted with the new drug application.

(vii) Paediatric Subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/legal guardian. However, all paediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand. Where appropriate, paediatric participants should additionally assent to enrol in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form. Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the Investigator and parent(s)/legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental/legal guardian consent should be sufficient to allow participation in the study.

(viii) For clinical trials conducted in the paediatric population, the reviewing ethics committee should include members who are knowledgeable about pediatric, ethical, clinical and psychosocial issues.

(3) Pregnant or nursing women.-

(i) Pregnant or nursing women should be included in clinical trials only when the drug is intended for use by pregnant/nursing women or foetuses/nursing infants and where the data generated from women who are not pregnant or nursing, is not suitable.

(ii) For new drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that drug) on the pregnancy, fetus and child will be required. Where applicable, excretion of the drug or its metabolites into human milk should be examined and the infant should be monitored for predicted pharmacological effects of the drug.

(2) Post Marketing Surveillance.-

(i) Subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed. The applicants shall furnish Periodic Safety Update Reports (PSURs) in order to-

  (a) report all the relevant new information from appropriate sources;

  (b) relate these data to patient exposure ;

  (c) summarize the market authorization status in different countries and any significant variations related to safety; and

  (d) indicate whether changes should be made to product information in order to optimize the use of the product.

(ii) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one PSUR. Within the single PSUR separate presentations of data for different dosage forms, indications or separate population need to be given.

(iii) All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The PSURs shall be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years – the PSURs need to be submitted annually. Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. PSURs due for a period must be submitted within 30 calendar days of the last

day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

(iv) New studies specifically planned or conducted to examine a safety issue should be described in the PSURs.

(v) A PSUR should be structured as follows:

(a) A title page stating: Periodic safety update report for the product, applicant's name, period covered by the report, date of approval of new drug, date of marketing of new drug and date of reporting;

(b) Introduction,

(c) Current worldwide market authorization status,

(d) Update of actions taken for safety reasons,

(e) Changes to reference safety information,

(f) Estimated patient exposure,

(g) Presentation of individual case histories,

(h) Studies,

(i) Other information,

(j) Overall safety evaluation,

(k) Conclusion,

(l) Appendix providing material relating to indications, dosing, pharmacology and other related information.

(5) Special studies: Bioavailability/Bioequivalence Studies.-

(i) For drugs approved elsewhere in the world and absorbed systemically, bioequivalence with the reference formulation should be carried out wherever applicable. These studies should be conducted under the labeled conditions of administration. Data on the extent of systemic absorption may be required for formulations other than those designed for systemic absorption.

(ii) Evaluation of the effect of food on absorption following oral administration should be carried out. Data from dissolution studies should also be submitted for all solid oral dosage forms.

(iii) Dissolution and bioavailability data submitted with the new drug application must provide information that assures bioequivalence or establishes bioavailability and dosage correlations between the formulation(s) sought to be marketed and those used for clinical trials during clinical development of the product. (See items 8.1, 8.2 and 8.3 of Appendix I).

(iv) All bioavailability and bioequivalence studies should be conducted according to the Guidelines for Bioavailability and Bioequivance studies as prescribed.

Note.- The data requirements stated in this Schedule are expected to provide adequate information to evaluate the efficacy, safety and therapeutic rationale of new drugs (as defined under rule 122-E) prior to the permission for sale. Depending upon the nature of new drugs and disease(s), additional information may be required by the Licensing Authority. The applicant shall certify the authencity of the data and documents submitted in support of an application for new drug. The Licensing Authority reserves the right to reject any data or any document(s) if such data or contents of such documents are found to be of doubtful integrity.

APPENDIX I

DATA TO BE SUBMITTED ALONG WITH THE APPLICATION TO CONDUCT CLINICAL TRIALS/IMPORT/MANUFACTURE OF NEW DRUGS FOR MARKETING IN THE COUNTRY.

1. Introduction

A brief description of the drug and the therapeutic class to which it belongs.

2. Chemical and pharmaceutical information

2.1. Information on active ingredients

Drug information (Generic Name, Chemical Name or INN)

2.2. Physicochemical Data

a. Chemical name and Structure
Empirical formula
Molecular weight

b. Physical properties
Description
Solubility
Rotation
Partition coefficient
Dissociation constant

2.3. Analytical Data

Elemental analysis
Mass spectrum
NMR spectra
IR spectra
UV spectra
Polymorphic identification

2.4. Complete monograph specification including

Identification
Identity/quantification of impurities
Enantiomeric purity
Assay

2.5. Validations

Assay method
Impurity estimation method
Residual solvent/other volatile impurities (OVI) estimation method

2.6. Stability Studies (for details refer Appendix IX)

Final release specification
Reference standard characterization
Material safety data sheet

2.7. Data on Formulation

Dosage form
Composition
Master manufacturing formula
Details of the formulation (including inactive ingredients)
In process quality control check
Finished product specification
Excipient compatibility study
Validation of the analytical method
Comparative evaluation with international brand(s) or approved Indian brands, if applicable
    Pack presentation
    Dissolution
    Assay
    Impurities
    Content uniformity
    pH
Force degradation study
Stability evaluation in market intended pack at proposed storage conditions
Packing specifications
Process validation

When the application is for clinical trials only, the international non-proprietary name (INN) or generic name, drug category, dosage form and data supporting stability in the intended container-closure system for the duration of the clinical trial (information covered in item nos. 2.1, 2.3, 2.6, 2.7) are required.

3. Animal Pharmacology (for details refer Appendix IV)

    3.1. Summary
    3.2. Specific pharmacological actions
    3.3. General pharmacological actions
    3.4. Follow-up and Supplemental Safety Pharmacology Studies
    3.5. Pharmacokinetics: absorption, distribution; metabolism; excretion

4. Animal Toxicology (for details refer Appendix III)
   - 4.1. General Aspects
   - 4.2. Systemic Toxicity Studies
   - 4.3. Male Fertility Study
   - 4.4. Female Reproduction and Developmental Toxicity Studies
   - 4.5. Local toxicity
   - 4.6. Allergenicity/Hypersensitivity
   - 4.7. Genotoxicity
   - 4.8. Carcinogenicity
5. Human/Clinical pharmacology (Phase I)
   - 5.1. Summary
   - 5.2. Specific Pharmacological effects
   - 5.3. General Pharmacological effects
   - 5.4. Pharmacokinetics, absorption, distribution, metabolism, excretion
   - 5.5. Pharmacodynamics/early measurement of drug activity
6. Therapeutic exploratory trials (Phase II)
   - 6.1. Summary
   - 6.2. Study report(s) as given in Appendix II
7. Therapeutic confirmatory trials (Phase III)
   - 7.1. Summary
   - 7.2. Individual study reports with listing of sites and Investigators.
8. Special studies
   - 8.1. Summary
   - 8.2. Bio-availability/Bio-equivalence.
   - 8.3 Other studies e.g. geriatrics, paediatrics, pregnant or nursing women
9. Regulatory status in other countries
   - 9.1. Countries where the drug is
     - a. Marketed
     - b. Approved
     - c. Approved as IND
     - d. Withdrawn, if any, with reasons

9.2. Restrictions on use, if any, in countries where marketed/approved
9.3. Free sale certificate or certificate of analysis, as appropriate.

10. Prescribing information

10.1. Proposed full prescribing information
10.2. Drafts of labels and cartons

11. Samples and Testing Protocol/s

11.1. Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical doses if prescribed by the Licensing Authority), with testing protocol/s, full impurity profile and release specifications.

NOTES:

(1) All items may not be applicable to all drugs. For explanation, refer text of Schedule Y.
(2) For requirements of data to be submitted with application for clinical trials refer text of this Schedule.

APPENDIX I-A

DATA REQUIRED TO BE SUBMITTED BY AN APPLICANT FOR GRANT OF PERMISSION TO IMPORT AND/OR MANUFACTURE A NEW DRUG ALREADY APPROVED IN THE COUNTRY

1. Introduction
   A brief description of the drug and the therapeutic class

2. Chemical and pharmaceutical information

2.1 Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physico-chemical properties

2.2 Dosage form and its composition
2.3 Test specifications
(a) active ingredients
(b) inactive ingredients
2.4 Tests for identification of the active ingredients and method of tis assay
2.5 Outline of the method of manufacture of active ingredients
2.6 Stability data

3. Marketing information
3.1 Proposed package insert/promotional literature
3.2 Draft specimen of the label and carton

4. Special studies conducted with approval of Licensing Authority
4.1 Bioavailability/Bioequivalence and comparative dissolution studies for oral dosage forms
4.2 Sub-acute animal toxicity studies for intravenous infusions and injectables

Appendix II

STRUCTURE, CONTENTS AND FORMAT FOR CLINICAL STUDY REPORTS

1. Title Page:-

This page should contain information about the title of the study, the protocol code, name of the investigational product tested, development Phase, indication studied, a brief description of the trial design, the start and end date of patient accrual and the names of the Sponsor and the participating Institutes (Investigators)

2. Study Synopsis (1 to 2 pages): A brief overview of the study from the protocol development to the trial closure should be given here. This section will only summarize the important conclusions derived from the study.

3. Statement of compliance with the 'Guidelines for Clinical Trials on Pharmaceutical Products in India – GCP Guidelines' issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India.
4. List of Abbreviations and Definitions
5. Table of contents
6. Ethics Committee:

   This section should document that the study was conducted in accordance with the ethical principles of Declaration of Helsinki. A detailed description of the Ethics Committee constitution and date(s) of approvals of trial documents for each of the participating sites should be provided. A declaration should state that EC notifications as per Good Clinical Practice Guidelines issued by Central Drugs Standard Control Organization and Ethical Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research have been followed.
7. Study Team:

   Briefly describe the administrative structure of the study (Investigators, site staff, Sponsor/designates, Central laboratory etc.).
8. Introduction:

   A brief description of the product development rationale should be given here.
9. Study Objective:

   A statement describing the overall purpose of the study and the primary and secondary objectives to be achieved should be mentioned here.
10. Investigational Plan:

    This section should describe the overall trial design, the Subject selection criteria, the treatment procedures, blinding/ randomization techniques if any, allowed/disallowed concomitant treatment, the efficacy and safety criteria assessed, the data

quality assurance procedures and the statistical methods planned for the analysis of the data obtained.

11. Trial Subjects

A clear accounting of all trial Subjects who entered the study will be given here. Mention should also be made of all cases that were dropouts or protocol deviations. Enumerate the patients screened, randomised, and prematurely discontinued. State reasons for premature discontinuation of therapy in each applicable case.

12. Efficacy evaluation

The results of evaluation of all the efficacy variables will be described in this section with appropriate tabular and graphical representation. A brief description of the demographic characteristics of the trial patients should also be provided along with a listing of patients and observations excluded from efficacy analysis.

13. Safety Evaluation

This section should include the complete list.

13.1 all serious adverse events, whether expected or unexpected and

13.2 unexpected advese events whether serious or not (compliled from data received as per Appendix XI).

The comparison of adverse events across study groups may be presented in a tabular or graphical form. This section should also give a brief narrative of all important events considered related to the investigational product.

14. Discussion and overall Conclusion

Discussion of the important conclusions derived from the trial and scope for further develo.

15. List of References

16. Appendices

List of Appendices to the Clinical Trial Report

a. Protocol and amendments
b. Specimen of Case Record Form

c. Investigators' name(s) with contact addresses, phone, email etc.
d. Patient data listings
e. List of trial participants treated with investigational product
f. Discontinued participants
g. Protocol deviations
h. CRFs of cases involving death and life threatening adverse event cases
i. Publications from the trial
j. Important publications referenced in the study
k. Audit certificate, if available
l. Investigator's certificate that he/she has read the report and that the report accurately describes the conduct and the results of the study.

Apendix III

ANIMAL TOXICOLOGY (NON-CLINICAL TOXICITY STUDIES)

1. General Principles

Toxicity studies should comply with the norms of Good Laboratory Practice (GLP). Briefly, these studies should be performed by suitably trained and qualified staff employing properly calibrated and standardized equipment of adequate size and capacity. Studies should be done as per written protocols with modifications (if any) verifiable retrospectively. Standard operating procedures (SOPs) should be followed for all managerial and laboratory tasks related to these studies. Test substances and test systems (in-vitro or in-vivo) should be properly characterized and standardized. All documents belonging to each study, including its approved protocol, raw data, draft report, final report, and histology slides and paraffin tissue blocks should be preserved for a minimum of 5 years after marketing of the drug.

Toxicokinetic studies (generation of pharmacokinetic data either as an integral component of the conduct of non-clinical toxicity

studies or in specially designed studies) should be conducted to assess the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study. Other objectives of toxicokinetic studies include obtaining data to relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety, to support the choice of species and treatment regimen in nonclinical toxicity studies and to provide information which, in conjunction with the toxicity findings, contributes to the design of subsequent non-clinical toxicity studies.

1.1 Systemic Toxicity Studies

1.1.1 Single-dose Toxicity Studies: These studies (see Appendix I item 4.2) should be carried out in 2 rodent species (mice and rats) using the same route as intended for humans. In addition, unless the intended route of administration in humans is only intravenous, at least one more route should be used in one of the species to ensure systemic absorption of the drug. This route should depend on the nature of the drug. A limit of 2g/kg (or 10 times the normal dose that is intended in humans, whichever is higher) is recommended for oral dosing. Animals should be observed for 14 days after the drug administration, and minimum lethal dose (MLD) and maximum tolerated dose (MTD) should be established. If possible, the target organ of toxicity should also be determined. Mortality should be observed for up to 7 days after parenteral administration and up to 14 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary. LD_{10} and LD_{50} should be reported preferably with 95 percent confidence limits. If LD_{50}s cannot be determined, reasons for the same should be stated.

The dose causing severe toxic manifestations or death should be defined in the case of cytotoxic anticancer agents, and the post-dosing observation period should be to 14 days. Mice should first be used for determination of MTD. Findings should then be confirmed in rat for establishing linear relationship between toxicity and body surface area. In case of nonlinearity, data of the more sensitive species should be used to determine the Phase I starting dose. Where

rodents are known to be poor predictors of human toxicity (e.g., antifolates), or where the cytotoxic drug acts by a novel mechanism of action, MTD should be established in non-rodent species.

1.1.2 Repeated-dose Systemic Toxicity Studies: These studies (see Appendix I, item 4.2) should be carried out in at least two mammalian species, of which one should be a non-rodent. Dose ranging studies should precede the 14-, 28-, 90- or 180-day toxicity studies. Duration of the final systemic toxicity study will depend on the duration, therapeutic indication and scale of the proposed clinical trial. (see Item 1.8). If a species is known to metabolize the drug in the same way as humans, it should be preferred for toxicity studies.

In repeated-dose toxicity studies the drug should be administered 7 days a week by the route intended for clinical use. The number of animals required for these studies, i.e. the minimum number of animals on which data should be available, is shown in Item 1.9.

Wherever applicable, a control group of animals given the vehicle alone should be included, and three other groups should be given graded doses of the drug. The highest dose should produce observable toxicity; the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans or a multiple of it . To make allowance for the sensitivity of the species the intermediate dose should cause some symptoms, but not gross toxicity or death, and should be placed logarithmically between the other two doses.

The parameters to be monitored and recorded in long-term toxicity studies should include behavioral, physiological, biochemical and microscopic observations. In case of parenteral drug administration, the sites of injection should be Subjected to gross and microscopic examination. Initial and final electrocardiogram and fundus examination should be carried out in the non-rodent species.

In the case of cytotoxic anticancer agents dosing and study design should be in accordance with the proposed clinical schedule in terms of days of exposure and number of cycles. Two rodent species may be tested for initiating Phase I trials. A non-rodent species should be

added if the drug has a novel mechanism of action, or if permission for Phase II, III or marketing is being sought.

For most compounds, it is expected that single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half life, incomplete elimination or unanticipated organ toxicity.

Notes:

(i) Single Dose Toxicity Study: Each group should contain at least 5 animals of either sex. At least four graded doses should be given. Animals should be exposed to the test substance in a single bolus or by continuous infusion or several doses within 24 hours. Animals should be observed for 14 days. Signs of intoxication, effect on body weight, gross pathological changes should be reported. It is desirable to include histo-pathology of grossly affected organs, if any.

(ii) Dose-ranging Study: Objectives of this study include the identification of target organ of toxicity and establishment of MTD for subsequent studies.

(a) Rodents: Study should be performed in one rodent species (preferably rat) by the proposed clinical route of administration. At least four graded doses including control should be given, and each dose group as well as the vehicle control should consist of a minimum of 5 animals of each sex. Animals should be exposed to the test substance daily for 10 consecutive days. Highest dose should be the maximum tolerated dose of single-dose study. Animals should be observed daily for signs of intoxication (general appearance, activity and behaviour etc),

and periodically for the body weight and laboratory parameters. Gross examination of viscera and microscopic examination of affected organs should be done.

(b) Non-rodents: One male and one female are to be taken for ascending Phase MTD study. Dosing should start after initial recording of cage-side and laboratory parameters. Starting dose may be 3 to 5 times the extrapolated effective dose or MTD (whichever is less), and dose escalation in suitable steps should be done every third day after drawing the samples for laboratory parameters. Dose should be lowered appropriately when clinical or laboratory evidence of toxicity are observed. Administration of test substance should then continue for 10 days at the well-tolerated dose level following which, samples for laboratory parameters should be taken. Sacrifice, autopsy and microscopic examination of affected tissues should be performed as in the case of rodents.

(iii) 14–28 Day repeated-dose toxicity studies: One rodent (6–10/sex/group) and one non-rodent (2–3/sex/group) species are needed. Daily dosing by proposed clinical route at three dose levels should be done with highest dose having observable toxicity, mid-dose between high and low dose, and low dose. The doses should preferably be multiples of the effective dose and free from toxicity. Observation parameters should include cage-side observations, body weight changes, food/water intake, blood biochemistry, haematology, and gross and microscopic studies of all viscera and tissues.

(iv) 90-Day repeated-dose toxicity studies: One rodent (15–30/sex/group) and one non-rodent (4–6/sex/group) species are needed. Daily dosing by proposed clinical route at three graded dose levels should be done. In addition to the control a "high-dose-reversal" group and its control group should be also included. Parameters should include signs of intoxication (general appearance, activity and behaviour etc), body weight, food intake, blood biochemical parameters, hematological values, urine analysis, organ weights, gross and microscopic study of

viscera and tissues. Half the animals in "reversal" groups (treated and control) should be sacrificed after 14 days of stopping the treatment. The remaining animals should be sacrificed after 28 days of stopping the treatment or after the recovery of signs and/or clinical pathological changes – whichever comes later, and evaluated for the parameters used for the main study.

(v) 180-Day repeated-dose toxicity studies: One rodent (15–30/sex/group) and one non-rodent (4–6/sex/group) species are needed. At least 4 groups, including control, should be taken. Daily dosing by proposed clinical route at three graded dose levels should be done. Parameters should include signs of intoxication, body weight, food intake, blood biochemistry, hematology, urine analysis, organ weights, gross and microscopic examination of organs and tissues.

1.2 Male Fertility Study

One rodent species (preferably rat) should be used. Dose selection should be done from the results of the previous 14 or 28-day toxicity study in rat. Three dose groups, the highest one showing minimal toxicity in systemic studies, and a control group should be taken. Each group should consist of 6 adult male animals. Animals should be treated with the test substance by the intended route of clinical use for minimum 28 days and maximum 70 days before they are paired with female animals of proven fertility in a ratio of 1:2 for mating.

Drug treatment of the male animals should continue during pairing. Pairing should be continued till the detection of vaginal plug or 10 days, whichever is earlier. Females getting thus pregnant should be examined for their fertility index after day 13 of gestation. All the male animals should be sacrificed at the end of the study. Weights of each testis and epididymis should be separately recorded. Sperms from one epididymis should be examined for their motility and morphology. The other epididymis and both testes should be examined for their histology.

1.3 Female Reproduction and Developmental Toxicity Studies

These studies (see Appendix I, item 4.4) need to be carried out for all drugs proposed to be studied or used in women of child bearing age. Segment I, II and III studies (see below) are to be performed in albino mice or rats, and segment II study should include albino rabbits also as a second test species.

On the occasion, when the test article is not compatible with the rabbit (e.g. antibiotics which are effective against gram positive, anaerobic organisms and protozoas) the Segment II data in the mouse may be substituted.

1.3.1 Female Fertility Study (Segment I): The study should be done in one rodent species (rat preferred). The drug should be administered to both males and females, beginning a sufficient number of days (28 days in males and 14 days in females) before mating. Drug treatment should continue during mating and, subsequently, during the gestation period. Three graded doses should be used, the highest dose (usually the MTD obtained from previous systemic toxicity studies) should not affect general health of the parent animals. At least 15 males and 15 females should be used per dose group. Control and the treated groups should be of similar size. The route of administration should be the same as intended for therapeutic use.

Dams should be allowed to litter and their medication should be continued till the weaning of pups. Observations on body weight, food intake, clinical signs of intoxication, mating behaviour, progress of gestation/parturition periods, length of gestation, parturition, post-partum health and gross pathology (and histopathology of affected organs) of dams should be recorded. The pups from both treated and control groups should be observed for general signs of intoxication, sex-wise distribution in different treatment groups, body weight, growth parameters, survival, gross examination, and autopsy. Histopathology of affected organs should be done.

1.3.2 Teratogenicity Study (Segment II): One rodent (preferably rat) and one non-rodent (rabbit) species are to be used. The drug should be administered throughout the period of organogenesis, using three dose levels as described for segment I. The highest dose should cause

minimum maternal toxicity and the lowest one should be proportional to the proposed dose for clinical use in humans or a multiple of it. The route of administration should be the same as intended for human therapeutic use.

The control and the treated groups should consist of at least 20 pregnant rats (or mice) and 12 rabbits, on each dose level. All foetuses should to be subjected to gross examination, one of the foetuses should be examined for skeletal abnormalities and the other half for visceral abnormalities. Observation parameters should include: (Dams) signs of intoxication, effect on body weight, effect on food intake, examination of uterus, ovaries and uterine contents, number of corpora lutea, implantation sites, resorptions (if any); and for the foetuses, the total number, gender, body length, weight and gross/visceral/skeletal abnormalities, if any.

1.3.3 Perinatal Study (Segment III): This study is specially recommended if the drug is to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development. One rodent species (preferably rat) is needed. Dosing at levels comparable to multiples of human dose should be done by the intended clinical route. At least 4 groups (including control), each consisting of 15 dams should be used. The drug should be administered throughout the last trimester of pregnancy (from day 15 of gestation) and then the dose that causes low foetal loss should be continued throughout lactation and weaning. Dams should then be sacrificed and examined as described below.

One male and one female from each litter of F_1 generation (total 15 males and 15 females in each group) should be selected at weaning and treated with vehicle or test substance (at the dose levels described above) throughout their periods of growth to sexual maturity, pairing, gestation, parturition and lactation. Mating performance and fertility of F_1 generation should thus be evaluated to obtain the F_2 generation whose growth parameters should be monitored till weaning. The criteria of evaluation should be the same as described earlier (3.4.1).

Animals should be sacrificed at the end of the study and the observation parameters should include (Dams) body weight, food

intake, general signs of intoxication, progress of gestation/parturition periods and gross pathology (if any); and for pups, the clinical signs, sex-wise distribution in dose groups, body weight, growth parameters, gross examination, survival and autopsy (if needed) and where necessary, histopathology.

1.4 Local toxicity

These studies (see Appendix I, item 4.5) are required when the new drug is proposed to be used by some special route (other than oral) in humans. The drug should be applied to an appropriate site (e.g., skin or vaginal mucous membrane) to determine local effects in a suitable species. Typical study designs for these studies should include three dose levels and untreated and/or vehicle control, preferably use of 2 species, and increasing group size with increase in duration of treatment. Where dosing is restricted due to anatomical or humane reasons, or the drug concentration cannot be increased beyond a certain level due to the problems of solubility, pH or tonicity, a clear statement to this effect should be given. If the drug is absorbed from the site of application, appropriate systemic toxicity studies will also be required.

Notes:

(i) Dermal toxicity study: The study should be done in rabbit and rat. Daily topical (dermal) application of test substance in its clinical dosage form should be done. Test material should be applied on shaved skin covering not less than 10% of the total body surface area. Porous gauze dressing should be used to hold liquid material in place. Formulations with different concentrations (at least 3) of test substance, several fold higher than the clinical dosage form should be used. Period of application may vary from 7 to 90 days depending on the clinical duration of use. Where skin irritation is grossly visible in the initial studies, a recovery group should be included in the subsequent repeated-dose study. Local signs (erythema, oedema and eschar formation) as well as histological examination of sites of application should be used for evaluation of results.

(ii) Photo-allergy or dermal photo-toxicity: It should be tested by Armstrong/Harber Test in guinea pig. This test should be done if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential (e.g., drugs to be used in treatment of leucoderma). Pretest in 8 animals should screen 4 concentrations (patch application for 2 hours ±15 min.) with and without UV exposure (10 J/cm^2). Observations recorded at 24 and 48 hours should be used to ascertain highest nonirritant dose. Main test should be performed with 10 test animals and 5 controls. Induction with the dose selected from pretest should use 0.3 ml/patch for 2 hour ±15 min. followed by 10 J/cm^2 of UV exposure. This should be repeated on day 0, 2,4,7,9 and 11 of the test. Animals should be challenged with the same concentration of test substance between day 20 to 24 of the test with a similar 2-hour application followed by exposure to 10 J/cm^2 of UV light. Examination and grading of erythema and oedema formation at the challenge sites should be done 24 and 48 hours after the challenge. A positive control like musk ambrett or psoralin should be used.

(iii) Vaginal Toxicity Test: Study is to be done in rabbit or dog. Test substance should be applied topically (vaginal mucosa) in the form of pessary, cream or ointment. Six to ten animals per dose group should be taken. Higher concentrations or several daily applications of test substance should be done to achieve multiples of daily human dose. The minimum duration of drug treatment is 7 days (more according to clinical use), Subject to a maximum of 30 days. Observation parameters should include swelling, closure of introitus and histopathology of vaginal wall.

(iv) Rectal Tolerance Test: For all preparations meant for rectal administration this test may be performed in rabbits or dogs. Six to ten animals per dose group should be taken. Formulation in volume comparable to human dose (or the maximum possible volume) should be applied once or several times daily, per rectally, to achieve administration of multiples of daily human dose. The minimum duration of application is 7 days (more

according to clinical use), Subject to a maximum of 30 days. Size of suppositories may be smaller, but the drug content should be several fold higher than the proposed human dose. Observation parameters should include clinical signs (sliding on backside), signs of pain, blood and/or mucus in faeces, condition of anal region/sphincter, gross and (if required) histological examination of rectal mucosa.

(v) Parenteral Drugs: For products meant for intravenous or intramuscular or subcutaneous or intradermal injection the sites of injection in systemic toxicity studies should be specially examined grossly and microscopically. If needed, reversibility of adverse effects may be determined on a case to case basis.

(vi) Ocular toxicity studies (for products meant for ocular instillation): These studies should be carried out in two species, one of which should be the albino rabbit which has a sufficiently large conjunctival sac. Direct delivery of drug onto the cornea in case of animals having small conjunctival sacs should be ensured. Liquids, ointments, gels or soft contact lenses (saturated with drug) should be used. Initial single dose application should be done to decide the exposure concentrations for repeated-dose studies and the need to include a recovery group. Duration of the final study will depend on the proposed length of human exposure Subject to a maximum of 90 days. At least two different concentrations exceeding the human dose should be used for demonstrating the margin of safety. In acute studies, one eye should be used for drug administration and the other kept as control. A separate control group should be included in repeated-dose studies.

Slit-lamp examination should be done to detect the changes in cornea, iris and aqueous humor. Fluorescent dyes (sodium fluorescein, 0.25 to 1.0%) should be used for detecting the defects in surface epithelium of cornea and conjunctiva. Changes in intra-ocular tension should be monitored by a tonometer. Histological examination of eyes should be done at the end of the study after fixation in Davidson's or Zenker's fluid.

(vii) Inhalation toxicity studies: The studies are to be undertaken in one rodent and one non-rodent species using the formulation

that is to be eventually proposed to be marketed. Acute, subacute and chronic toxicity studies should be performed according to the intended duration of human exposure. Standard systemic toxicity study designs (described above) should be used. Gases and vapors should be given in whole body exposure chambers; aerosols are to be given by nose-only method. Exposure time and concentrations of test substance (limit dose of 5mg/l) should be adjusted to ensure exposure at levels comparable to multiples of intended human exposure. Three dose groups and a control (plus vehicle control, if needed) are required. Duration of exposure may vary Subject to a maximum of 6 hours per day and five days a week. Food and water should be withdrawn during the period of exposure to test substance.

Temperature, humidity and flow rate of exposure chamber should be recorded and reported. Evidence of exposure with test substance of particle size of 4 micron (especially for aerosols) with not less that 25% being 1 micron should be provided. Effects on respiratory rate, findings of bronchial lavage fluid examination, histological examination of respiratory passages and lung tissue should be included along with the regular parameters of systemic toxicity studies or assessment of margin of safety.

1.5 Allergenicity/Hypersensitivity:

Standard tests include guinea pig maximization test (GPMT) and local lymph node assay (LLNA) in mouse. Any one of the two may be done.

Notes:

(i) Guinea Pig Maximization Test: The test is to be performed in two steps; first, determination of maximum nonirritant and minimum irritant doses, and second, the main test. The initial study will also have two components. To determine the intradermal induction dose, 4 dose levels should be tested by the same route in a batch of 4 male and 4 female animals (2 of each sex should be given Freund's adjuvant). The minimum irritant dose should be used for induction. Similarly, a topical minimum irritant dose should be determined for challenge. This should be established in 2 males

and 2 females. A minimum of 6 male and 6 female animals per group should be used in the main study. One test and one control group should be used. It is preferable to have one more positive control group. Intradermal induction (day 1) coupled with topical challenge (day 21) should be done. If there is no response, re-challenge should be done 7–30 days after the primary challenge. Erythema and oedema (individual animal scores as well as maximization grading) should be used as evaluation criteria.

(ii) Local Lymph Node Assay: Mice used in this test should be of the same sex, either only males or only females. Drug treatment is to be given on ear skin. Three graded doses, the highest being maximum nonirritant dose plus vehicle control should be used. A minimum of 6 mice per group should be used. Test material should be applied on ear skin on three consecutive days and on day 5, the draining auricular lymph nodes should be dissected out 5 hours after i.v. ^{3}H-thymidine or bromo-deoxy-uridine (BrdU). Increase in ^{3}H-thymidine or BrdU incorporation should be used as the criterion for evaluation of results.

1.6 Genotoxicity

Genotoxic compounds, in the absence of other data, shall be presumed to be trans-species carcinogens, implying a hazard to humans. Such compounds need not be Subjected to long-term carcinogenicity studies. However, if such a drug is intended to be administered for chronic illnesses or otherwise over a long period of time – a chronic toxicity study (up to one year) may be necessary to detect early tumorigenic effects.

Genotoxicity tests are *in vitro* and *in vivo* tests conducted to detect compounds which induce genetic damage directly or indirectly. These tests should enable a hazard identification with respect to damage to DNA and its fixation.

The following standard test battery is generally expected to be conducted:

(i) A test for gene mutation in bacteria.
(ii) An *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma tk assay.

(iii) An *in vivo* test for chromosomal damage using rodent hematopoietic cells.

Other genotoxicity tests e.g. tests for measurement of DNA adducts, DNA strand breaks, DNA repair or recombination serve as options in addition to the standard battery for further investigation of genotoxicity test results obtained in the standard battery. Only under extreme conditions in which one or more tests comprising the standard battery cannot be employed for technical reasons, alternative validated tests can serve as substitutes provided sufficient scientific justification should be provided to support the argument that a given standard battery test is not appropriate.

Both in-vitro and in-vivo studies should be done. In-vitro studies should include Ames' Salmonella assay and chromosomal aberrations (CA) in cultured cells. In-vivo studies should include micronucleus assay (MNA) or CA in rodent bone marrow. Data analysis of CA should include analysis of 'gaps.'

Cytotoxic anticancer agents: Genotoxicity data are not required before Phase I and II trials. But these studies should be completed before applying for Phase III trials.

Notes:

Ames' Test (Reverse mutation assay in Salmonella): S. typhimurium tester strains such as TA98, TA100, TA102, TA1535, TA97 or *Escherichia coli* WP2 *uvrA* or *Escherichia coli* WP2 *uvrA* (pKM101) should be used.

(i) In-vitro exposure (with and without metabolic activation, S9 mix) should be done at a minimum of 5 log dose levels. "Solvent" and "positive" control should be used. Positive control may include 9-amino-acridine, 2-nitrofluorine, sodium azide and mitomycin C, respectively, in the tester strains mentioned above. Each set should consist of at least three replicates. A 2.5 fold (or more) increase in number of revertants in comparison to spontaneous revertants would be considered positive.

(ii) In-vitro cytogenetic assay: The desired level of toxicity for *in vitro* cytogenetic tests using cell lines should be greater than 50%

reduction in cell number or culture confluency. For lymphocyte cultures, an inhibition of mitotic index by greater than 50% is considered sufficient. It should be performed in CHO cells or on human lymphocyte in culture. In-vitro exposure (with and without metabolic activation, S9 mix) should be done using a minimum of 3 log doses. "Solvent" and "positive" control should be included. A positive control like Cyclophosphamide with metabolic activation and Mitomycin C for without metabolic activation should be used to give a reproducible and detectable increase clastogenic effect over the background which demonstrates the sensitivity of the test system. Each set should consist of at least three replicates. Increased number of aberrations in metaPhase chromosomes should be used as the criteria for evaluation.

(iii) In-vivo micronucleus assay: One rodent species (preferably mouse) is needed. Route of administration of test substance should be the same as intended for humans. Five animals per sex per dose groups should be used. At least three dose levels, plus "solvent" and "positive" control should be tested. A positive control like mitomycin C or cyclophosphamide should be used. Dosing should be done on day 1 and 2 of study followed by sacrifice of animals 6 hours after the last injection. Bone marrow from both the femora should be taken out, flushed with fetal bovine serum (20 min.), pelletted and smeared on glass slides. Giemsa-MayGruenwald staining should be done and increased number of micronuclei in polychromatic erythrocytes (minimum 1000) should be used as the evaluation criteria.

(iv) In-vivo cytogenetic assay: One rodent species (preferably rat) is to be used. Route of administration of test substance should be the same as intended for humans. Five animals/sex/dose groups should be used. At least three dose levels, plus "solvent" and "positive" control should be tested. Positive control may include cyclophosphamide. Dosing should be done on day 1 followed by intra-peritoneal colchicine administration at 22 hours. Animals should be sacrificed 2 hours after colchicine administration.

Bone marrow from both the femora should be taken out, flushed with hypotonic saline (20 min.), pelletted and resuspended in Carnoy's fluid. Once again the cells should be pelletted and dropped on clean glass slides with a Pasteur pipette. Giemsa staining should be done and increased number of aberrations in metaPhase chromosomes (minimum 100) should be used as the evaluation criteria.

1.7 Carcinogenicity (see Appendix I, item 4.8)

Carcinogenicity studies should be performed for all drugs that are expected to be clinically used for more than 6 months as well as for drugs used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. Carcinogenicity studies are also to be performed for drugs if there is concern about their carcinogenic potential emanating from previous demonstration of carcinogenic potential in the product class that is considered relevant to humans or where structure-activity relationship suggests carcinogenic risk or when there is evidence of preneoplastic lesions in repeated dose toxicity studies or when long-term tissue retention of parent compound or metabolite(s) results in local tissue reactions or other pathophysiological responses. For pharmaceuticals developed to treat certain serious diseases, Licensing Authority may allow carcinogenicity testing to be conducted after marketing permission has been granted.

In instances where the life-expectancy in the indicated population is short (i.e., less than 2–3 years) – no long-term carcinogenicity studies may be required. In cases where the therapeutic agent for cancer is generally successful and life is significantly prolonged there may be later concerns regarding secondary cancers. When such drugs are intended for adjuvant therapy in tumour free patients or for prolonged use in non-cancer indications, carcinogenicity studies may be/are needed. Completed rodent carcinogenicity studies are not needed in advance of the conduct of large scale clinical trials, unless there is special concern for the patient population.

Carcinogenicity studies should be done in a rodent species (preferably rat). Mouse may be employed only with proper scientific

justification. The selected strain of animals should not have a very high or very low incidence of spontaneous tumors.

At least three dose levels should be used. The highest dose should be sub-lethal, and it should not reduce the life span of animals by more than 10% of expected normal. The lowest dose should be comparable to the intended human therapeutic dose or a multiple of it, e.g. 2.5x; to make allowance for the sensitivity of the species. The intermediate dose to be placed logarithmically between the other two doses. An untreated control and (if indicated) a vehicle control group should be included. The drug should be administered 7 days a week for a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Generally, the period of dosing should be 24 months for rats and 18 months for mice.

Observations should include macroscopic changes observed at autopsy and detailed histopathology of organs and tissues. Additional tests for carcinogenicity (short-term bioassays, neonatal mouse assay or tests employing transgenic animals) may also be done depending on their applicability on a case to case basis.

Note:

Each dose group and concurrent control group not intended to be sacrificed early should contain atleast 50 animals of each sex. A high dose sattelite group for evaluation of pathology other than neoplasia should contain 20 animals of each sex while the sattelite control group should contain 10 animals of each sex. Observation parameters should include signs of intoxication, effect on body weight, food intake, clinical chemistry parameters, hematology parameters, urine analysis, organ weights, gross pathology and detailed histopathology. Comprehensive descriptions of benign and malignant tumour development, time of their detection, site, dimensions, histological typing etc. should be given.

1.8 Animal toxicity requirements for clinical trials and marketing of a new drug.

Systemic Toxicity Studies			
Route of administration	Duration of proposed human administration	Human Phase(s) for which study is proposed to be conducted	Long term toxicity requirements
Oral or Parenteral or Transdermal	Single dose or several doses in one day, Upto 1wk	I,II,III	2sp,2wk
	> 1 wk but upto 2wk	I,II,III	2sp;4wk
	> 2 wk but upto 4wk	I,II,III	2sp;12wk
	Over 1mo	I,II,III	2sp;24wk
Inhalation (general anaesthetics, aerosols)	Upto 2 wk	I,II,III	2sp;1mo; (Exposure time 3h/d, 5d/wk)
	Upto 4wk	I,II,III	2sp;12wk, (Exposure time 6h/d, 5d/wk)
	> 14wk	I,II,III	2sp;24wk, (Exposure time 6h/d, 5d/wk)
Local Toxicity Studies			
Dermal	Upto 2 wk	I,II	1sp;4wk
		III	2sp;4wk
	> 2 wk	I,II,III	2sp;12wk

Ocular or Otic or Nasal	Upto 2 wk	I,II	1sp;4wk
		III	2sp;4wk
	> 2 wk	I,II,III	2sp;12wk
Vaginal or Rectal	Upto 2 wk	I,II	1sp;4wk
		III	2sp;4wk
	> 2 wk	I,II,III	2sp;12wk

Special Toxicity Studies

Male Fertility Study:

☐ Phase I, II, III in male volunteers/patients

Female Reproduction and Developmental Toxicity Studies:

☐ Segment II studies in 2 species; Phase II, III involving female patients of child-bearing age.

☐ Segment I study; Phase III involving female patients of child-bearing age.

☐ Segment III study; Phase III for drugs to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development.

Allergenicity/Hypersensitivity:

☐ Phase I, II, III – when there is a cause of concern or for parenteral drugs (including dermal application)

Photo-allergy or dermal photo-toxicity:

☐ Phase I, II, III – if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential.

Genotoxicity:

☐ In-vitro studies – Phase I

☐ Both in-vitro and in-vivo – Phase II, III

arcinogenicity:

☐ Phase III - when there is a cause for concern, or when the drug is to be used for more than 6 months.

Abbreviations: sp-species; mo-month; wk-week; d-day; h-hour; I, II, III – Phases of clinical trial;

Note: 1. Animal toxicity data generated in other countries may be accepted and may not be asked to be repeated/duplicated in India on a case to case basis depending upon the quality of data and the credentials of the laboratory (ies) where such data has been generated.

2. Requirements for fixed dose combinations are given in Appendix VI.

1.9 Number of animals required for repeated-dose toxicity studies

Group	14–28 days				84–182 days			
	Rodent (Rat)		Non-rodent (Dog or Monkey)		Rodent (Rat)		Non-rodent (Dog or Monkey)	
	M	F	M	F	M	F	M	F
Control	6–10	6–10	2–3	2–3	15–30	15–30	4–6	4–6
Low dose	6–10	6–10	2–3	2–3	15–30	15–30	4–6	4–6
Intermediate dose	6–10	6–10	2–3	2–3	15–30	15–30	4–6	4–6
High dose	6–10	6–10	2–3	2–3	15–30	15–30	4–6	4–6

2.0 Laboratory parameters to be included in toxicity studies.

Haematological parameters

☐ Haemoglobin	☐ Total RBC Count	☐ Haematocrit	☐ Reticulocyte Count
☐ Total WBC Count	☐ Differential WBC Count	☐ Platelet Count	☐ Terminal Bone Marrow Examination

☐ ESR (Non-rodents only)	☐ General Blood Picture: A special mention of abnormal and immature cells should be made.
☐ Coagulation Parameters (Non-rodents only): Bleeding Time, Coagulation Time, Prothrombin Time, Activated Partial Thromboplastin Time	

Urinalysis Parameters

☐ Colour	☐ Appearance	☐ Specific Gravity	☐ 24-hour urinary output
☐ Reaction (pH)	☐ Albumin	☐ Sugar	☐ Acetone
☐ Bile pigments	☐ Urobilinogen	☐ Occult Blood	
☐ Microscopic examination of urinary sediment.			

Blood Biochemical Parameters

☐ Glucose	☐ Cholesterol	☐ Triglycerides	☐ HDL Cholesterol (Non-rodents only)
☐ LDL Cholesterol (Non-rodents only)	☐ Bilirubin	☐ SGPT (ALT)	☐ SGOT (AST)
☐ Alkaline Phosphatase (ALP)	☐ GGT (Non-rodents only)	☐ Blood Urea Nitrogen	☐ Creatinine
☐ Total Proteins	☐ Albumin	☐ Globulin (Calculated values)	☐ Sodium
☐ Potassium	☐ Phosphorus	☐ Calcium	

Gross and Microscopic Pathology

☐ Brain*: Cerebrum, cerebellum, Midbrain	☐ (Spinal Cord)	☐ Eye	☐ (Middle Ear)
☐ Thyroid	☐ (Parathyroid)	☐ Spleen*	☐ Thymus
☐ Adrenal*	☐ (Pancreas)	☐ (Trachea)	☐ Lung*
☐ Heart*	☐ Aorta	☐ Oesophagus	☐ Stomach
☐ Duodenum	☐ Jejunum	☐ Terminal ileum	☐ Colon
☐ (Rectum)	☐ Liver*	☐ Kidney*	☐ Urinary bladder
☐ Epididymis	☐ Testis*	☐ Ovary	☐ Uterus*
☐ Skin	☐ Mammary gland	☐ Mesenteric lymph node	☐ Skeletal muscle

* Organs marked with an asterisk should be weighed.

() Organs listed in parenthesis should be examined if indicated by the nature of the drug or observed effects.

Non-clinical toxicity testing and safety evaluation data of an IND needed for the conduct of different phases of clinical trials

Note: Refer Appendix III (Points 1.1 through 1.7 and tables 1.8 and 1.9) for essential features of study designs of the non-clinical toxicity studies listed below.

For Phase I Clinical Trials

Systemic Toxicity studies

i. Single dose toxicity studies
ii. Dose Ranging Studies
iii. Repeat-dose systemic toxicity studies of appropriate duration to support the duration to support the duration of proposed human exposure.

Male fertility study

In-vitro genotoxicity tests

Relevant local toxicity studies with proposed route of clinical application (duration depending on proposed length of clinical exposure):

Allergenicity/Hypersensitivity tests (when there is a cause for concern or for parenteral drugs, including dermal application)

Photo-allergy or dermal photo-toxicity test (if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential)

For Phase II Clinical Trials

Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I trial, with appropriate references.

In case of an application for directly starting a Phase II trial - complete details of the non-clinical safety data needed for obtaining the permission for Phase I trial, as per the list provided above must be submitted.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure

In-vivo genotoxicity tests

Segment II reproductive/developmental toxicity study (if female patients of child bearing age are going to be involved)

For Phase III Clinical Trials

Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I and II trials, with appropriate references.

In case of an application for directly initiating a Phase III trial – complete details of the non-clinical safety data needed for obtaining the permissions for Phase I and II trials, as per the list provided above must be provided.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

Reproductive/developmental toxicity studies.

Segment I (if female patients of child bearing age are going to be involved), and

Segment III (for drugs to be given to pregnant or nursing mothers or where there are indications of possible adverse effects on foetal development).

Carcinogenicity studies (when there is a cause for concern or when the drug is to be used for more than 6 months).

For Phase IV Clinical Trials

Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I, II and III trials, with appropriate references.

In case an application is made for initiating the Phase IV trial, complete details of the non-clinical safety data needed for obtaining the permissions for Phase I, II and III trials, as per the list provided above must be submitted.

Application Of Good Laboratory Practices (GLP)

The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.

Appendix IV

ANIMAL PHARMACOLOGY

1. General Principles

Specific and general pharmacological studies should be conducted to support use of therapeutics in humans. In the early stages of drug development enough information may not be available to rationally select study design for safety assessment. In such a situation, a general approach to safety pharmacology studies can be applied. Safety

pharmacology studies are studies that investigate potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range or above.

1.1 Specific Pharmacological Actions

Specific pharmacological actions are those which demonstrate the therapeutic potential for humans.

The specific studies that should be conducted and their design will be different based on the individual properties and intended uses of investigational drug. Scientifically validated methods should be used. The use of new technologies and methodologies in accordance with sound scientific principles should be preferred.

1.2 General Pharmacological Actions

1.2.1 Essential Safety Pharmacology

Safety pharmacology studies need to be conducted to investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range and above. These studies should be designed to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; to evaluate adverse pharmacodynamic and/or pathophysiological effects observed in toxicology and/or clinical studies; and to investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected.

The aim of the essential safety pharmacology is to study the effects of the test drug on vital functions. Vital organ systems such as cardiovascular, respiratory and central nervous systems should be studied. Essential safety pharmacology studies may be excluded or supplemented based on scientific rationale. Also, the exclusion of certain test(s) or exploration(s) of certain organs, systems or functions should be scientifically justified.

1.2.1.1 Cardiovascular System

Effects of the investigational drug should be studied on blood pressure, heart rate, and the electrocardiogram. If possible *in vitro, in vivo* and/or *ex vivo* methods including electrophysiology should also be considered.

1.2.1.2 Central Nervous System

Effects of the investigational drug should be studied on motor activity, behavioral changes, coordination, sensory and motor reflex responses and body temperature.

1.2.1.3 Respiratory System

Effects of the investigational drug on respiratory rate and other functions such as tidal volume and hemoglobin oxygen saturation should be studied.

1.3 Follow-up and Supplemental Safety Pharmacology Studies

In addition to the essential safety pharmacological studies, additional supplemental and follow-up safety pharmacology studies may need to be conducted as appropriate. These depend on the pharmacological properties or chemical class of the test substance, and the data generated from safety pharmacology studies, clinical trials, pharmacovigilance, experimental *in vitro* or *in vivo* studies, or from literature reports.

1.3.1 Follow-up Studies For Essential Safety Pharmacology

Follow-up studies provide additional information or a better understanding than that provided by the essential safety pharmacology.

1.3.1.1 Cardiovascular System

These include ventricular contractility, vascular resistance and the effects of chemical mediators, their agonists and antagonists on the cardiovascular system.

1.3.1.2 Central Nervous System

These include behavioral studies, learning and memory, electrophysiology studies, neurochemistry and ligand binding studies.

1.3.1.3 Respiratory System

These include airway resistance, compliance, pulmonary arterial pressure, blood gases and blood pH.

1.3.2 Supplemental Safety Pharmacology Studies

These studies are required to investigate the possible adverse pharmacological effects that are not assessed in the essential safety pharmacological studies and are a cause for concern.

1.3.2.1 Urinary System

These include urine volume, specific gravity, osmolality, pH, proteins, cytology and blood urea nitrogen, creatinine and plasma proteins estimation.

1.3.2.2 Autonomic Nervous System

These include binding to receptors relevant for the autonomic nervous system, and functional response to agonist or antagonist responses *in vivo* or *in vitro,* and effects of direct stimulation of autonomic nerves and their effects on cardiovascular responses.

1.3.2.3 Gastrointestinal System

These include studies on gastric secretion, gastric pH measurement, gastric mucosal examination, bile secretion, gastric emptying time *in vivo* and ileocaecal contraction *in vitro*.

1.3.2.4 Other Organ Systems

Effects of the investigational drug on organ systems not investigated elsewhere should be assessed when there is a cause for concern. For example dependency potential, skeletal muscle, immune and endocrine functions may be investigated.

1.4 Conditions Under Which Safety Pharmacology Studies Are Not Necessary

Safety pharmacology studies are usually not required for locally applied agents e.g. dermal or ocular, in cases when the pharmacology of the investigational drug is well known, and/or when systemic absorption from the site of application is low. Safety pharmacology testing is also not necessary, in the case of a new derivative having similar pharmacokinetics and pharmacodynamics.

1.5 Timing Of Safety Pharmacology Studies In Relation To Clinical Development

1.5.1 Prior To First Administration In Humans

The effects of an investigational drug on the vital functions listed in the essential safety pharmacology should be studied prior to first administration in humans. Any follow-up or supplemental studies identified, should be conducted if necessary, based on a cause for concern.

1.5.2 During Clinical Development

Additional investigations may be warranted to clarify observed or suspected adverse effects in animals and humans during clinical development.

1.5.3 Before applying for marketing Approval

Follow-up and supplemental safety pharmacology studies should be assessed prior to approval unless not required, in which case this should be justified. Available information from toxicology studies addressing safety pharmacology endpoints or information from clinical studies can replace such studies.

1.6 Application Of Good Laboratory Practices (GLP)

The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.

Appendix V

INFORMED CONSENT

1. Checklist for study Subject's informed consent documents

1.1 Essential Elements:

1. Statement that the study involves research and explanation of the purpose of the research
2. Expected duration of the Subject's participation
3. Description of the procedures to be followed, including all invasive procedures and
4. Description of any reasonably foreseeable risks or discomforts to the Subject
5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.

6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.
7. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records
8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)
9. Compensation and/or treatment(s) available to the Subject in the event of a trial-related injury
10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
11. The anticipated prorated payment, if any, to the Subject for participating in the trial
12. Subject's responsibilities on participation in the trial
13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled.
14. Any other pertinent information

1.2 Additional elements, which may be required

a. Statement of foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent.
b. Additional costs to the Subject that may result from participation in the study.
c. The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.
d. Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the Subject's willingness to continue participation will be provided

e. A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or fetus, if the Subject is or may become pregnant), which are currently unforeseeable

f. Approximate number of Subjects enrolled in the study

2. Format of informed consent form for Subjects participating in a clinical trial

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject's Initials: _____ Subject's Name:_____

Date of Birth/Age: _____

		Please initial box (Subject)
(i)	I confirm that I have read and understood the information sheet dated ___ for the above study and have had the opportunity to ask questions.	[ ]
(ii)	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
(iii)	I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____ Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness _____ Date:_____/_____/_____

Name of the Witness: _____

Appendix VI

FIXED DOSE COMBINATIONS (FDCs)

Fixed Dose Combinations refer to products containing one or more active ingredients used for a particular indication(s). FDCs can be divided into the following groups and data required for approval for marketing is described below:

(a) The first group of FDCs includes those in which one or more of the active ingredients is a new drug. For such FDCs to be approved for marketing data to be submitted will be similar to data required for any new drug (including clinical trials) [see rule 122E, item (a)].

(b) (i) The second group FDCs includes those in which active ingredients already approved/marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature [see rule 122E,

item (c)]. If clinical trials have been carried out with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory status in other countries should be stated. (see Appendix I, item 9).

(ii) For marketing permission, appropriate chemical and pharmaceutical data will be submitted. In case such a combination is not marketed anywhere in the world but these drugs are already in use concomitantly (not as an FDC but individually) for the said claim, marketing permission may be granted based on chemical and pharmaceutical data. Data showing the stability of the proposed dosage form will also have to be submitted.

(iii) For any other such FDCs, clinical trials may be required. For obtaining permission to carry out clinical trials with such FDCs a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (LD 50) and pharmacological data should be submitted on the individual ingredients as well as their combination in the proposed ratio.

(c) The third group of FDCs includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim. For such FDCs, the appropriate rationale including published reports (if any) should be submitted to obtain marketing permission. Permission will be granted depending upon the nature of the claim and data submitted.

(d) The fourth group of FDC includes those whose individual active ingredients (or drugs from the same class) have been widely used in a particular indication(s) for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience. It will have to be demonstrated that the proposed dosage form is stable and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.

No additional animal or human data are generally required for these FDCs, and marketing permission may be granted if the FDC has an acceptable rationale.

Appendix VII

UNDERTAKING BY THE INVESTIGATOR

1. Full name, address and title of the Principal Investigator (or Investigator(s) when there is no Principal Investigator).
2. Name and address of the medical college, hospital or other facility where the clinical trial will be conducted: Education, training & experience that qualify the Investigator for the clinical trial (Attach details including Medical Council registration number, and/or any other statement(s) of qualification(s)).
3. Name and address of all clinical laboratory facilities to be used in the study.
4. Name and address of the Ethics Committee that is responsible for approval and continuing review of the study.
5. Names of the other members of the research team (Co- or sub-Investigators) who will be assisting the Investigator in the conduct of the investigation (s).
6. Protocol Title and Study number (if any) of the clinical trial to be conducted by the Investigator.
7. Commitments:
   (i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary Ethics Committee and regulatory approvals have been obtained.
   (ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to the trial Subjects or when the change(s) involved are only logistical or administrative in nature.
   (iii) I agree to personally conduct and/or supervise the clinical trial at my site.

(iv) I agree to inform all Subjects, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and ethics committee review and approval specified in the GCP guidelines are met.

(v) I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory and GCP guidelines.

(vi) I have read and understood the information in the Investigator's brochure, including the potential risks and side effects of the drug.

(vii) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the trial.

(viii) I agree to maintain adequate and accurate records and to make those records available for audit/inspection by the Sponsor, Ethics Committee, Licensing Authority or their authorized representatives, in accordance with regulatory and GCP provisions. I will fully cooperate with any study related audit conducted by regulatory officials or authorized representatives of the Sponsor.

(ix) I agree to promptly report to the Ethics Committee all changes in the clinical trial activities and all unanticipated problems involving risks to human Subjects or others.

(x) I agree to inform all unexpected serious adverse events to the Sponsor as well as the Ethics Committee within seven days of their occurance.

(xi) I will maintain confidentiality of the identification of all participating study patients and assure security and confidentiality of study data.

(xii) I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical trials

8. Signature of Investigator with Date

Appendix VIII

ETHICS COMMITTEE

1. The number of persons in an Ethcis Committee should have atleast seven members. Ethics Committee should appoint, from among its members, a Chairperson (who is from outside the institution) and a Member Secretary. Other members should be a mix of medical/non-medical, scientific and non-scientific persons, including lay public, to reflect the different viewpoints.

For review of each protocol the quorum of Ethics Committee should be atleast 5 members with the following representations:

(a) basic medical scientists (preferably one pharmacologist).
(b) clinicians
(c) legal expert
(d) social scientist/representative of non-governmental voluntary agency/philosopher/ethicist/theologian or a similar person
(e) lay person from the community.

In any case, the ethics committee must include at least one member whose primary area of interest/specialization is nonscientific and at least one member who is independent of the institution/trial site. Besides, there should be appropriate gender representation on the Ethics Committee. If required, Subject experts may be invited to offer their views. Further, based on the requirement of research area, e.g. HIV AIDS, genetic disorders etc. specific patient groups may also be represented in the Ethics Committee as far as possible.

Only those Ethics Committee members who are independent of the clinical trial and the Sponsor of the trial should vote/provide opinion in matters related to the study.

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2. Format for Approval of Ethics Committee

To

Dr.

Dear Dr. _____

The Institutional Ethics Committee/Independent Ethics Committee (state name of the committee, as appropriate) reviewed and discussed your application to conduct the clinical trial entitled "……" on …….(date).

The following documents were reviewed

a. Trial Protocol (including protocol amendments), dated_____ Version no (s)._____

b. Patient Information Sheet and Informed Consent Form (including updates if any) in English and/or vernacular language.

c. Investigator's Brochure, dated_____, Version no._____

d. Proposed methods for patient accrual including advertisement (s) etc. proposed to be used for the purpose.

e. Principal Investigator's current CV.

f. Insurance Policy/Compensation for participation and for serious adverse events occurring during the study participation.

g. Investigator's Agreement with the Sponsor.

h. Investigator's Undertaking (Appendix VII).

The following members of the ethics committee were present at the meeting held on (date, time, place).

_____ Chairman of the Ethics Committee

_____ Member secretary of the Ethics Committee

_____ Name of each member with designation

We approve the trial to be conducted in its presented form.

The Institutional Ethics Committee/Independent Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

Yours sincerely,

Member Secretary, Ethics Committee.

Appendix IX

STABILITY TESTING OF NEW DRUGS

Stability testing is to be performed to provide evidence on how the quality of a drug substance or formulation varies with time under the influence of various environmental factors such as temperature, humidity and light, and to establish shelf life for the formulation and recommended storage conditions.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. In case of formulations the testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system).

Validated stability-indicating analytical procedures should be applied. For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance.

In general, a drug substance should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the length of studies chosen should be sufficient to cover storage, shipment and subsequent use.

Stress testing of the drug substance should be conducted to identify the likely degradation products, which in turn establish the degradation pathways, evaluate the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of formulation involved.

Stress testing may generally be carried out on a single batch of the drug substance. It should include the effect of temperatures), humidity where appropriate, oxidation, and photolysis on the drug substance.

Data should be provided for (a) Photostability on at least one primary batch of the drug substance as well as the formulation, as the

case may be and (b) the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.

Long-term testing should cover a minimum of 12 months' duration on at least three primary batches of the drug substance or the formulation at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Accelerated testing should cover a minimum of 6 months duration at the time of submission.

In case of drug substances, the batches should be manufactured to a minimum of pilot scale by the same synthetic route and using a method of manufacture that simulates the final process to be used for production batches. In case of formulations, two of the three batches should be at least pilot scale and the third one may be smaller. The manufacturing process(es) used for primary batches should simulate that to be applied to production batches and should provide products of the same quality and meeting the same specifications as that intended for marketing.

The stability studies for drug substances should be conducted either in the same container – closure system as proposed for storage and distribution or in a container – closure system that simulates the proposed final packaging. In case of formulations, the stability studies should be conducted in the final container – closure system proposed for marketing.

Stability Testing of new drug substances and formulations:

(i) Study conditions for drug substances and formulations intended to be stored under general conditions

Study	Study conditions	Duration of study
Long term	30°C ± 2°C/65% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

If at any time during 6 months' testing under the accelerated storage condition, such changes occur that cause the product to fail in complying with the prescribed standards, additional testing under an intermediate storage condition should be conducted and evaluated against significant change criteria.

(ii) Study conditions for drug substances and formulations intended to be stored in a refrigerator

Study	Study conditions	Duration of study
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

(iii) Study conditions for drug substances and formulations intended to be stored in a freezer

Study	Study conditions	Duration of study
Long term	– 20°C ± 5°C	12 months

(iv) Drug substances intended for storage below –20°C shall be treated on a case-by-case basis.

(v) Stability testing of the formulation after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period.

Appendix X

CONTENTS OF THE PROPOSED PROTOCOL FOR CONDUCTING CLINICAL TRIALS

1. **Title Page**
   a. Full title of the clinical study
   b. Protocol/Study number, and protocol version number with date
   c. The IND name/number of the investigational drug
   d. Complete name and address of the Sponsor and contract research organization if any
   e. List of the Investigators who are conducting the study, their respective institutional affiliations and site locations
   f. Name(s) of clinical laboratories and other departments and/or facilities participating in the study.

2. Table of Contents

A complete Table of Contents including a list of all Appendices.

1. Background and Introduction

a. Preclinical experience
b. Clinical experience

Previous clinical work with the new drug should be reviewed here and a description of how the current protocol extends existing data should be provided. If this is an entirely new indication, how this drug was considered for this should be discussed. Relevant information regarding pharmacological, toxicological and other biological properties of the drug/biologic/medical device, and previous efficacy and safety experience should be described.

2. **Study Rationale**

This section should describe a brief summary of the background information relevant to the study design and protocol methodology. The reasons for performing this study in the particular population included by the protocol should be provided.

3. Study Objective(s) (primary as well as secondray) and their logical relation to the study design.

3. Study Design

a. Overview of the Study Design: Including a description of the type of study (i.e., double-blind, multicentre, placebo controlled, etc.), a detail of the specific treatment groups and number of study Subjects in each group and investigative site, Subject number assignment, and the type, sequence and duration of study periods.
b. Flow chart of the study
c. A brief description of the methods and procedures to be used during the study.
d. Discussion of Study Design: This discussion details the rationale for the design chosen for this study.

5. Study Population: the number of Subjects required to be enrolled in the study at the investigative site and by all sites along with a brief

description of the nature of the Subject population required is also mentioned.

6. Subject Eligibility

a. Inclusion Criteria
b. Exclusion Criteria

7. Study Assessments – plan, procedures and methods to be described in detail

8. Study Conduct stating the types of study activities that would be included in this section would be: medical history, type of physical examination, blood or urine testing, electrocardiogram (ECG), diagnostic testing such as pulmonary function tests, symptom measurement, dispensation and retrieval of medication, Subject cohort assignment, adverse event review, etc.

Each visit should be described separately as Visit 1, Visit 2, etc.

Discontinued Subjects: Describes the circumstances for Subject withdrawal, dropouts, or other reasons for discontinuation of Subjects. State how drop outs would be managed and if they would be replaced

Describe the method of handling of protocol waivers, if any. The person(s) who approves all such waivers should be identified and the criteria used for specific waivers should be provided.

Describes how protocol violations will be treated, including conditions where the study will be terminated for non-compliance with the protocol.

9. Study Treatment

a. Dosing schedule (dose, frequency, and duration of the experimental treatment). Describe the administration of placebos and/or dummy medications if they are part of the treatment plan. If applicable, concomitant drug(s), their doses, frequency, and duration of concomitant treatment should be stated.
b. Study drug supplies and administration: A statement about who is going to provide the study medication and that the

investigational drug formulation has been manufactured following all regulations. Details of the product stability, storage requirements and dispensing requirements should be provided.

c. Dose modification for study drug toxicity: Rules for changing the dose or stopping the study drug should be provided.

d. Possible drug interactions

e. Concomitant therapy: The drugs that are permitted during the study and the conditions under which they may be used are detailed here. Describe the drugs that a Subject is not allowed to use during parts of or the entire study. If any washout periods for prohibited medications are needed prior to enrollment, these should be described here.

f. Blinding procedures: A detailed description of the blinding procedure if the study employs a blind on the Investigator and/or the Subject

g. Unblinding procedures: If the study is blinded, the circumstances in which unblinding may be done and the mechanism to be used for unblinding should be given

10. Adverse Events (See Appendix XI): Description of expected adverse events should be given.
Procedures used to evaluate an adverse event should be described.

11. Ethical Considerations: Give the summary of:

a. Risk/benefit assessment:

b. Ethics Committee review and communications

c. Informed consent process

d. Statement of Subject confidentiality including ownership of data and coding procedures

12. Study Monitoring and Supervision: A description of study monitoring policies and procedures should be provided along with the proposed frequency of site monitoring visits, and who is expected toperform monitoring.

Case Record Form (CRF) completion requirements, including who gets which copies of the forms and any specifics required in

filling out the forms CRF correction requirements, including who is authorized to make corrections on the CRF and how queries about study data are handled and how errors, if any, are to be corrected should be stated.

Investigator study files, including what needs to be stored following study completion should be described.

13. Investigational Product Management

    a. Give Investigational product description and packaging (stating all Ingredients and the formulation of the investigational drug and any placebos used in the study)
    b. The precise dosing required during the study
    c. Method of packaging, labeling, and blinding of study substances
    d. Method of assigning treatments to Subjects and the Subject identification code numbering system
    e. Storage conditions for study substances
    f. Investigational product accountability: Describe instructions for the receipt, storage, dispensation, and return of the investigational products to ensure a complete accounting of all investigational products received, dispensed, and returned/destroyed.
    g. Describe policy and procedure for handling unused investigational products.

14. Data Analysis

Provide details of the statistical approach to be followed including sample size, how the sample size was determined, including assumptions made in making this determination, efficacy endpoints (primary as well as secondary) and safety endpoints.

Statistical analysis: Give complete details of how the results will be analyzed and reported along with the description of statistical tests to be used to analyze the primary and secondary endpoints defined above. Describe the level of significance, statistical tests to be used, and the methods used for missing data; method of evaluation of the

data for treatment failures, non-compliance, and Subject withdrawals; rationale and conditions for any interim analysis if planned.

Describe statistical considerations for Pharmacokinetic (PK) analysis, if applicable.

15. Undertaking by the Investigator (see Appendix VII)

16. Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); CRF and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol.

Appendix XI

Data Elements for reporting serious adverse events occuring in a clinical trial

1. Patient Details

Initials & other relevant identifier (hospital/OPD record number etc.)*

Gender

Age and/or date of birth

Weight

Height

2. Suspected Drug(s)

Generic name of the drug*

Indication(s) for which suspect drug was prescribed or tested

Dosage form and strength

Daily dose and regimen (specify units – e.g., mg, ml, mg/kg)

Route of administration

Starting date and time of day

Stopping date and time, or duration of treatment

3. Other Treatment(s)

Provide the same information for concomitant drugs (including non prescription/OTC drugs) and non-drug therapies, as for the suspected drug(s).

4. Details of Suspected Adverse Drug Reaction(s)

Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the reaction.*

Start date (and time) of onset of reaction

Stop date (and time) or duration of reaction

Dechallenge and rechallenge information

Setting (e.g., hospital, out-patient clinic, home, nursing home)

5. Outcome

Information on recovery and any sequelae; results of specific tests and/or treatment that may have been conducted

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction; Any post-mortem findings.

Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc.

6. Details about the Investigator*

Name

Address

Telephone number

Profession (specialty)

Date of reporting the event to Licensing Authority:

Date of reporting the event to Ethics Committee overseeing the site:

Signature of the Investigator

Note: Information marked * must be provided."

(F.No. X-11014/1/2003-DMS & PFA)

(RITA TEOTIA),

Foot Note:- The Principal Rules were published in the Official Gazette vide notification No.F.28-10/-45-H(i), dated the 21st December, 1945 and last amended vide G.S.R. 810(E) dated 12.12.2004.

Appendix 5: Various forms for application for licensing

FORM 8

(See rule 24)

Application for license to import drugs (excluding those specified in Schedule X) to the Drugs and Cosmetics Rules, 1945

I/We* ..... (full address with telephone number, fax number and e-mail address) hereby apply for a license to import drugs specified below manufactured by M/s.....(full address with telephone no, fax and e-mail no.).

2. Names of the drugs to be imported:

(1)

(2)

(3)

3. I/We* ..... enclose herewith an undertaking in Form 9 dated ……signed by the manufacturer as required by rule 24 of the Drugs and Cosmetics Rules, 1945.

4. I/We* ..... enclose herewith a copy of Registration Certificate concerning the drugs to be imported in India, issued under Form 41 of the rules, vide Registration Certificate No.....dated ..... issued through M/s..... (name and full address).....valid up to.....

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5 I/We*..... hold a valid wholesale license for sale or distribution of drugs or valid license to manufacture drugs, under the provisions of the Act and rules made thereunder. A copy of the said license is enclosed.

6. A fee of.....has been credited to Government under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines" under the Drugs and Cosmetics Rules, 1945 – Central vide Challan No..... dated..... (attached in original)

Signature.....

Name.....

Designation.....

Seal/Stamp of Manufacturer's agent in India.

Place: .....

Date: .....

*Delete whichever is not applicable.

FORM 8A

(See rule 24)
Application for license to import drugs specified in Schedule X to the Drugs and Cosmetics Rules, 1945

I/We* .....(full address with telephone number, fax number and e-mail address) hereby apply for a license to import drugs specified below manufactured by M/s..... (full address with telephone no, fax and e-mail no.).

2. Name of the drugs to be imported:

(1)

(2)

(3)

3. I/We* .....enclose herewith an undertaking in Form 9 dated……signed by the manufacturer as required by rule 24 of the Drugs and Cosmetics Rules, 1945.

4. I/We* .....enclose herewith a copy of Registration Certificate concerning the drugs to be imported in India, issued under Form 41 of the rules, vide Registration Certificate No dated issued through M/s..... (name and full address) ..... valid upto……

5. I/We* .....hold a valid wholesale license for sale or distribution of drug or license to manufacture drugs, under the provisions of the Act and rules made thereunder. A copy of the said license is enclosed.

6. A fee of.....has been credited to Government under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines" under the Drugs and Cosmetics Rules 1945 – Central vide Challan No..... dated ..... (attached in original).

Signature.....

Name.....

Designation.....

Seal/Stamp of Manufacturer's agent in India.]

Place: .....

Date: .....

*Delete whichever is not applicable.

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FORM 9

(See rule 24)
Form of undertaking to accompany an application for an import license

Whereas ..... of..... intends to apply for a license under the Drugs and Cosmetics Rules, 1945, for the import into India, of the drugs specified below manufactured by us, we……of……..hereby give this undertaking that for the duration of the said license—

(1) the said applicant shall be our agent for the import of drugs into India;

(2) we shall comply with the conditions imposed on a license by rules 74 and 78 of the Drugs and Cosmetics Rules, 1945;

(3) we declare that we are carrying on the manufacture of the drugs mentioned in this undertaking at the premises specified below, and we shall from time to time report any change of premises on which manufacture will be carried on and in cases where manufacture is carried on in more than one factory any change in the distribution of functions between the factories;

(4) we shall comply with the provisions of Part IX of the Drugs and Cosmetics Rules;

(5) every drug manufactured by us for import under license into India shall as regards strength, quality and purity conform with the provisions of Chapter III of the Drugs and Cosmetics Act, 1940, and the Drugs and Cosmetics Rules, 1945;

(6) we shall comply with such further requirements, if any, as may be specified by Rules, by the Central Government under the Act and of which the licensing authority has given to the licensee not less than four months' notice.

Names of drugs and classes of drugs

Particulars of premises where manufacture is carried on.

Date.....

[Signature, Name, Designation Seal/Stamp of manufacturer or on behalf of the manufacturer.]

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FORM 10

(See rules 23 and 27)
License to import drugs (excluding those specified in Schedule X)
to the Drugs and Cosmetic Rules, 1945

License Number..... Date.....

.....
(Name and full address of the importer)
is hereby licensed to import into India during the period for which the license is in force, the drugs specified below, manufactured by M/s..... (name and full address) and any other drugs manufactured by the said manufacturer as may from time to time be endorsed on this license.

2. This license shall be in force from ..... to ..... unless it is sooner suspended or cancelled under the said rules.

3. Names of drugs to be imported.

Place: …….

Date: …….

Licensing Authority
Seal/Stamp

* Delete whichever is not applicable.

Conditions of License.

1. A photocopy of license shall be displayed in a prominent place in a part of the premises, and the original license shall be produced, whenever required.

2. Each batch of drug imported into India shall be accompanied with a detailed batch test report and a batch release certificate, duly signed and authenticated by the manufacturer with date of testing, date of release and the date of forwarding such reports. The imported batch of each drug shall be subjected to examination and testing as the licensing authority deems fit prior to its marketing.

3. The licensee shall be responsible for the business activities of the manufacturer in India along with the registration holder and his authorised agent.

4. The licensee shall inform the licensing authority forthwith in writing in the event of any change in the constitution of the firm operating under the license. Where any change in the constitution of the firm takes place, the current license shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh license has been taken from the licensing authority in the name of the firm with the changed constitution.

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FORM 10A

(See rules 23 and 27)
License to import drugs specified in Schedule X to the Drugs and Cosmetics Rules, 1945

License Number..... Date…….

.....
(Name and full address of the importer) is hereby licensed to import into India during the period for which the license is in force, the drugs specified below, manufactured by M/s..... (name and full address) and any other drugs manufactured by the said manufacturer as may from time to time be endorsed on this license.

2. This license shall be in force from..... to.....unless it is sooner suspended or cancelled under the said rules.

3. Names of drugs to be imported.

Place: .....

Date: .....

Licensing Authority
Seal/Stamp.

*Delete whichever is not applicable.

Conditions of License

1. A photocopy of license shall be displayed in a prominent place in a part of the premises, and the original license shall be produced, whenever required.

2. Each batch of drug imported into India shall be accompanied with a detailed batch test report and a batch release certificate, duly signed and authenticated by the manufacturer with date of testing, date of release and the date of forwarding such reports. The imported batch of each drug shall be subjected to examination and testing as the licensing authority deems fit prior to its marketing.

3. The licensee shall be responsible for the business activities of the manufacturer in India along with the registration holder and his authorised agent.

4. The licensee shall inform the licensing authority forthwith in writing in the event of any change in the constitution of the firm operating under the license. Where any change in the constitution of the firm takes place, the current license shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh license has been taken from the licensing authority in the name of the firm with the changed constitution.

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FORM 11

(See rule 33)
License to import drugs for the purposes of examination, test or analysis

1 ……of.....is hereby licensed to import from .....the drugs specified below for the purposes of examination, test or analysis at .....or in such other places as the licensing authority may from time to time authorise.

2. This license is subject to the conditions prescribed in the Rules under the Drugs and Cosmetics Act, 1940.

3. This license shall, unless previously suspended or revoked, be in force for a period of one year from the date specified below:–

Names of drugs Quantities which may be imported

Date.....

Licensing Authority

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FORM 12

(See rule 34)
Application for license to import drugs for purpose of examination, test or analysis

I,... .....(Full Name) resident of ..... (Full Address) by occupation..... hereby apply for a license to import the drugs specified below for the purposes of examination, test or analysis at..... (Name and address, where test/analysis is to be carried out) from..... .....(Name and address, from where the medical devices are to be imported) and I undertake to comply with the conditions applicable to the license.

A fee of rupees..... has been credited to Government under the head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines" under the Drugs and Cosmetics Rules, 1945—Central vide Challan No.....dated..... (attached in original).

Names of Drugs and classes of Medical Devices: Quantities:

1.

2.

Date..... Signature.....

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FORM 40

(*See* rule 24-A)

Application for issue of Registration Certificate for import of drugs into India under the Drugs and Cosmetics Rules 1945

I/We*_____ _____ (Name and full address) hereby apply for the grant of Registration Certificate for the manufacturer, M/s. _____ (full address with telephone, fax and E-mail address of the foreign manufacturer) for his premises, and manufactured drugs meant for import into India.

1. Names of drugs for registration.

2. I/We enclose herewith the information and undertakings specified in Schedule D (1) and Schedule D(II) duly signed by the manufacturer for grant of Registration Certificate for the premises stated below.

3. A fee of _____for registration of premises, the particulars of which are given below, of the manufacturer has been credited to the Government under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines" under the Drugs and Cosmetics Rules, 1945-Central *vide* Challan No._____ dated_____(attached in original).

4. A fee of _____for registration of the drugs for import as specified at Serial No. 2 above has been credited to the Government under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines" under the Drugs and Cosmetics Rules, 1945-Central vide Challan No._____, dated_____. (attached in original).

5. Particulars of premises to be registered where manufacture is carried on:

Address (es)_____

Telephone No._____ Fax_____ _

E-mail_____

I/We* undertake to comply with all terms and conditions required to obtain Registration Certificate and to keep it valid during its validity period.

Place: _____

Date: _____

*Signature*_____

*Name*_____

*Designation*_____

Seal/Stamp of manufacturer or his authorised Agent in India.

(**Note:** In case the applicant is an authorised agent of the manufacturer in India, the Power of Attorney is to be enclosed).

FORM 41

(*See* rule 27 A)
Registration Certificate
Registration Certificate to be issued for import of drugs into India under Drugs and Cosmetics Rules, 1945

Registration Certificate No._____ Date_____
M/s _____ (Name and full address of registered office) having factory premises at full address) has been registered under rule 27-A as a manufacturer and is hereby issued this Registration Certificate.

2. Name (s) of drugs which may be imported under this Registration Certificate:

3. This Registration Certificate shall be in force from _____ to_____unless it is sooner suspended or cancelled under the rules.

4. This Registration Certificate is issued through the office of the manufacturer or his authorised agent in India M/s (name and full address)_____ who will be responsible for the business activities of the manufacturer, in India in all respects.

5. This Registration Certificate is subject to the conditions, stated below and to such other conditions as may be specified in the Act and the rules, from time to time.

Place:_____

Date: _____ *Licensing Authority*

Seal/Stamp

Conditions of the Registration Certificate

1. The Registration Certificate shall be displayed at a prominent place by the authorised agent.

2. No drug shall be registered unless it has a free sale approval in the country of origin, and/or in other major countries.

3. The manufacturer or his authorised agent in India shall comply with the conditions of the import license issued under the Drugs and Cosmetics Rules, 1945.

4. The manufacturer or his authorised agent in India shall inform the licensing authority forthwith in the event of any administrative action taken due to adverse reaction, viz. market withdrawal, regulatory restrictions, or cancellation of authorization, and/or not of standard quality report of any drug pertaining to this Registration Certificate declared by the Regulatory Authority of the country of origin or by any Regulatory Authority of any other country, where the drug is marketed/sold or distributed.

The dispatch and marketing of the drug in such cases shall be stopped immediately, and the licensing authority shall be informed immediately. Further action in respect of such stopped marketing of drug shall be followed as per the direction of the licensing authority. In such cases, action equivalent to that taken with reference to the concerned drug in the country of origin or in the country of marketing shall be followed in India also, in consultation with the licensing authority. The licensing authority may, however, direct any further modification to this course of action, including the withdrawal of the drug from Indian market within 48 hours time period.

5. The manufacturer or his authorised agent in India shall inform the licensing authority within 30 days in writing in the event of any change in manufacturing process, or in packaging, or in labelling or in testing, or in documentation of any of the drugs pertaining to this Registration Certificate.

In such cases, where there shall be any major change/modification in manufacturing, or in processing or in testing, or in documentation as the case may be, at the discretion of the licensing authority, the manufacturer or his authorised agent in India shall obtain necessary approval within 30 days by submitting a separate application along with the registration fee, as specified in clause (ii) of sub-rule (3) of rule 24-A.

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6. The manufacturer or his authorised agent in India shall inform the licensing authority immediately in writing in the event of any change in the constitution of the firm and / or address of the registered office/ factory premises operating under this Registration Certificate. Where any such change in the constitution of the firm and/or address takes place, the current Registration Certificate shall be deemed to be valid for a maximum period of three months from the date on which the change has taken place unless, in the meantime, a fresh Registration Certificate has been taken from the licensing authority in the name of the firm with the changed constitution of the firm and/or changed address of the registered office or factory premises.

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FORM 44

(See rules 122A, 122B, 122D and 122 DA)

Application for grant of permission to import or manufacture a New Drug or to undertake clinical trial.

I/We*…… of M/s.....…….. (address) hereby apply for grant of permission for import of and/or clinical trial or for approval to manufacture a new drug or fixed dose combination or subsequent permission for already approved new drug. The necessary information / data is given below:

1. Particulars of new drug:

(1) Name of the drug.

(2) Dosage form.

(3) Composition of the formulation :

(4) Test specification. (i) active ingredients. (ii) inactive ingredients.

(5) Pharmacological classification of the drug.

(6) Indications for which proposed to be used.

(7) Manufacturer of the raw material (bulk drug substances).

(8) Patent status of the drug.

2. Data submitted along with the application (as per Schedule Y with indexing and page numbers:)

A. Permission to market a new drug:

(1) Chemical and Pharmaceutical information.

(2) Animal Pharmacology.

(3) Animal Toxicology.

(4) Human / Clinical Pharmacology (Phase I).

(5) Exploratory Clinical Trials (Phase II).

(6) Confirmatory Clinical Trials (Phase III) (including published review articles)

(7) Bio-availability, dissolution and stability study data.

(8) Regulatory status in other countries.

(9) Marketing information:

(a) Proposed product monograph.

(b) Drafts of labels and cartons.

(10) Application for test license.

B. Subsequent approval / permission for manufacture of already approved new drug:

(a) Formulation:

(1) Bio-availability / bio-equivalence protocol.

(2) Name of the investigator/center.

(3) Source of raw material (bulk drug substances) and stability study data.

(b) Raw material (bulk drug substances):

(1) Manufacturing method.

(2) Quality control parameters and/or analytical specification, stability report.

(3) Animal toxicity data.

(C) Approval / Permission for fixed dose combination:

(1) Therapeutic Justification.(authentic literature in pre-reviewed journals/text books)

(2) Data on pharmacokinetics/pharmacodynamics combination.

(3) Any other data generated by the applicant on the safety and efficacy of the combination.

(D) Subsequent Approval or approval for new indication – new dosage form:

(1) Number and date of Approval / permission already granted.

(2) Therapeutic justification for new claim / modified dosage form

(3) Data generated on safety, efficacy and quality parameters.

A total fee of rupees.....(in words)..... has been credited to the Government under the Head of Account .....(Photocopy of receipt is enclosed).

Dated:..... Signature…….....

Designation…….

Note: *Delete whichever is not applicable.

FORM 45

(See rules 122 A, 122 D and 122 DA)
Permission to import Finished Formulation of the New Drug

Number of the permission and date of issue……
M/s.....of……
(address) is hereby permitted to import the following new drug formulation under rule 122 A /122 D/122 DA of the Drugs and Cosmetics Rules, 1945.

(1) Name of the New Drug:

(2) Dosage form:

(3) Composition:

(4) Indications:

Dated: ..... Signature.....

Name and designation of Licensing Authority

Conditions for Grant of Approval/Permission

(1) The formulation shall conform to the specifications approved by the Licensing Authority.

(2) The proper name of the drug shall be printed or written in indelible ink and shall appear in a more conspicuous manner than the trade name, if any, which shall be shown immediately after or under the proper name on the label of the innermost container of the drug or every other covering in which the container is packed.

(3) The label of the innermost container of the drug and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which shall not be less than 1 mm in width and without disturbing the other conditions printed on the label to depict it as prescription drug.

(4) The label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:

"WARNING: To be sold by retail on the prescription of a ..... Only."

(5) Post marketing surveillance study shall be conducted during initial period of two years of marketing of the new drug formulation, after getting the protocol and the names of the investigator duly approved by the Licensing Authority.

(6) All reported adverse reactions related to the drug shall be intimated to the Drugs Controller, India and Licensing Authority and regulatory action resulting from their review should be complied with.

(7) No claims except those mentioned above shall be made for the drug without the prior approval of the Licensing Authority.

(8) Specimen of the carton, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Licensing Authority before the drugs is marketed.

(9) Each consignment of imported drug shall be accompanied by a test/analysis report.

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FORM 45A

(See rules 122 A and 122 DA)
Permission to import raw material (new bulk drug substance)

Number of the permission and date of issue……
M/s.....of…..……
(address) is hereby permitted to import the following raw material (new bulk drug substances) under rule 122 A / 122DA of the Drugs and Cosmetics Rules, 1945, namely :-

Name of the raw material (new bulk drug substances):

(1).....

(2) .....

(3).....

Dated ..... Signature.....

Name and Designation of the Licensing Authority……

Conditions for Grant of Approval/Permission

(1) The raw material (new bulk drug substance) shall conform to the test specifications as approved by the Licensing Authority.

(2) For manufacture of raw material (new bulk drug substance) or its formulation in the country, separate approval under rule 122-B shall be obtained from the Licensing Authority.

(3) The permission to import shall not be used to convey or imply that the raw material (new bulk drug) is categorized as "life saving or essential drug."

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FORM 46

(See rules 122 B, 122 D and 122 DA)
Permission / Approval for manufacture of new drug formulation

Number of permission and date of issue.....
M/s of ..... (address) is hereby granted Permission/Approval to manufacture following new drug formulation under rule 122B/122D/122DA of the Drugs and Cosmetics Rules, 1945, namely:-

(1) Name of the formulation:

(2) Dosage form:

(3) Composition:

(4) Indications:

Dated .....

Signature.....

Name and designation of Licensing Athority.....

Conditions for Grant of Approval / Permission

(1) The formulation shall conform to the specifications approved by the Licensing Authority.

(2) The proper name of the drug shall be printed or written in indelible ink and shall appear in a more conspicuous manner than the trade name, if any, which shall be shown immediately after or under the proper name on the label of he innermost container of the drug or every other covering in which the container is packed.

(3) The label of the innermost container of the drug and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which shall not be less than 1 mm in width and without disturbing the other conditions printed on the label to depict it as prescription drug.

(4) The label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:

"WARNING: To be sold by retail on the prescription of a .....only."

(5) Post marketing surveillance study shall be conducted during initial period of two years of marketing of the new drug formulation, after getting the protocol and the names of the investigator duly approved by the Licensing Authority.

(6) All reported adverse reactions related to the drug shall be intimated to the Drugs Controller, India and Licensing Authority and regulatory action resulting from their review should be complied with.

(7) No claims except those mentioned above shall be made for the drug without the prior approval of the Licensing Authority.

(8) Specimen of the carton, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Licensing Authority before the drug is marketed.

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FORM 46A

(See rules 122 B and 122 DA)
Permission/Approval for manufacture of raw material (new bulk drug substance)

Name of the permission/ approval and date of issue.....
M/s.....of.....
(address) is hereby granted Permission/Approval to manufacture the following raw material (new bulk drug substance) under rule 122 B/122 DA of the Drugs and Cosmetics Rules, 1945.

Name of the raw material (new bulk drug substance)

(1) .....

(2) .....

(3) .....

Dated..... Signature.....

Name and designation of Licensing Authority.

Conditions for Grant of Permission /Approval

(1) The raw material (new bulk drug substance) shall conform to the specifications approved by the Licensing Authority.

(2) The raw material (new bulk drug substance) can be sold to only those manufacturers who have permission, in writing, from Licensing Authority, either to use the drug for development purpose/clinical trial-bio-equivalence study or to manufacture the formulation.

(3) For manufacture of the formulation in the country, separate approval under rule 122-B shall be obtained from the Licensing Authority.

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FORM 24

(See rule 69)

Application for the grant of or renewal of a license to manufacture for sale or for distribution of drugs other than those specified in Schedules C and C (1) and X

1. I/We .....of..... hereby apply for the grant / renewal of a license to manufacture on the premises situated at ..... the following drugs being drugs other than those specified in Schedules C and C (1) and X of the Drugs and Cosmetics Rules, 1945.

2. Names of drugs categorized according to Schedule M.

3. Names, qualifications and experience of technical staff employed for manufacture and testing.

4. A fee of rupees ..... has been credited to Government under the head of account..... .....

Date..... Signature.....

Note: The application should be accompanied by a plan of the premises.

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FORM 24A

(See rule 69A)

Application for grant or renewal of a loan license to manufacture for sale or for distribution of drugs other than those specified in Schedules C and C (I) and X

1.I/ We*.....of# ....hereby apply for the grant / renewal of a loan license to manufacture on the premises situated at..... ..... C/o§ ..... the under-mentioned drugs, other than those specified in Schedules C and C (1) and X to the Drugs and Cosmetics Rules.

Names of drugs (each substance to be separately specified).

2. The names, qualifications and experience of the expert staff actually connected with the manufacture and testing of the specified products in manufacturing premises.

3. I/We enclose–

(a) A true copy of a letter from me/us to the manufacturing concern whose manufacturing capacity is intended to be utilized by me/us.

(b) A true copy of a letter from the manufacturing concern that they agree to lend the services of their expert staff, equipment and premises for the manufacture of each item required by me/us and that they will analyse every batch of finished product and maintain the registers of raw materials, finished products and reports of analysis separately in this behalf.

(c) Specimens of labels, cartons of the products proposed to be manufactured.

4. A fee of rupees ..... has been credited to Government under the head of account .....

Date.....

Signature.....……

* Enter here the name of the proprietor, partners of Managing Director as the case may be.

#Enter here the name of the applicant firm and the address of the principal place of business.

§ Enter here the name and address of the manufacturing concern where the manufacture will be actually carried out and also the License number under which the latter operates.

FORM 24B

(See rule 69)

Application for grant or renewal of license to repack for sale or distribution of drugs, being drugs other than those specified in Schedules C and C (1) excluding those specified in Schedule X

1. I/We ……of……. hereby apply for grant/renewal of a license to repack the following drugs at the premises situated at……...

2. Names of the drugs to be repacked.....
.....……

3. Name, qualification and experience of competent staff.....
.....

4. A fee of rupees ……..…… has been credited to Government under the head of account.....……
…….

Date.....

Signature of applicant……..

NOTE:- The application shall be accompanied by a plan of the premises.

FORM 25

(See rule 70)

License to manufacture for sale or for distribution of drugs other than those specified in Schedules C and C(1) and X

Number of License and date of issue.....

1.....is hereby licensed to manufacture the following categories of drugs being drugs other than those specified in Schedules C and C (1) and X to the Drugs and Cosmetics Rules, 1945, on the premises situated at .....under the direction and supervision of the following competent technical staff:

(a) Competent technical staff. (Names)……..……

(b) Names of Drugs (each item to be separately specified) .....……

2. The license authorises the sale by way of wholesale dealing and storage for sale by the licensee of the drugs manufactured under the license, subject to the conditions applicable to license for sale.

3. The license shall be in force from..... to.....

4. The license is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date.....

Signature.....

Designation.....

*Licensing Authority _____

*Central License Appoving Authority.

*Delete whichever is not applicable.

Conditions of License

1. This license and any certificate of renewal in force shall be kept on the approved premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. Any change in the expert staff named in the license shall be forthwith reported to the Licensing Authority.

3. If the licensee wants to manufacture for sale additional items of drugs not included above he should apply to the Licensing Authority for the necessary endorsement as provided in Rule 69(5). This license will be deemed to extend to the categories so endorsed.

4. The licensee shall inform the Licensing Authority in writing in the event of any change in the constitution of the firm operating under the license. Where any change in the constitution of the firm takes place, the current license shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh license has been taken from the Licensing Authority in the name of the firm with the changed constitution.

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FORM 25A

(See rule 70A)

Loan license to manufacture for sale or for distribution of drugs other than those specified in Schedules C and C (1) and X

1. Number of license and date of issue.....

2.....of.....is hereby granted a loan license to manufacture the following drugs other than those specified in Schedules C and C(1) and X to the Drugs and Cosmetics Rules, 1945, on the premises situated at C/o under the direction and supervision of the following competent technical staff:

(a) competent technical staff. (Names):.....

(c) Names of drugs.....

3. The license authorises the sale by way of wholesale dealing and storage for sale by the licensee of the drugs manufactured under the license subject to the conditions applicable to licenses for sale.

4. The license is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date..... Signature.....

Designation.....

Conditions of License

1. This license and any certificate of renewal in force shall be kept on the approved premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. Any change in the competent technical staff named in the license shall be forthwith reported to the Licensing Authority.

3. If the licensee wants to undertake during the currency of the license the manufacture for of sale additional drugs he should apply to the Licensing Authority for the necessary endorsement to the license as provided in Rule 69-A. This license will be deemed to extend to the drugs so endorsed.

4. The licensee shall inform the Licensing Authority in writing in the event of any change in the constitution of the firm operating under the license. Where any change in the constitution of the firm takes place, the current license shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh license has been taken from the Licensing Authority in the name of the firm with the changed constitution.

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FORM 25B

(See rule 70)

License to repack for sale or distribution of drugs being drugs other than those specified in Schedules C and C (1) excluding those specified in Schedule X

Number of license and date of issue.

1. …….. .....of.....is hereby granted a license to repack the following drugs for sale or distribution on the premises situated at.....under the supervision of the following competent staff.

(a) Names of drugs to be repacked.

(b) Names of competent staff.

2. The license shall be in force from.....to.....

3. The license authorises the sale by way of wholesale dealing by the licensee and storage for sale by the licensee of the drugs repacked under the license subject to conditions applicable to licenses for sale.

4. The license is subject to the conditions stated below and to such other conditions as may be specified in the Rules for the time being in force under the Drugs and Cosmetics Act, 1940.

Date.....

Signature.....

Conditions of License

1. This license and any certificate of renewal in force shall be kept on the approved premises and shall be produced at the request of an Inspector appointed under the Drugs and Cosmetics Act, 1940.

2. Any change in the expert staff named in the license shall be forthwith reported to the Licensing Authority.

3. If the licensee wants to repack for sale or distribution additional items he should apply to the Licensing Authority for the necessary endorsement to this license. This license will be deemed to extend to only those items so endorsed.

4. The drugs repacked under this license shall bear on their label, apart from other particulars required by these Rules, the name and address of the licensee and the number of the license under which the drug is repacked preceded by the words "Rpg. Lic. No.".

5. The licensee shall inform the Licensing Authority in writing in the event of any change in the constitution of the firm operating under the license. Where any change in the constitution of the firm takes place, the current license shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh license has been taken from the Licensing Authority in the name of the firm with the changed constitution.

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