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Pharmaceutical Supply Chains—Medicines Shortages

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Pharmaceutical Supply Chains—Medicines Shortages

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Foreword

"Medicines shortages." Two words representing a severe problem across the globe, even in the most developed healthcare systems and top-quality industry. Something that one would not expect in the twenty-first century, when we see an accelerating development of modern technologies, modern medicine (and the science of drug development) being closer and closer to the molecular essence of diseases, giving birth to neologisms such as "omics". But first of all, it gives hope to patients that did not have any in not so distant past.

Despite all this progress, lately, we are experiencing medicines shortages more and more frequently. I, as hospital pharmacist from Central European country, which used to be an unwilling part of the former Eastern bloc, do remember anecdotal stories told by my older colleagues or by my mother, a paediatrician, describing how often even the essential drugs, such as aminopenicillins or ibuprofen, were missing for weeks or barely available, due to monopolized and (poorly) planned production of pharmaceuticals. What seemed to be just an echo from the past during the substantial part of my professional career, now have returned with the same urgency, despite the open competition between pharmaceutical companies. We missed aminopenicillins back in the 80s, and now we did not have carbapenems for our patients. During the last December, there was no digoxin available in the whole country, and the list goes on. And that is just one country. The time and circumstances have changed, and the problem is back. Some of the reasons for the medicines' shortages may be similar, such as monopolization of the active substances production; the others are different. While the causes are multifactorial, the impact on the patients is the same, having many possible implications from the delay of the treatment, the need to substitute a missing medicine, to stopping the therapy. European Association of the Hospital Pharmacists conducted surveys focused on the problem in Europe in 2014 and 2018, and the results are disturbing. They show that almost every hospital pharmacist who responded to the survey struggled with the shortages, more of two-thirds of them at least once weekly. It is important to raise awareness of the problem because even though hospital pharmacists solve a lot of shortages by

themselves, they spend a lot of time and energy by that they could use on other valuable activities improving patients' outcomes.

For all the reasons mentioned above, the more profound knowledge of the possible causes and solutions of the complex problem of the medicines' shortages is very much needed. Although medicines shortages are becoming often spelt, one would even say buzzword in the pharmacy community, and now even beyond it, there is an apparent lack of reliable resources studying the issue.

I am delighted that the interested readership will now find an excellent summary of multiple perspectives and much information about the causes of the shortages, case studies and proposed solutions to the problem in this book. It studies the pharmaceutical supply chain in its whole complexity, discusses the shortages from the most important (read patients') perspective, discusses the economic, regulatory and manufacturing challenges. It addresses the impact of shortages on the daily practice of hospital pharmacists. Moreover, it also proposes solutions based on the involvement of various stakeholders, seeking for concepts from both historical context and advanced cloud computing and data processing by most potent computer technology to assist in finding a treatment for the ill medicines supply chain.

At this place, I must congratulate the authors, who, with the support of COST Action 15105, created an exceptional contribution to the solving of the worldwide medicines' shortages problem.

Enjoy the reading!

Brussels, Belgium

Petr Horák
President of the European Association
of Hospital Pharmacists

Preface

Since the 90s, when mergers of multinational researching industries became a current objective of optimization of return on investments, medicines shortages have become a global phenomenon endangering patients' outcomes. The speed of quantitative increase is frightening as numbers have doubled within 12 months since summer 2017 and triples since 3 years.

This book "Pharmaceutical Supply Chains—Medicines Shortages" presents a set of research results discussed in two training schools organized within the COST Action European Medicines Shortages Research Network—addressing supply problems to patients, "Medicines Shortages" (CA15105). This COST action aims at contributing significantly to a qualitative and quantitative improvement of the availability of medicines (including drugs, medical devices, foodstuff for special medical purposes, nutriceuticals) as well as to a decrease in the number of shortages.

The first training school occurred at Instituto Superior Técnico, Lisbon and was a first introduction to drugs shortages and disruptions of pharmaceutical Supply Chain (SC), while discussing how these could be minimized through the development of an integrated SC using modelling, optimization and data science tools. The second training school occurred at Instituto Politécnico de Portalegre, Portalegre where the same topics were explored and more advanced tools explored.

This book presents perspectives of main pharmaceutical stakeholders, broadening from the industry supplies to the impact on patients and healthcare systems, the decision-making in the international and European contexts. Considering that the transdisciplinary cooperation is crucial to mitigate the impacts of drugs shortages, the book and the contributed chapters are associated with the homonymous training schools, allowing a better understanding of the challenges and opportunities within "Medicines Shortages".

In Chapter "The European Medicines Shortages Research Network and Its Mission to Strategically Debug Disrupted Pharmaceutical Supply Chains", Jenzer et al. addressed the "European Medicines Shortages Research Network" and its mission to strategically debug disrupted pharmaceutical SC. It was the declared aim to attain a constructive agreement on adequate next steps of all key players, as well

as to reveal any restrictive legal and economic frames, erroneous incentives along the SC, conflicts of interest, and an unfavourable overall cost–benefit ratio. For this purpose, all key players along the SC would have to assume their responsibility for an undisrupted medicines flow. The approach to reach this objective is to negotiate with stakeholders at a round table. In terms of responsibility, each key player should contribute at his best to reduce induced costs to health systems, to reduce risks to patients and to reduce diversion of healthcare professional time.

The design and planning of sustainable vaccine SC is presented by Carvalho, Ribeiro, and Barbosa-Povoa in Chapter "Design and Planning of Sustainable Vaccine Supply Chain". The three dimensions of the Triple Bottom Line (economic, environmental and social) are modelled considering a multi-objective approach with the maximization of the net present value, minimization of environmental impacts and maximization of social impacts. The model is applied to a representative European case study, and the outcomes clearly show how strategic and tactical decision-making impacts on the key performance indicators. By the results, the authors remarked the trade-offs between the sustainability dimensions, as well as the importance of the multi-objective approach to find feasible and sustainable solutions.

In Chapter "Drug Shortages and Their Impact on Patients and Health Care Systems—How Can Systemic and Organizational Frameworks Help to Prevent or Mitigate Them?", Truong, Rothe, and Bochenek presented the impact of drug shortages on patients and on healthcare systems, and also questioned how the systemic and organizational frameworks can help to prevent or mitigate shortages. The authors discussed the multiple dimensions of the shortages impact and included a non-systematic review of literature and information from selected stakeholders. They confirmed that drug shortages are negatively impacting the treatment outcomes, the quality and efficiency of patient care, as well as they pose organizational, managerial and financial burdens.

Ziemele reported about the hemophilia-A case in Latvia through the patient perspective in Chapter "Patient Perspective: Reporting on Medicines Shortages—Hemophilia a Case in Latvia". Due to the austerity measures and their impact in the reimbursement system, the coagulation factor concentrates were moved to a reference list, meaning that only the cheapest treatments included in the reimbursement system were to be paid. Patients continued to receive special prescriptions in line with Baltic Hemophilia guidelines, and they were instructed to report shortages to the Latvian Hemophilia Society, which then reported the shortages to Health Inspection. The reimbursement system did not react to shortages and it continued to function without patients' involvement, that is., with processes only between the paying authority, industry, wholesalers, pharmacies and medical doctors.

In Chapter "Shortages of Medicines Originating from Manufacturing", Battistini presented the key issues related with the shortages of medicines originating from manufacturing. Considering the entire set of activities from the materials procurement until the delivery of finished products, either to the hospitals or the intermediate distributors/wholesalers, the author detailed the different factors that may be the source of shortages. The risk factors were analysed and the management of emergency situations is addressed too, namely, the supply of critical medicines.

Battistini has a significant experience in the pharmaceutical field, and he highlighted the practical aspects of the risk analysis/containment for the shortages originating from manufacturing.

In Chapter "Risk Mitigation and Preventing Medicines Shortages", Roque, Miranda, and Féher-Polgar outlined and discussed the risk mitigation and the prevention of medicines shortages within AbbVie, a global pharmaceutical company. The key factors for risk mitigation were introduced, while both the management of external risks and the management of product supply risks were focused. At AbbVie, the Sales and Operations Planning and demand forecasting are jointly addressed, and the global processes are treated all together too. Then, the customer satisfaction, the operational excellence and the assurance of supply during a 3-year period are presented as the key performance indicators for the AbbVie successful strategy on preventing shortages.

Ward and Hargaden described an exploratory assessment of risk and resilience in pharmaceutical SC, in Chapter "An Exploratory Assessment of Risk and Resilience in Pharmaceutical Supply Chains". Survey data was collected from a number of managers using the Supply Chain Risk Assessment Method, and the findings suggested a number of areas in which pharmaceutical SC is requiring more resilience, namely, flexibility in sourcing, flexibility in order fulfilment, and visibility and collaboration.

In Chapter "Review of Pharmaceutical Sea Freight and Malaysian Third-Party Logistics Service Providers—A Supply Chain Perspective", Wong and Soh presented a review on the pharmaceutical sea freight and third-party logistics service providers in Malaysia. The authors reviewed pharmaceutical ocean logistics trends and issues, and selected four research publications on the Malaysian third-party logistics aiming at the service quality, the cost and service differentiation, the SC integration of depot and hauliers, and the information systems freight. Based on the logistics service quality and noting the agility and robustness of logistics providers, Wong and Soh indicated that medicine shortages attributed to freight forwarders are unlikely in this country of Southeast Asia.

The needs and barriers within the Hospital Pharmacy are presented by Batista, Miranda, and Teixeira in Chapter "The Needs and Barriers Within the Supply Chain Actors—Hospital Pharmacy Needs". The roles and daily practice of a hospital pharmacist were revisited, while the needs, outcomes and prevalence related with medicines shortages were discussed. Shortages directly increase costs for health systems, but also occur invisible costs such as time spent on solving the shortages, changes in management procedures and additional risks to patients. Then, the in-depth collaboration with health professionals, with pharmaceutical stakeholders, and the effective usage of databases on medicine shortages were pointed out as key factors for enhancing the European pharmacy practice.

In Chapter "Patients Perspectives on Medicines Shortages in Hospital Setting", Kuruc Poje addressed the patients' perspectives on medicines shortages in the hospital setting, noting that the European research was mainly focused on stakeholders, community and hospital pharmacists. Furthermore, the patients' perspectives had not been well documented in the literature, and a qualitative study is

ongoing in several European countries with the purpose of quantifying the effect of medicine shortages on patients. In addition, the study is filling informational gaps from previous surveys and gathering contemporary data on patient care issues.

Also in the hospital setting and with a professional approach too, in Chapter "Rationing of Nursing Care: An International and Multidimensional Problem", Casa Nova, Cordeiro, and Riklikiene addressed the international and multidimensional problem "Rationing of Nursing Care". This problem occurs when resources are insufficient to provide the necessary care to all patients; it impacts care delivery and patient safety, and it is caused either by reduced staff numbers, skill mix variation, increased demands for care, or a changing patient profile. A consensus work on the construction of a Guide for Nursing Managers is being developed, and several stages were considered: the proposal development is followed by enlarged discussion in several scientific nursing events throughout Europe, and the work completion is planned within the current Horizon 2020.

A future perspective on cloud computing and Linear Programming, or a technological context within which pharmaceutical SC will be provided with advanced optimization tools, is presented by Casquilho, Miranda, and Barros, in Chapter "Linear Programming and Cloud Computing for Pharmaceutical Supply Chains". The study proposed the resolution of Linear Programming problems by cloud computing, other approaches and online solvers were compared, and typical cases within pharmaceutical SC (transportation, transshipment, assignment, scheduling) were selected for reference.

With a similar IT-based approach, Cecil and Soares presented a platform to transform data to intelligence, the IBM Watson Studio, in Chapter "IBM Watson Studio: A Platform to Transform Data to Intelligence". Nowadays, data scientists are transforming raw data through a systematic process of data understanding and model building, but they are challenged with a disjointed collection of tools, processes and unsatisfactory data acquisition/curation techniques. In this chapter, the authors surveyed the steps involved in intelligence creation, the challenges facing data scientists and the solutions approach with the help of IBM Watson Studio as reference.

The integration of a flow model into a stakeholder-based framework for vaccine SC design is presented by Lemmens et al. in Chapter "The Integration of a Flow Model into a Stakeholder-Based Framework for Vaccine Supply Chain Design". The authors described the flow model that covers the manufacturing part of a rotavirus vaccine SC and elaborated on how it is embedded in a stakeholder-based framework. In order to enhance the impacts on the SC service delivery, the relevant key performance indicators were the vaccine manufacturer's capacity utilization, the total lead time and the total SC stock.

The concept of medicines shortage is addressed by Burinskiene, in Chapter "The Concept of Medicines Shortage: Identifying and Resolving Shortage". Whether identifying and resolving shortages, the author investigated shortage cases both theoretically and empirically, and using scientific literature analysis and synthesis methods. Namely, Burinskiene described historical concept changes, and presented inventory simulations that highlighted the negative influence of handling errors on logistics costs.

In Chapter "Logistic Operations in a Hospital: A Multi-item Inventory Distribution Problem with Heterogeneous Fleet", Agra, Cerveira, and Requejo presented a logistic operations case in a hospital, where a single warehouse supplies several nursing wards. The authors faced the multi-item inventory distribution problem with heterogeneous fleet, and due to the difficulty associated with the instances dimension for this real problem, a matheuristic was proposed to solve the problem. By satisfying a balanced workload for the working teams, inventory capacities, safety stock levels and vehicle capacities, then the weekly distribution plan of medical products was defined in a way to minimize the visits to the nursing wards.

In Chapter "A Multiple-Criteria Decision Sorting Model for Pharmaceutical Suppliers Classification Under Multiple Uncertainties", Pelissari, Ben-Amor, and Oliveira presented a multiple-criteria decision sorting model for pharmaceutical suppliers' classification under multiple uncertainties. The proposed model is based on an integration of the FlowSort and Stochastic Multicriteria Acceptability Analysis methods, and Fuzzy theory. Supplier selection is a complex task involving a variety of conflicting criteria (e.g. quality, performance history, guarantee policies, productive capacity, price and time), and the model allowed pharmaceutical companies to develop a rating system and to classify suppliers into categories, namely, as actual and potential suppliers.

The role of agility in mitigating drug shortages and resilience strategies for the pharmaceutical SC is studied by Yaroson, in Chapter "Resilience Strategies and the Pharmaceutical Supply Chain: The Role of Agility in Mitigating Drug Shortages". The applicability of agility within the pharmaceutical SC was examined through existing literature when dynamic disruptions like drug shortages occur. The study indicated the main dimensions of SC agility capable of reducing the impact of drug shortages, namely, alertness, accessibility, connectivity and visibility.

In conclusion, the book "Pharmaceutical Supply Chains-Medicines Shortages" provides an insight of some and complementary topics on Pharmaceutical SC and "Medicines Shortages" and explores the most important notions related within. It presents relevant case studies and updated practices, as well as main tools for the modelling, simulation and optimization of pharmaceutical SC. In this way, the book can be useful to young researchers (M.Sc./Ph.D. students, Post-Docs), to policy-makers, managers, practitioners, and to general readers interested on the topics.

At last, we very much thank all the authors, as this book was only possible due to their important contributions. We are also very grateful to all the reviewers, both for their efforts with the texts quality and the pertinent inputs that enhanced the entire volume.

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The European Medicines Shortages Research Network and Its Mission to Strategically Debug Disrupted Pharmaceutical Supply Chains

Helena Jenzer, Leila Sadeghi, Patrick Maag, Franziska Scheidegger-Balmer, Katja Uhlmann and Stefan Groesser

Abstract The problems created by supply shortages of medicines have been widely reported by healthcare professionals and patients over recent years and acknowledged by the European Medicines Agency and European Commission. Shortages result in the suffering of individuals and negative consequences for an economy. An option to overcome shortage situations is to use a different medicine as a substitute. However, alternatives are not always feasible and available. When shortages arise, risk increases through substitution from other excipients, other concentrations, foreign language vials, or untranslated package leaflets. Such risks have not yet been quantified in a scientifically credible way. Thus, a decrease of the number of shortages

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will have a global economic and societal impact which is in the interest of clinicians, patients, public health, and of taxpayers. The supply chain can be parted into processes such as production of active ingredients, manufacturing, wholesaling, clinical need, and measures of poor clinical, financial and quality of life outcomes arising from shortages. The cited causes are multifaceted ranging from production disruptions, natural disasters, discontinuations, difficulties created by various restrictive and disincentive legal, trade and pricing frameworks, unfavorable decision making in medicines production and trade, insufficient stocks, as well as conflicts of interest of stakeholders. The European Medicines Shortages Research Network addresses these causes and debugging strategies by the bottom-up approach of COST (cooperation in science and technology) Action CA15105 which joins together all stakeholders and particular interests along the supply chain. The COST platform is sustained by nationally funded research projects which aim to respond to clinical, financial and quality of life interests, to achieve analytical clarity on disruption causes, to simulate decision making in order to anticipate new shortages, and to reflect on best coping practices. Approach to improvements of the situation comprises novel approaches such as System Dynamics and the repromotion of hospital pharmacy manufacturing and preparation. Activities of the European Medicines Shortages Research Network will make a significant contribution to strategic thinking about how to respond to product shortage problems by systematically analyzing the situation from key player perspectives. This includes round table negotiations with the stakeholders. It is the declared aim of the project to bring together all the primary stakeholders in the medicines supply chain process to find an agreement on the paths towards resolution by a bottom-up approach. The final objective is to stimulate constructive agreement between all participating stakeholders and to reveal any restrictive legal and economic frameworks, erroneous incentives in the supply chain, conflicts of interest, and problematic cost-benefit ratios that induce or exacerbate shortages.

1 Introduction

Medicine shortages (also referred to as drug shortages) have become a global phenomenon and are recognized to affect all health systems. It is a problem that has grown to become a crisis in terms of delivering patient care. This concern is known to affect all countries in Europe and beyond including the USA, Canada, and Australia. Medicine affected by shortages includes those used to prevent and treat cancer, infections, emergencies, cardiovascular conditions, anesthetic products, neurology and many more. The major challenge is that the economic incentive system in place is aligned in such a way that participating stakeholders are motivated to maneuver themselves into a deadlock situation. A critical issue today is that the key players do not collaborate sufficiently to guarantee a security of supply of essential medicines. What is needed is a systems perspective to understand and loosen this deadlock situation as well as to create innovative incentives on a legal and regulatory level.

Shortages result in the suffering of individuals and negative consequences for an economy. An option to overcome shortage situations is to use a different medicine as a substitute. However, alternatives are not always feasible and available. When shortages arise, risk increases through substitution from other excipients, other concentrations, foreign language vials, or untranslated package leaflets. Such risks have not yet been quantified in a scientifically credible way. Thus, a decrease of the number of shortages as a result of network projects will have a global economic and societal impact which is in the interest of careers, patients, public health, and of taxpayers.

This European Medicines Shortages Research Network intends to contribute to how medicine shortage problems can be detected, reduced, or avoided respectively by employing a systemic ecosystems perspective taking in account strategic and quality issues along the supply chain. Several steps will need to be developed to fulfil the set objectives. First, the list of factors and causes for medicines and nutraceuticals shortages need to be more precisely updated. Second, this research is to be shared with relevant actors. And third, a collaborative community of relevant stakeholders is to be established to overcome these reasons. The output of the European Medicines Shortages Research Network is intended to disclose and unravel restrictive legal, economic, or organizational frameworks and routines, erroneous incentives in the supply chain, conflicts of interest, and problematic cost-benefit ratios that serve to exacerbate or create shortages. The network members want to motivate and integrate key players and to bring excellence together in order to elucidate and resolve the supply chain-inherent problems at every step from raw material up to the patient's need. Finally, the network members will identify and enable obvious synergies arising from current national research reports and coping strategies by offering an excellent platform for an academia-practice partnership. This will require:

- to analyse development, history, and causes of medicines and nutraceuticals shortages along the supply chain by an independent, scientific and integrating approach,
- to bring the key players together at a round table to find a consensus policy and an agreement which can be approved in a frame of respect and in the interest of all key players,
- to elaborate what is required to improve the interaction between the relevant stakeholders regarding medicine shortages,
- to identify and design areas of mutual benefits to lessen the increasing problem of drug shortages and to decrease the number of shortages to exceptional incidences and to short-termed interruptions of the supply chain,
- to attain a constructive agreement on adequate next steps of producers, store keepers, wholesalers, hospital pharmacists, authorities and administrators on a qualitative and quantitative improvement of the availability of medicines.

The main research questions are:

- What restrictive legal and economic frameworks and routines favor decisions inducing consequences on shortages and availability of medicine and nutraceuticals?
- What is the scale of the problem of medicines shortages and what are the effects in providing patient care?

– What are the (erroneous) incentives systems along the supply chain which might favor incidences of medicine shortages?
– What are the conflicts of interest between private industrial enterprises and public health suppliers that hinder the search and development of a negotiated agreement?
– Which common and consensus-enabling standards or guidelines can be developed?
– Which over-all cost-benefit and cost-risk ratios are arising from shortages if a global assessment over the whole supply-chain is conducted?

Further information such as Technical Annexes and a Memorandum of Understanding can be retrieved from the COST Action's websites (e.g., http://www.medicinesshortages.eu).

As a number of stakeholders (manufacturers, suppliers, carers, patients) on a global level are concerned by shortages, a new COST Action was proposed from a bottom-up approach by an independent institution (represented by Bern University of Applied Sciences BFH), supported by co-proposers from European professional associations. COST (i.e. the cooperation in science and technology) seemed to be the most promising option as its declared philosophy was to offer a platform for exchange and to enable "breakthrough scientific and technological developments leading to new concepts and products". It aimed to create a multi-disciplinary partnership, platform and network of researchers from science, technology and business management in collaboration with the professionals from the relevant practice settings (represented by professional associations and manufacturing industry). This academy–practice partnership was new to the COST platform as usually scientists and technologists from universities built trans-European networks in the COST frame. New research approaches on complex systems were planned to be integrated into the medicines shortages topic to untangle interrelated activities in a complex production and supply system (Groesser et al. 2018; Groesser and Duminy 2018).

The New COST Action Proposal was approved by the COST Committee of Senior Officials (CSO) based on the social importance depicted and the recognized need to find solutions for a steadily growing threat. The new COST Action CA15105 had the MoU reference COST 037/15 (Table 1). Until the end of the second Grant Period, 27 European countries joined the Action. In the Action contacts participants from all WHO regions are listed. As associations are not fostered by COST, recruitment of all relevant stakeholders as declared by Capacity Building Objectives is not entirely obtained on a European level, interprofessional collaboration on an association level has to be addressed in national projects.

The Action wants to contribute significantly to a qualitative and quantitative improvement of the availability of medicines (including drugs, medical devices, foodstuff for special medical purposes, nutraceuticals) as well as to a decrease the number of shortages. It is the declared aim to attain a constructive agreement on adequate next steps of all key players as well as to reveal any restrictive legal and economic frames, erroneous incentives along the supply chain, conflicts of interest, and an unfavourable over-all cost-benefit ratio. For this purpose, all key players

Table 1 The declared COST Action CA15105 objectives as adopted by the Committee of Senior Officials

- Capacity-building objectives
  - To stimulate new research by early career investigators
  - To expand the network and recruit all relevant stakeholders identified
  - To include WHO regions, less research-intensive & NNC
  - To achieve a year on year increase of as early career investigators
  - To provide training and knowledge transfer *(STSM, Training Schools)*
- Research coordination objectives
  - Prevalence *(landscape, definition, common understanding) [end of YEAR 1]*
  - Impact *(directly on patients and healthcare systems, socioeconomic)*
  - Causes *(overview of primary causes, processes needing globally priority research)*
  - Solutions *(consensus statement on long-term international solutions)*
- Strategic approach
  - To create a research network of all stakeholders within the medicines supply
  - To assemble, synchronise and share the existing and current knowledge
  - To promote stakeholder-government dialogue on the evidence, research findings and potential solutions
  - To create a positive environment for innovative solution identification and implementation

along the supply chain will have to assume their responsibility for an undisrupted medicines flow. The approach to reach this objective is to negotiate at a round table. In terms of responsibility, each key player must contribute at his best

– to reduce induced costs to health systems
– to reduce risks to patients
– to reduce diversion of healthcare professional time

The Action has improved professional exchange over the whole supply chain. Formerly, only isolated activities were performed. The serious work is perceived as constructive by stakeholders that hesitated so far to join an integrated approach. Slowly, but lagging far behind the launch of the Action, true collaboration and national funding are granted to enable elucidation of the (new) research fields and proposals of improvements of the global and regional situations of shortages.

2 European Medicines Shortages Research Network Under the COST Roof

The Research Network has agreed on priority in the massive afflux of factors causing shortages, in order to reduce the number, severity and frequency of medicines shortages in Europe. Improvements recommended include greater transparency and flow of information related to predictable and unpredictable shortages, rigorous assessment of the true causes and solutions proposed, and guidance for healthcare professionals and patients on how to manage situations of medicine shortage. The Research Network has therefore created a clear outline of how shortages are reported in 28

countries (Bochenek 2018). Related to security of medicines supply, having made a European comparison, a basis is available on how legal frameworks might be improved. Information and proactive prevention mechanisms have been identified. The good practices already existing such as identification of products at high risk and supply chain vulnerabilities can help to prevent shortages reaching the patient. The negative impacts of medicines shortages could be mitigated through a step change improvement in best-practice sharing.

Preliminary troubleshooting strategies such as reporting systems or provider-user negotiations have been implemented separately in many countries. Actions, however, are therefore isolated and uncoordinated. Therefore, only a limited number of users participate in such an action. In addition, consensus papers on how to deal with medicine shortages are pro-posed by working groups or national associations, but do not rely on a very broad approval. This is an asynchronous and ineffective way to obtain sustainability. A more promising approach would be to assemble all stakeholders along the supply chain and to map their interests. This would serve as a basis for analysis and improving the whole complex dynamic supply chain (Jenzer 2018).

3 A History and Review of Medicines Shortages

Medicines shortages (also referred to as drug shortages) are a challenging global phenomenon affecting all hospital and health systems (McLaughlin 2013a; Lynas 2013; FIP 2012; EAHP 2014; Jenzer 2015). Furthermore, it is a phenomenon that if left alone threatens to become a crisis in terms of delivering patient care (McLaughlin 2013b; The Pharmaceutical Journal 2014). The dimension of the challenge is obviously of a multi-disciplinary context.

Medicine shortages as a global phenomenon grew steadily and increased sharply in the USA with-in a few years from 2006 (70 shortages) to 2011 (267 shortages). In 2012, 99% of over 300 respondents from 27 European countries had to cope with drug shortage problems. 63% of hospital pharmacists experienced it weekly, sometimes even daily, with an increasing frequency and magnitude of the problem. In Belgium in 2013, some 30 drugs are regularly unavailable (Jenzer and Fenton-May 2015).

Today, in Europe not only isolated cases are in the focus, but examples representing all therapeutic groups. In the Netherlands, they are monitored and published on a website. From 2004 to 2011, more than 1400 products were mentioned. The number increased from 91 in 2004 to 242 in 2011. The average duration of a shortage increased from 139 to 242 days in the same period. Substitution (62%), alternatives (25%), and compounding (2%) have been the method of choice to cope with such situations. To bridge a gap arising from a case of drug shortage will take one to seven hours. In any case, as a drug from the hospital formulary has been selected for its favorable cost–benefit ratio, alternatives are in general more expensive compared to

the standard product. A simple intermediate substitution of a drug on the formulary costs, on average, €1800, a definite substitution between €3800 and €4690 (figures valid for Germany; Jenzer and Fenton-May 2015).

Already in 2011, when an increase from 60 (2006) to 267 (2011) cases was seen, the situation prompted authorities to intervene in the market and remind manufacturers and suppliers about their responsibility. US president Obama signed the Executive Order 13588 instructing the FDA to require manufacturers to provide adequately advanced notices of discontinuation of certain prescription drugs and to review modifications of the production processes of these drugs more quickly. These requirements comprised of an obligation to notify and inform on drug shortages but did not include a disclosure of the reasons nor of the decisions which led to a withdrawal of products from the market, except of cases where only one provider for a medically necessary active ingredient is available, which have to be announced adequately. The FDA has created a task force for strategic planning and the EMA reflects on shortages caused by GMP compliance problems. As a result, 38 shortages were prevented in 2010, 195 in 2011, and 180 in 2012 (Fischer 2013; White House 2013; FDA 2014; EMA 2014; Klein and Myers 2006; Frontini 2014).

Relief may arise from less restricted importation frames and their induced disadvantages such as overflowing administrative effort, exclusion of an imported product from reimbursement, if the assurance company is not courteous. The most severe among a list of multifactorial reasons which have induced a drug shortage, were (Jenzer 2015; Drug Shortages 2010; Bonneux 2006; Birgli 2013; Agence Nationale 2014; Haller 2005; Howard 2017; Jenzer 1997; Liu et al. 2009; Jensen 2010; Lumbard 2011; Ganslandt 2004; Barron 2012; DeCamp 2014; McKeever et al. 2013):

- Quality or availability problems related to active ingredients or to production processes or equipment (e.g. heparin contamination and propofol case);
- Restrictions imposed by authorities;
- Absence of alternatives (e.g. Piperacillin–Tazobactam Chinese manufacturing plant destroyed by fire);
- Demand spikes (e.g. oseltamivir following flu pandemia scenarios);
- Inappropriate contracting by large buyers leading to the loss of small suppliers;
- Overstocking caused by panic buying (especially when alternatives are lacking);
- Parallel exports from low-price to upper-price countries to maximise gains;
- Globalisation of supply chains creating new vulnerabilities;
- High cost and low gain inducing some discontinuation decisions taken by industry.

An underlying reason for the latter is the capital, which is bound in a stock of medicines. From the perspective to optimise the working capital structure of an organisation, such bound capital stocks are considered important leverage points. The risk of losing capital is reinforced by the availability of new technologies and new products, which might diminish or degrade the stock's value due to a loss of demand for old products. However, medicines are not electrotechnical commodities nor do they have equally short half-lives. General economic rules are hardly applicable one-to-one for medicine and in no way for special product groups such as antidotes, narcotics, anti-neoplastics, parenteral nutrition, chemicals and toxics, disinfectants

and anti-infectives. Thus, commercial items and lean production are not convincing arguments for small stocks.

Most drugs on a shortage represent highly active ingredients bound to patient safety and to product quality issues (EAHP 2018 Medicines Shortage Survey). Deviations from GMP-rules and major product quality problems disclosed on inspections require improvements and investment in expensive renovations. Avoidance of investments may play an important role for the decision to further supply a medicine or not. The risk of negatively impacting a global market and disrupting the supply chain will be higher in the case of one large production facility being affected than the risk of a single cease-production within a cluster of many smaller plants which are able to absorb the absent capacity. It is even worse, if medicine production is relocated into countries with lower human resources costs or temporary exchange rate advantages. Moreover, the respective countries may have significantly less or even no experience in a reliable industrial production free of major operational disruptions. From a delivery security and ethical perspective, the economic pressure on medicine production has led to a disastrous situation from which several stakeholders suffer.

The situation has been exacerbating in Switzerland as well (GSASA 2013; Gatesman 2011). As a result, by the ordinance 531.215.32 of 12-August-2015, the Federal Office for National Economic Supply (FONES) has been assigned the task to develop and operate an alert system to prevent medicine shortages (BWL 2015). This measure is widely appreciated and approved by the stakeholders, who were involved in the consultation process, and likely to bring a certain degree of relief. However, the causes and the improvements along the supply chain will remain understudied. In general, instead of a release, an exacerbation is seen globally. The length of a shortage increased from 91 days (2004) to 242 days (2011) in the Netherlands. Whereas 30 medicinal products were permanently on short supply in Belgium in 2013 (Huys 2013), in Switzerland an increase within a few months has been seen from an average 250 cases to an actual stable high average of 430 medicines (Martinelli Consulting 2018).

The Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) has edited guidelines to cope with drug shortages (GSASA 2013) and, supported by the most important Swiss Associations and Federations of pharmacists (Swisspharma), physicians (FMH), and hospitals (H+), has signed an agreement with the leading associations of pharmaceutical industry (ASSGP, Intergenerica, Interpharma, scienceindustries, and vips) to readily provide pharmacies with active ingredients for individualized preparations and small scale stock production of commercially not available formulations or dosages (GSASA e-News 2013). Obviously, it has not been possible to provide sustainable relief to those players at the end of the supply chain, i.e. the staff treating patients, the patients themselves, and the taxpayer having to finance an ineffective system (Jenzer and Fenton-May 2015).

4 Identification of the Stakeholders

The COST platform aims to exchange methodologies and knowledge between scientists and technologists. When the Action was proposed, co-proposers and stakeholders had to be identified. The Action's members were then recruited among this pool of professionals. Their expertise was assigned to a sequence of processes broken down from the supply chain (Fig. 1).

When in 2016 the situation presented itself even worse than ever (and this tendency is ongoing), more and more uncoordinated initiatives were launched to manage the supply chain disruptions, but none was convincing enough to become a success story. Whatever the problem for a shortage might have been, adaptation and synchronisation of the stakeholders' interests revealed to become more and more important. As there is a common interest, i.e. to consider the health of the patient on the highest priority according to the humanitarian goals of the Hyppocratic Oath and of the codices of all professional associations, to agree on synergies and added values seemed to be realistic, although special interests such as maximization of the return on investment would obviously be extremely disturbing in tackling together what individuals did not succeed. In a negotiated agreement, the frame between BATNAs (best alternative to negotiated agreement) and WATNAs (worst alternative to negotiated agreement) will have to be considered. Compromises must be found between financial interests and requirements and humanitarian objectives of various codes of conduct (such as the Pharma Code and the Pharma Cooperation Code—Code of Conduct of the Pharmaceutical Industry in Switzerland, of December 4, 2003, revised on September 6, 2013; or the Pharma Cooperation Code—Code of Conduct of the Pharmaceutical Industry in Switzerland on cooperation with Healthcare Professional Circles and Patient Organisations of September 6, 2013; Science Industries 2014).

5 Defining the Term "Medicines Shortages"

As a rule, dealing with shortages needs an adequately precise definition of the term "shortages". The Research Network repeatedly tried to finalise such a definition. None of the 26 referenced definitions could satisfy in covering all requirements emerging from the network of researchers (De Weerdt et al. 2015, 2018). It was a concern that with a too specific definition some of the stakeholders would be lost. Therefore, a flexible one containing the compulsory cornerstones was formulated. This flexibility should account for the understanding of manufacturers and wholesalers as well as to clinicians (Table 2).

An unanimously accepted definition does not seem to be *condition sine qua non* for finding and initiate actions to stop the deterioration of medicines availability. It is more important to identify inducers and causations of shortages if solutions are the declared aim of the research network.

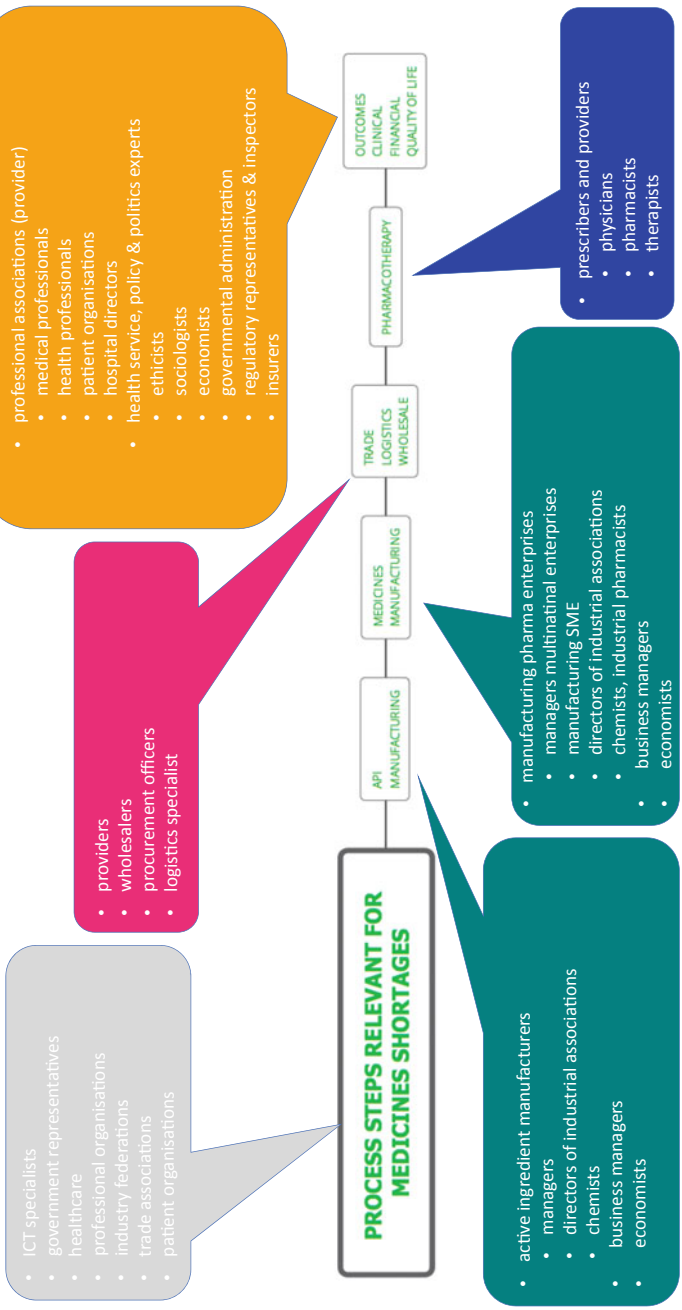

Fig. 1 Stakeholders along the pharmaceutical supply chain with their activity and interest for a particular or comprehensive interest and/or outcome (own source)

Table 2 A flexible definition of the term "shortage" as a frame, i.e. as a function of registration status, timeframe, indication, and reimbursement eligibility accounting for general and for more requiring interests (own source)

"Medicines Shortages"
"*… is the non-availability of a registered … life-saving … medicinal product …* *…reimbursed or not-reimbursed by insurers …* *… containing a defined active ingredient or a defined set of active pharmaceutical ingredient(s)…* *… not-substitutable by a product of the same compound(s) with equal bioavailability … nor by an active ingredient of the same therapeutic group indicated for the same pathology…* *… for a period between … days and the time-point of its deregistration…*"

6 First and Analytical Milestone of the Network's Mission: Mapping Causations of Shortages

Causations can be classified from a root cause assessment or from a procedural aspect (Figs. 2 and 3). The management of suppliers of medicines should have a convincing strategy of visibility and knowledge of the status of operating assets and the environment. Business intelligence and people visibility by aid of information technology and information exchange are vital to survive in unsteady times and environments. The skill to adapt to changing conditions as soon as early warning signals emerge from a consequent monitoring will provide advantages for any business. Even if a supplier cannot omit shortages, recovery of a damaged reputation will pay for further business-to-client relations. Crisis management, disperse and distribute decision making, collaborative forecasting, customer management, key account management will help to recover and regain confidence.

Among the inducers of shortages, some can be omitted whereas other external factors are beyond our control (e.g. turbulences such as natural disasters, diseases, pandemics, geopolitical disruptions, demand variation, currency and price fluctuation). Even deliberate threats such as terrorism, labour disputes, or espionage can be prevented only with a certain probability. In addition, there are external pressures being hardly anticipated and coped, e.g. competitive innovation, social, political and/or cultural change, price changes.

A vulnerability may arise from the connectivity management as to whether the interdependence and reliance on outside entities can be satisfied by the scale of a network, by the reliance upon information, and import and export channels. From industry, it is expected that resources are precisely disposed and capacities of production and distribution are generously allocated. However, steadily growing requirements may put limits to the feasibility of conforming to all requirements which in general increases costs. Capacity is not all. It must be related to efficiency. Reserves must be foreseen, redundancies and excess of production omitted, backup energy and communications sources might be vital in special circumstances. More and more financial resources have to be allocated for product purity, restricted material, and reliability of equipment. Flexibility in sourcing (modular product design, multiple uses, multiple sources, supplier contracts) and flexibility in order fulfilment (alternate distribution,

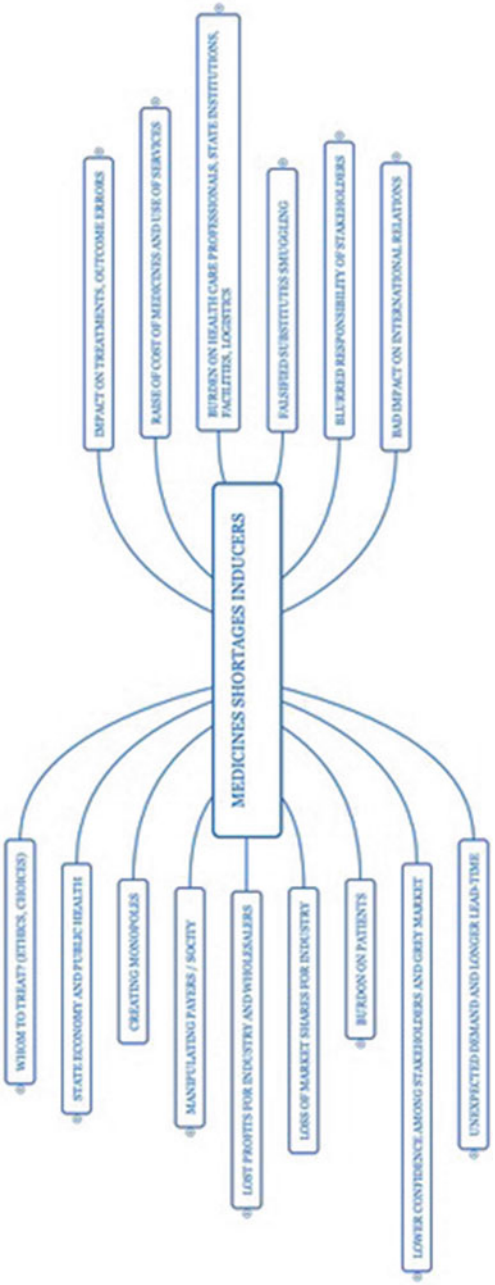

Fig. 2 Elements likely to induce medicines shortages (own source)

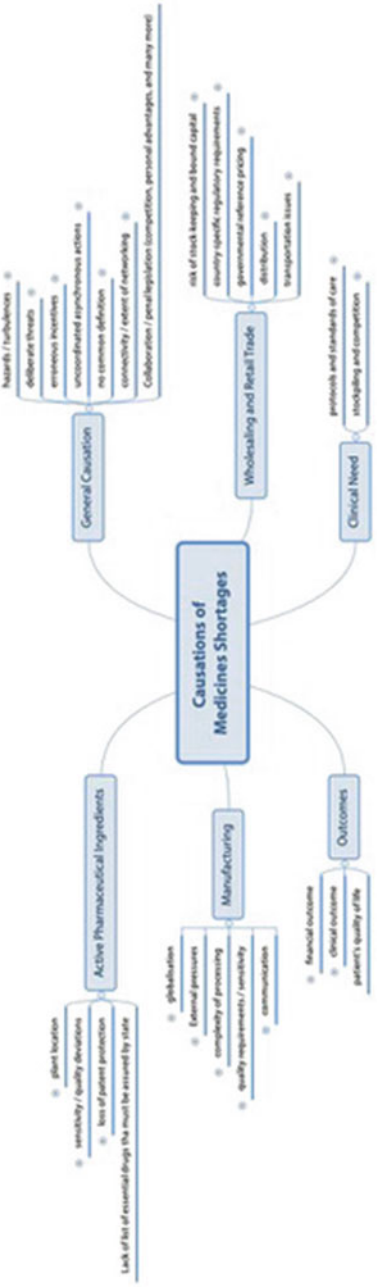

Fig. 3 Causations of medicines shortages. The map shows inducers grouped according to their appearance in the supply chain (own source)

risk sharing, multi sourcing) are further key issues to production and distribution security.

For a systematic analysis of medicines shortages it is highly recommended to group causes according to the step along the supply chain (Fig. 3). Anticipation, creativity, and innovation can be developed more readily.

7 Second and Creative-Innovative Milestone of the Network's Mission: A Methodological Approach to Improve the Medicines Shortages Situation

«Gouverner, c'est prévoir; ne rien prévoir, c'est ne pas gouverner.» (Emile de Girardin, Pensées et maximes, 1867)

For finding feasible solution, public health does not need more databases, but creativity, anticipation, and innovation, with the participation of all stakeholders. In current business and economy scenarios, hospital pharmacy is facing major challenges to fulfil its mandate to provide medicines due to repeated disruptions of the supply chain and shortages of any kind. Regardless as to whether such situations could have been avoided by early and proper actions such as key account management, future behaviour of managing hospital pharmacists should ensure a high degree of compliance to the mandate and accountability for the patients' interest. Efforts invested in the evaluation of indicators of change, scenarios, trends as well as in the strategic planning will prevent tiresome troubleshooting and major deviations from effective task fulfilling in future practice. Managing hospital pharmacists should timely construct the framework of indicators of change and analyse their interrelationship. By doing so, they may recognise more readily patterns which deviate from linear developments and anticipate future inconvenient circumstances. A decision taken within a net of interrelations may induce several consequences on the whole framework. Simulation of decision taking and of personal stakeholder constellation is one of the most delicate challenges hospital pharmacy managers will face when managing organisational development and business re-engineering (Groesser and Duminy 2018) (Fig. 4).

The general approach in this project is a multimethod research design (Mingers 2001) combining several research methods. First, the project uses conceptual work, i.e. a protocol driven comprehensive review and synthesis of data focusing on a topic or related key questions (Petticrew and Roberts 2005), which uncovers variables, system elements, existing routines and their interrelations which result in medicine shortage situations. The conceptual work is followed by empirical work: the research follows the (participatory) action research method (Eden and Huxham 1996; Reason and Bradbury 2001) with relevant system actors (Müller et al. 2012). For this, expert interviews and cognitive mapping with actors described below will be conducted employing the method "visible thinking"(Bryson et al. 2004; Groesser and Schaffernicht 2012). The interviewees' action theories (Argyris and Schön 1996)

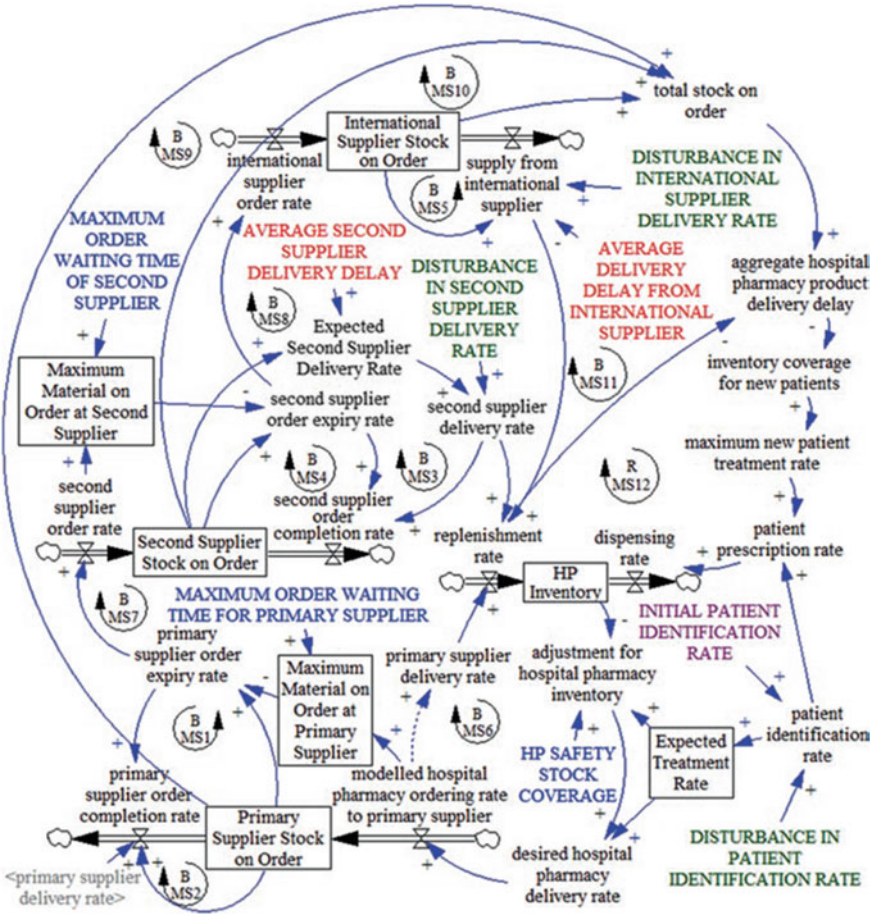

Fig. 4 Complex network, dependences and interrelation of medicines shortages. Aggregate structure of the medicines sourcing section of the hospital pharmacy echelon (Groesser and Duminy 2018)

or mental models (Groesser and Schaffernicht 2012) in use will be represented in cognitive maps (Axelrod 1976). The mental models of dynamic systems of roughly 15 key actors will be mapped separately and then integrated and contrasted in a comprehensive model of the medical and economic ecosystem (Groesser and Duminy 2018).

The decision-making process as related to the availability of medicines is actually simulated by Vensim® and a System Dynamics approach (Grösser 2018; Groesser and Duminy 2018). Vensim® is providing a more precise foresight tool for growth curve projections than it is available from linear models (Vensim 2018). The S-shaped logistic curve seems to be particularly useful for shortages forecast as growth curves in nature follow sigmoid curves arising from an exponential increase and corrections

by rate limiting decay factors such as shortages of nutrition or predator–prey impacts. More precise foresight is one of the key elements to obtain more reliable forecasts and to omit surprises of medicines taken out of the market.

This project assembles stakeholders and key players who are experts in distinct steps of the supply chain. Their collaboration and synergy will bring about a consensus policy on how to fight against drug shortages. The conclusion of the project will identify and balance the main issues which increase the problem of shortages. In this way, a condition is created for developing solutions and potential towards optimised quality and efficiency in terms of undisrupted supply. Patients will profit from an improved availability of restricted medicines.

The role of a Swiss Academia-Practice Network to cope with medicine shortages is a determining one if consequences such as decreased safety, worse patient outcome, and induced cost on a national level should be prevented. This work will also provide a tool to prevent the same errors in the food domain which have been encountered in the pharma domain. The projects output is suitable to complete some preliminary troubleshooting strategies such as the Swiss shortages reporting systems or provider-user negotiated agreement not having been sufficiently successful so far.

So far, it has been clear that no stakeholder has ever taken nor will take sufficiently its responsibility for individual patients. Reactions are seen on deteriorations only leading to a major threat for public health and the population. The Confederation will intervene only in need if the private sector fails to fulfil its economic supply function and if this condition is fulfilled as stipulated in the Epidemia Act of the Swiss Confederation. It is unanimously accepted that not the State but the private sector is required to override its own problems along the supply chain independently if the economic freedom should keep its primacy while medicines supply is warranted. Therefore, only life-threatening situation threatening the population's health will be reason enough to activate task forces of the Confederation (Flück and Groesser 2017).

In parallel to the described research process, the thread is drawn from negotiation and game theory to the establishment of a collaborative community of practice of the relevant system actors. This community will be used to develop a new governance scheme which is likely to overcome the reasons for medicine shortages. In the course of the steps of elicitation and analysis, discrepancies resistant to direct agreements may arise. In this case, the regrouped teams will be separated again and best alternatives to negotiate agreements (BATNAs) and worst alternatives to negotiate agreements (WATNAs) will be negotiated and mediated at the round table until an agreement is found. To follow, the full diffusion and acceptance of this scheme into the medical and health industry will be evaluated. The findings will be debated in reframing round-table meetings with the key players in order find a negotiated agreement.

Why not learn from nature? Nature is an inspiring prototype for laminar flow. Natural laws are demonstrating where interventions in the supply chain should go to. A river has a steady flow as long as the riverbed is broad and obstacles imped flow only marginally. The situation changes when the river has to pass a gorge. The flow becomes wild and turbulent. The same is applicable for congestions in traffic situations (Fig. 5).

Fig. 5 A small diameter of a cross-section favors supply chain bottlenecks and, sooner or later, stock-outs (own source)

Following nature's laws, it becomes obvious that lose the capacity to provide sufficiently the downstream need with narrow diameters of the channels. For the supply chain this means that medicines availability is at high risk of shortages in case of mergers of producing industry, insufficient scale of production plants, low afflux of starting material, of minimal stocks, tendering, narrow channels, scarce channels. It has been detected that a formerly available back-up system, i.e. the hospital pharmacy production, is being resurrecting in many hospitals, as no intermediate scale production site being able to offer sufficient capacity to rapidly fill gaps arising from shortages (Jenzer 2018).

In two Delphi rounds, insights from the stakeholders interviews, elicitation and analysis process will be discussed with the relevant system actors. The findings will be translated by the end of 2019 into a set of proposals to attempt at a solution. The process structure of the supply chain did not only serve for identifying causes but also to depict proposed solutions in an equally structured mind-map (Fig. 6). The proposals will be resubmitted to the interview partners in up to two Delphi rounds for finding approvals. Agreements should be obtained in 2019. Preliminary results are currently shared on the Swiss National Science Foundation Database (Jenzer 2018).

8 Conclusions

It is in the interest of all stakeholders to support all option which shall help to improve the health of the patients, unanimously agreed as being in the centre of all activities performed in public and private health environments. The pharmaceutical supply chain and the stakeholders share in common values and codes of conducts which oblige them to act as advocates of the patient. However, there are two more layer of interests and emotions which have destroyed every attempt to improve the situation for patients. These layers comprise several interests such as a financial one, but mainly the emphasis on the importance of free trade. Except of epidemic situations, the stakeholders did not manage so far to share responsibilities.

The Medicines Shortages Research Network implies and promotes the urgently needed dialogue at an international and national level, which is not taking place via other platforms at the current time. By harnessing the exchange of evidence and ideas that the proposed actions are foreseen to create, it is hoped that dialogue

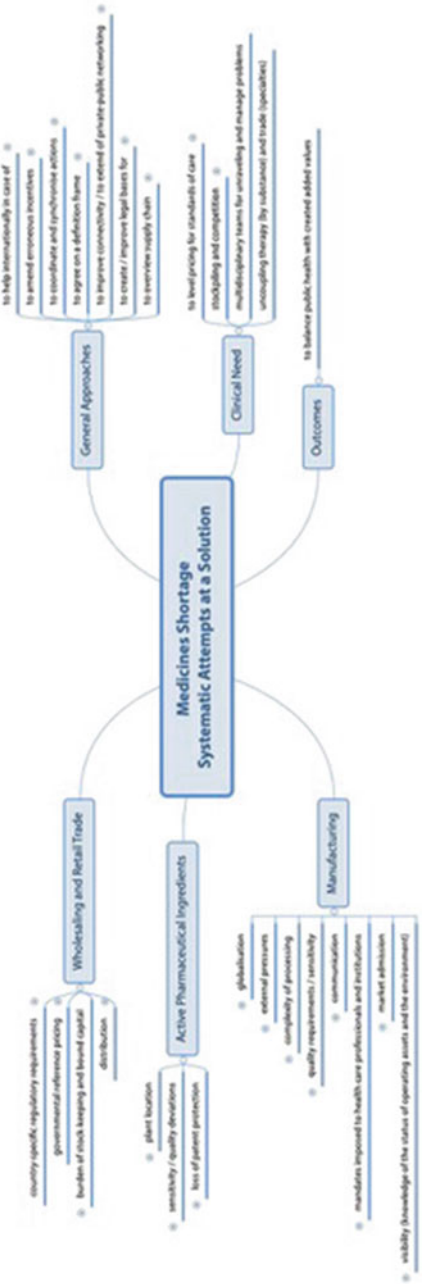

Fig. 6 Systematic attempts at a solution of medicines shortages. The map shows proposals grouped according to their location in the supply chain (own source)

between stakeholders, governmental and regulatory agencies can stimulate the formation of appropriate suggestions for remedial action and solutions to prevent and reverse the current growing trend of medicines shortages. Further, the approach is to attain constructive agreement between all participating stakeholders and to reveal any restrictive legal and economic frameworks, erroneous incentives in the supply chain, conflicts of interest, and problematic cost-benefit ratios that serve to exacerbate or create shortages. With a focus too on stimulating the proposition of policy solutions, it is intended that patients and healthcare systems will ultimately benefit from an improved situation of medicines supply sustainability.

The integration of the System Dynamics approach into the Medicines Shortages problem in order to improve the deteriorating shortages situation is new and innovative. This policy actually elaborated in a national project funded by Swiss National science Foundation will end up with the disclosure of erroneous system-inherent incentives, repromotion of hospital pharmacy manufacturing and preparation, an attribution of a leadership (a kind of referee system) and mandates to stakeholders, and elucidation of the lack of a legal frame which would allow governments to act not only in cases of epidemics. The Swiss national research project should yield stakeholder consensus by the end of 2019. The results of this national project will be feeding the European COST Action CA15105.

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Design and Planning of Sustainable Vaccine Supply Chain

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Abstract Sustainable supply chains are nowadays-targeted systems by both academics as well as industrial organizations. The Vaccines Supply Chain (VSC) being of utmost importance because of its great relevance in the world health, should be designed and operated in an optimized form not only aiming to guarantee high service levels at minimum costs but also considering environmental and social concerns. This study addresses such goal and proposes a Multi-Objective and multi-period Mixed Integer Linear Programming (MO-MILP) model for the simultaneous design and planning of sustainable VSC. The three dimensions of the Triple Bottom Line (TBL)—economic, environmental and social are modelled considering respectively the maximization of the Net Present Value (NPV); minimization of environmental impacts; and maximization of social impacts. The model is applied to a representative European supply chain case study, based in a European company. The outcomes obtained with the different scenarios studied clearly show how strategic and tactical decision-making impacts on key performance indicators in a VSC. Again, by the results, it becomes clear the existence of trade-offs between the sustainability dimensions considered and the importance of using multi-objective approach to find feasible and sustainable solutions.

Keywords Vaccine supply chain · Sustainability · Optimization · Design and planning

1 Introduction

The global healthcare sector has undergone fundamental changes throughout the last years to cope with the new challenges of the modern economy (Reklaitis 2017). The major drivers that have been fuelling this shift are related to demographic factors such as unprecedented and enduring ageing of populations, healthcare factors and the

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growing demand for new innovative treatments and technology, and lastly, evolving financial and quality regulations (Deloitte 2016).

Pharmaceutical companies are included in the group of healthcare companies facing the aforementioned challenges. In particular, pharmaceutical companies have been dealing with reinforced regulations regarding economic, environmental and social issues. Moreover, these same companies are confronted with planning and designing of their Supply Chain (SC) to reduce costs, waste and achieve highly effective supply networks. SC optimisation is then a major research theme in the process supply chains (Barbosa-Póvoa 2014).

Within pharmaceutical companies, the ones dealing with vaccines face special challenges. To deepen the difficulties, vaccines are not like commodities because their primary objective is to eradicate harmful diseases dealing with a product that needs special care such as special storage and transportation conditions (refrigeration or freezing). Bearing in mind this scenario for VSC, the intent of this work is to study how to make better strategic and tactical decisions that will help to attain several key objectives, namely economic, environmental and social goals. To do so, a multi-period mixed-integer linear programming is developed and applied to the design and planning of a VSC, aiming to determining the SC structure along with planning decisions that maximize profit, minimise environmental impact and maximize social benefits, in terms of the creation of jobs inside a VSC.

The central goal of this study is then to enable better utilisation of resources in VSC, and ultimately guarantee the fulfilment of vaccination.

The methodology followed to address the problem previously identified is described in the next sections. Besides this introduction this chapter is divided into six main parts. Section 2 presents an overview of the relevant literature on pharmaceutical industry and Supply Chain Management (SCM), with an emphasis on vaccine networks. Section 3 briefly introduces the description of VSC. Next, in Sect. 4, the problem is defined and a MO-MILP model is generically outlined and characterised for supply chain design and planning. The model used in this study was based in Mota et al. (2015). Subsequently, in Sect. 5, the model is applied to a virtual case study and the results are discussed. Lastly, final conclusions are drawn and future work directions presented.

2 Literature Review

According to EFPIA (2018) European citizens can expect to live up to 30 years long than they did a century ago due to the scientific and technological advances of the pharmaceutical industry. Being one of the top performing high-technology sectors in Europe, the pharma industry is a crucial asset of the Europe economy (EFPIA 2018), within this supply chains play a crucial role.

Pharmaceutical supply chains entail a complex set of processes, operations and organizations involved in the discovery, development and manufacture of drugs, medications and vaccines (Shah 2004). The goal of such systems is to deliver drugs

that help in the prevention of diseases, maintain health and cure or retard diseases, consequently reducing morbidity (Market Realist 2015).

From its early days, the pharmaceutical supply chains have enjoyed a very satisfying economic status, with profits commonly growing steadily. Nevertheless, market pressures and harsh socio-political regulations are among the present causes changing the way in which the pharmaceutical SC is operating (Gatica et al. 2003). As a consequence pharmaceutical SC must be flexible, resilient and efficient so as to guarantee end customer needs satisfaction at minimum costs (Barbosa-Póvoa and Pinto 2018). Additionally, as stated by Barbosa-Póvoa (2014), pharmaceutical SC should not only account for economical concerns but also special attention to sustainability aspects should be developed, as such systems are typically associated with high levels of resource consumption. To answer to such challenges SC optimization in terms of design, as well as planning and operation, is vital.

The following pages will briefly described the new paradigm of sustainable supply chain management and the relevant problem of supply network design that will be the focus of the present study.

2.1 Sustainable Supply Chain Management

Since 1982, when the topic was first discussed, SCM has attracted the attention of both academics and consultants (Barbosa-Póvoa et al. 2018). One of the main drivers for the quick development of SCM has been economic sustainability, established on the principle that a collaborative SC could bring benefits for all the concerned parties (Fawcett et al. 2008) and even result in a competitive advantage in the market. Melo et al. (2009) defined SCM as the set of procedures of planning, implementing and monitoring the operations of the SC in an efficient way. Regarding SCM, three basic levels of SC decisions can be defined depending on the time horizon: strategic, tactical and operational planning.

The first level of SC decisions comprises choices for long planning cycles say, of two to five years, since normally involves large investments and for that reason is characterized to have a long-lasting effect on the firm (Melo et al. 2009). This decision level includes choices concerning number, location and capacities of the different entities of the SC; technologies to be employed at each facility (Schmidt and Wilhelm 2000) and the material flows between entities (Melo et al. 2009). Once strategic level provides the network design of any SC, whose prime objective is to maximize the profit while the demand is satisfied, this level provides the conditions that will influence the strategic and operational decisions (Schmidt and Wilhelm 2000). On the other hand, the tactical level deals with decisions regarding resource allocation, such as production levels, assembly policies, inventory levels and lot sizes (Schmidt and Wilhelm 2000). The time horizon of this type of decisions is 6–24 months. Finally, the operational level intends to assure the on-time delivery of products to customers (Schmidt and Wilhelm 2000). This level includes the motorization of in-progress

activities and the planning for demand fulfilment, transportation and scheduling (Barbosa-Póvoa et al. 2018).

In recent times, new paradigms emerged in the field of SCM, due to the inherent complexity of globalized SC (Reuter et al. 2010), such as the attractive and popular field of Sustainable Supply Chain Management (SSCM).

In 2017, Dubey et al. performed an extensive and broad literature review concerning SSCM. Between the sixteen distinct definitions identified, the most recent belongs to Pagell and Shevchenko (2014). The authors described SSCM as the management of SC processes such as the design, coordination, control and organization, for achieving a truly sustainable SC on a long-term basis. In addition, from the point of view of Dubey et al. (2017), the authors state that an efficient SSCM should enable an organization to achieve a better economic performance while ensuring the minimization of harmful environmental and social impacts.

With the objective of competing towards innovation and sustainability companies have then to adjust their complex SCM processes, integrating and accounting the three dimensions of the TBL (Seuring and Müller 2008; Barbosa-Póvoa et al. 2018). Elkington (1998) introduced for the first time the TBL concept as a way to operationalize sustainability. The author proposed a framework to assess the performance of a business and the consequent success of an organization using the three different dimensions of sustainability, namely, the economic prosperity, the environmental quality and the social justice considering political and ethical issues (Elkington 1998).

In Barbosa-Póvoa et al. (2018) a detailed literature review is performed on Operational Research methods to support sustainable SC. One of the multiple topics approached on this article is the choice of indicators used in the literature to assess the different sustainability' pillars. In this research is concluded that: (1) the most applied indicator is minimization of costs, followed by profit and NPV to assess the economic pillar, which appears as more adequate as it not only considers costs but also revenues and capital actualization; (2) the job creation is the most used indicator to measure the social pillar, followed by safety; health; number of working hours; discrimination and satisfaction; and, lastly, (3) regarding the environmental impact, the most common indicator used measure the carbon dioxide (CO_2) emissions more precisely the carbon footprint.

In terms of the social pillar the scientific community should focus their efforts on defining the social aspects in a more clear and quantitative way promoting and following a holistic approach. The same wide perspective should be adopted when dealing with the environmental impact since the majority of published papers only focus on a single environmental indicator.

This phenomenon explains the embryonic implementation stage of Life Cycle Assessment (LCA) approaches (Barbosa-Póvoa et al. 2018). LCA is a promising method that enables the quantification of all the environmental impacts during a complete life cycle of the products (Goedkoop et al. 2016) from the extraction of resources to the disposal (Joint Research Centre 2011). LCA is composed of four different steps as required by ISO (2006), namely (i) goal and scope definition; (ii) inventory analysis; (iii) impact assessment, and (iv) interpretation. The major

advantage of this type of methods is the quantification of all the significant substance emissions; resource extractions; environmental consequences; health impacts and resource depletion issues associated with any products or services (Joint Research Centre 2011). In this context, ReCiPe is a method developed by Goedkoop et al. (2009) that explores the LCA third phase, the Life Cycle Impact Assessment (LCIA), so as to provide harmonized characterization factors at midpoint and endpoint levels (Goedkoop et al. 2016). ReCiPe is considered the most developed methodology so far to assess the environmental impact and is recommended as default method by the European Commission (Joint Research Centre 2011). The LCIA phase enables the interpretation of the LCA studies by translating the emissions and resources extractions into a limited set of environmental impact scores by means of so-called characterization factors, which indicate the environmental impact per unit of stressor (Hauschild and Huijbregts 2015).

2.2 Supply Networks

A supply network from a pharmaceutical company is similar to that of any other industry in the manufacturing sector. However, among the substantial published research on Supply Chain Network Design (SCND), only a small fraction of these studies directly deal with the pharmaceutical sector.

Despite all advances and improvements in the manufacturing, storage, and distribution methods, several pharmaceutical companies are still significantly far from effectively satisfying market demands in a consistent manner (Mousazadeh et al. 2015). Saki and Ebrahimnejad (2015) refers that the prime objective of this type of SC is delivery vital pharmaceuticals to the end-consumer at the right quality, place, and time, which makes it a complex and sensitive SC that has to be agile to ensure the deliver of the medicines without compromise health and safety (Mehralian et al. 2017).

Typically in this industry, the preferred mechanism to overcome productivity crises has been to increase investment, primarily, in the two extreme ends of the SC, R&D and sales. Yet, SC optimisation is a less costly way to increase profit margins and has becoming a current practice, as stated by Sousa et al. (2011).

Several key issues concerning pharmaceutical SC were studied and analysed by different authors in the last decade. Papageorgiou et al. (2001) studied the strategic SC decision-making process for pharmaceutical industries and to do so developed a Mixed Integer Linear Programming (MILP) model for the design of SC. Analogously, Gatica et al. (2003) expanded the research of the last paper by introducing uncertainty to clinical trials. The advantage of this model in comparison with the first one is that it allows discriminating between different risk management alternatives. In Shah (2004), pharmaceutical SC design difficulties are discussed. Low manufacturing velocities are highlighted and the quality assurance activities at several points are also mentioned as problems often presented within pharmaceutical SC. Amaro and Barbosa-Póvoa (2008) presented a generic integrated approach for the planning and

scheduling of SC, applied to a pharmaceutical case study, which consisted in a multi-product SC. Additionally Kumar et al. (2009) pointed out the obvious need to maintain traceability of pharmaceutical products throughout the SC so that reverse logistics become more effective. Later on, Sousa et al. (2011) built a model to optimise primary and secondary manufacturing independently for the whole SC. The model intended to allocate the manufacture of primary and secondary products to solve the optimal production amounts and inventory levels and establish the product flows between echelons.

Additionally, within pharmaceutical SC, the VSC is a very important system, as stated by Bloom et al. (2005), once its impacts on human health are tremendous.

Kaufmann et al. (2011) mention some regular problems in VSC such as temperature controlled transport, storage and shelf life issues. In addition, the authors comment that demand forecasting; financing and procurement processes; storage and transportation; human resources and maintenance, are key challenges of this type of SC. They also claim that if SC improvements do not occur, the money and time spent to develop and finance new vaccines will be put at risk. In the same tone of describing supply network problems, yet also presenting solutions, Zaffran et al. (2013) argue that effective vaccine delivery should be achieved and environmental impact of energy, materials and processes used in immunization should be minimized. Saif and Elhedhli (2016) also considered the environmental impact when structuring a cold supply chain, a SC for goods, such as vaccines, that should be stored in a temperature-controlled environment. The results of the implementation of their model to a real VSC show the existence of a trade-off between transportation costs and inventory costs.

According to Yadav et al. (2014), benefits of integrating VSC with other SC, such as health commodities, will outweigh the costs, providing a framework for deciding where such integration offers the most significant benefits. Lee et al. (2015) also explored the costs and impact of various alternative SC structures. By analysing the results the authors refer the importance of balance the decentralization of operations with coordination complications and increased time spent in storage, thus raising the risk of wastage as a result of temperature exposure or expiry. A common conclusion in several studies that analyse the relationship between the design of VSC and the multiple storage levels is that simplified systems may provide substantial cost savings and increase vaccine availability (Assi et al. 2013; Lee et al. 2015).

Some literature exists where authors explored distinct performance metrics of the VSC. Hovav and Tsadikovich (2015) developed mathematical models for optimizing costs of the healthcare organization while taking into account the public benefits of the vaccination programme. Another interesting publication was presented by Mvundura et al. (2015), which had the goal of estimating the costs of the VSC and service delivery for selected districts.

Recently, Lemmens et al. (2016) published a paper with the intention of providing a major literature review on SCND for vaccines. The problem addressed in this research has the primary objective of proposing a model that not only designs a VSC, but also provides a tactical plan for production, storage and distribution in a predefined time horizon In this paper, the authors highlight some considerations for

future research, such as: (1) the need to consider, simultaneously, time and difficult to reach customers when determining the transportation cost, and not simply the distance between them; (2) the necessity of integrate the decisions associated to facility location and the technology selection, due to the trade-off between lower labour costs and the maintenance of high standards of quality; (3) the relevance of studying the impact of increased investments due to cold chain requirements, in terms of additional cold storage equipment's and vehicles, often seen as a bottleneck of the VSC (Assi et al. 2013); (4) necessity of considered the shelf life requested by the consumers, adapting the inventory level to the perishability of vaccines; and, finally, (5) the negligent impact of biochemical composition and regulatory requirements on batch size requirements.

Some work has already been done when designing and planning pharmaceutical SC but more is required, in particular generic models should be developed that explore the VSC main characteristics and address the design of such systems towards sustainability while being efficient and responsive. Some interesting models have been proposed to design and planning SC (Mota et al. 2015, 2018) but no specific case of pharmaceutical supply chains has been considered. This is an actual problem, as society pressures are highly demanding adequate responses from organizations (Barbosa-Póvoa et al. 2018). This chapter tries to contribute to such goal and proposed a generic optimization model for the design and planning of sustainable VSC.

3 The Vaccine Supply Chain

The prevention of infections through vaccination has been among the most successful public health interventions; that is, it is one of the most cost-effective ways to save lives, improve health and ensure long-term prosperity (Pfizer Inc. 2017). In recent years the production, quality control and marketing authorization of vaccines have become increasingly complex. According to Duijzer et al. (2018), this complexity can be minimized by market coordination, among manufacturers and public health decision makers, to improve the match between demand and supply.

The complexity of a VSC is, arguably, due to three main factors: product complexity, globalization and regulation. The first factor is related to the complexity of vaccines, which result in large production lead times. Secondly, another factor of utmost importance concerns globalized SC. This phenomenon is trending amongst manufacturers so that they are able to increase their production capacity (multi-sourcing) and maximize their utilization to better meet patient demand. Thirdly, the regulatory requirements are becoming increasingly complex for manufacturers. Greater expectations for public safety continue to drive quality to higher standards, creating a strong focus upon vaccine quality, safety and efficacy. To answer these complexities, VSC need to be optimized in terms of structure, planning and operation, taking into account the associated SC characteristics.

As a way of preparing for the future changes and challenges of an unparalleled growth for immunization programs, in 2011 the World Health Organization (WHO)

defined three priority areas for future flexible and robust VSC, including products and packaging; immunization supply systems efficiency and environmental impact of immunization supply systems.

The first area compromises the design phase of vaccines with characteristics that best suit the requirements and constraints of the countries. Although the main goal of a vaccine is to induce immunity to a disease, logistics aspects such as the volume and temperature at which it must be stored can broadly affect the SC (WHO 2011; Duijzer et al. 2018). Failure to store and handle vaccines properly under the right temperature range can diminish vaccine effectiveness, consequently leading to inadequate immune responses in patients and poor protection against diseases (IFPMA 2016). Ultimately, the success of vaccinations campaigns is connected with good logistics, a fact that is sustained by the growing number of studies on the subject (Duijzer et al. 2018). Secondly, WHO (2011) stated that VSC should be designed to: boost effectiveness and agility, to meet different needs in multiple circumstances without compromising the quality; support continuous system improvement through monitoring, learning and innovation, and promoting synergies with third-party sectors. The last tenet defined, intends to evaluate and minimize the environmental impact of materials, energy and procedures used in immunization supply systems from the global to local levels.

Recently, a literature review concerning the VSC made by Duijzer et al. (2018) identify distinctive characteristics of VSC, namely: (1) misalignment of objectives and decentralized decision making between the various parties; (2) high uncertainty in both supply and demand; (3) complex political decisions concerning allocation, and the (4) crucial impact of deciding and acting in time. The authors also refer several factors that contribute to the uncertainty in the production phase, such as the existence of multiple stakeholders involved with distinct objectives and incentives; demand fluctuations as a result of seasonality or changes in the vaccine composition, and rigorous and extensive tests of safety and quality, before vaccines entering the market. One of the main causes referred for the significant supply deficit on this market is the uncertain yields in the production processes (Chick et al. 2008; Deo and Corbett 2009).

In this study, the design and planning of VSC is considered where two main parts characterize in an aggregate form the VSC, one being the manufacturing process and the other being the distribution process. Figure 1 demonstrates a generic representation of VSC. The first two steps (suppliers and manufacture) may be included in the manufacturing process, whereas the three other steps may be included in the delivery process. For the sake of simplicity, and if one considers clustering customers, one can consider customers and consumers to be in the same step of the SC.

After manufacturing, vaccines are shipped for distribution. In the distribution process vaccines go through international shipping and finally arrive at warehouses where they are stored. To store vaccines, it is necessary to consider the available storage space and capacity, as well as the electricity supply. The last step encompasses delivering vaccines to final markets as countries.

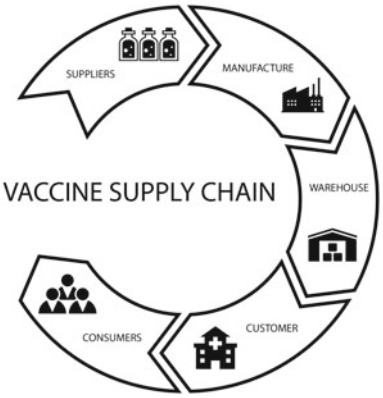

Fig. 1 Vaccine supply chain structure

All of these steps can take up to 24 months to complete, approximately, which represents a huge lead time in the delivery of vaccines from factories to warehouses (IFPMA 2014).

Given the structure of VSC discussed and the state-of-the-art studies being developed in the field of VSC, as the one presented in Lemmens et al. (2016), this paper proposes to foster a model to design and plan a supply network that integrates cold chain requirements that will guarantee a universal immunization coverage. On top of that, pharmaceutical companies have been pressed to maintain and improve their contribution in terms of corporate responsibility, which steer them to make more efforts in order to reduce greenhouse gases emissions, electricity consumption and improve their delivery rates to people who are not getting their products (vaccines). Furthermore, by implementing such supply network, the company would be creating jobs for citizens, which would also improve the social contribution of the company.

This research aims to mimic and simulate the task of designing and planning a VSC, based on the model presented in Mota et al. (2015). The objective is to determine a set of important features of the SC such as the network structure and the production and storage levels. Furthermore, the model comprises all the three dimensions of sustainability as target objectives.

In this work, the model is extended to address the decision of selecting and allocating specific storage technologies for vaccines and model the operations involved in VSC. Thus the contribution of this work is two-fold: (1) the successful application of the model to a very particular case, VSC, contributes to decreasing the gap that exists today on the literature and (2) the study supports the development of new models to design and planning SC with multiple objectives.

4 Problem Definition and Model Characterization

As stated, this work aims to determine the optimal SC structure for vaccines along with planning decisions that maximize the economic plus the social benefit, and minimizes environmental impact in a solution of compromise, as previously done by Mota et al. (2015, 2018). The first step was the selection of the indicators to measure each one of the three pillars mentioned.

Barbosa-Póvoa et al. (2018) refers that the NPV is the most suitable indicator when dealing with a network design problem since this economic indicator can better translate investments and other types of costs associated with revenues. In the context of SCND, work previously done by Cardoso et al. (2013), Mota et al. (2015, 2017, 2018) assess the impact of the economic pillar through NPV. Additionally, Barbosa-Póvoa et al. (2018) highlights the importance of choosing a LCA approach to evaluate the environmental impact, which is nowadays a more complete methodology that considers multiple environmental impact categories. Regarding the social pillar of the TBL, the most common metric used by the European Commission in his Sustainable Development Strategy Reports (European Commission 2018) is the Gross Domestic Product (GDP), a measure of the dynamism of the economy. Although GDP is not a complete measure of welfare, it gives an indication of an economy's potential to satisfy people's needs and its capacity to create jobs. It can also be used to monitor economic development (European Commission 2018).

Therefore, the present study follows these recommendations and the economic pillar is measured through NPV; the environmental impact of storage technologies, entities installation and transportation modes are measured through ReCiPe; and, lastly, the social pillar is measured through the GDP of the region at stake.

The generic representation depicted in Fig. 2 is implemented in a MO-MILP model. The SC is formed by three echelons: factories with a given minimum and maximum capacity, warehouses, where final products are stored and delivered to markets and, finally, patients' markets.

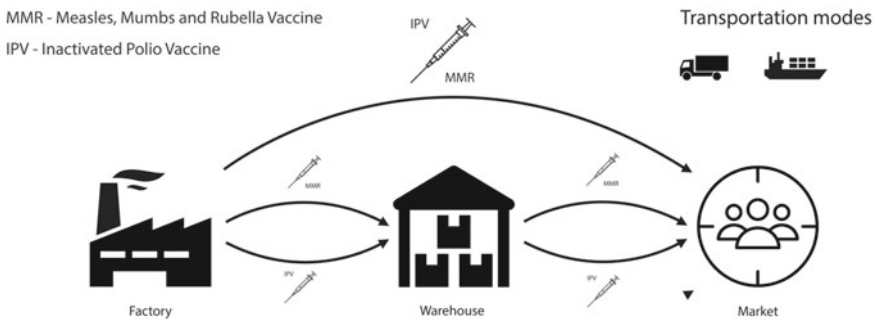

Fig. 2 Schematic representation of vaccine supply chains. Adapted from Salema et al. (2010) and Mota et al. (2015)

Final products (vaccines) flow to warehouses or directly to markets. It is considered that the inventory of final products is only allowed in warehouses. Final products entail both vaccines that rely on refrigeration and congelation to preserve their potency. At warehouses, technology selection is possible and both storage technologies (refrigerating and freezing technologies) can be allocated to each warehouse. Transhipment is allowed between warehouses and transportation between entities can be performed by unimodal or intermodal transportation. Intermodal transportation includes road, train and sea freight modes are considered.

A graph representation is utilized to characterize the SC structure that goes from the manufacturing sites to markets (countries). Nodes represent any SC entity (such as factories, warehouses and markets), whilst arcs between two nodes define an existing flow.

Nodes are characterized by a set of properties:

- Input flows: arcs that represent products coming from the previous network level;
- Output flows: arc that represent products going to the next network level;
- Operation: nodes indicate the transformation that products undergo and that is responsible for turning input products into output products. This process can be a storage operation or simply a cross-docking operation. The operation varies according to the function that the entity has on the SC. Any operation has also some specific characteristics such as time—any operation has a time of execution, which can take the value of zero if defined as instantaneous, and capacity—the operation may be performed within maximum and minimum pre-established values.

On the other hand, arcs represent any kind of flows between two entities. Each one of these flows are characterized by a point of origin (source entity) and a destination (target entity); a type of product; a time interval needed to go from the origin to the destination, and a capacity.

Overall the problem in study can be described as follows: **given**: (a) a possible superstructure for the SC entities; (b) investment costs for the location of SC entities, storage technology and transportation; (c) operating and installation costs for storage technology; (d) maximum and minimum supplying flow, storage, production and transportation capacities; (e) the environmental impacts of transportation, storage and of each facility for each impact category; (f) maximum and minimum installation area; (g) product's demand; (h) product volume; (i) price per sold product; (j) distances between each pair of entities; (k) variable and contracted fixed transportation costs; (l) handling costs at transport hubs; (m) initial stock levels at each facility; (n) number of workers necessary for each storage technology and for each transportation mode, **the goal is to determine**: (1) the network structure; (2) the production and storage levels; (3) the required entities capacities; (4) the transportation network (insourcing, outsourcing or combination of both); (5) the supply flow amounts (from factories); and (6) storage technology selection and allocation, **so as to** maximize the profit and the social benefit, while the environmental impact is minimized.

4.1 Mathematical Formulation

The problem is modelled through MILP and includes continuous, binary, positive and integer variables to be calculated. The MILP model was implemented in GAMS 24.7.4 software. The definition of sets; variables; parameters; objective function and constraints of the model are given in Appendix 1.

In this section, the description of the constraints and objective functions is made. Since the intention is modelling a multi-objective problem there are two options to do it: one can either condense several objectives in the same objective function or, contrarily, model the objective functions separately according to each specific objective. Due to the additional step of finding weighting factors, the first option owns an inherent subjectivity and uncertainty that may compromise the results of the model. Thereby, the decision was taken to model each objective of the TBL—economic, environmental and social—as individual objective functions.

4.2 Objective Functions

As mentioned before three objective functions are considered in the model, respectively economic, environmental and social goals.

4.3 Economic Objective Function

Equation (1) represents the model economic objective function, which maximizes the NPV for the time horizon modelled. Equations (2)–(6) are support equations used to calculate the NPV. This approach to quantify an economic objective is based on the work developed in Cardoso et al. (2013). The NPV is calculated, according to Brealey et al. (2014), as the sum of the discounted Cash Flows of each time period (denoted by CF_t), through the usage of the interest rate ir.

$$\max NPV = \sum_{t \in T} \frac{CF_t}{(1+ir)^t} \tag{1}$$

Equation (2) calculates the cash flow in each time period, obtained from the difference between the Net Earnings (NE_t) and the fraction of the Total Depreciable Capital (FDC_t). Additionally, Eq. (2) also calculates the cash flow for the last time period, where it is taken into account part of the total fixed capital investment (FCI) that may be recovered at the end of the time horizon, using a salvage value sv.

$$CF_t = \begin{cases} NE_t - FDC_t, & t = 1, \ldots, NT-1 \\ NE_t - FDC_t + sv \times FCI, & t = NT \end{cases} \tag{2}$$

Equation (3) represents the formula for the net earnings. Net earnings are given by the difference between the incomes and the total cost, as shown in Eq. (3).

$$
\begin{aligned}
NE_t = (1-tr)\Bigg[& \sum_{\substack{(m,i,j)\in F_{INC}\\(a,m,i,j)\in NetP}} pus_m X_{maijt} \\
& - \Bigg(\sum_{\substack{(m,g)\in H\\ i\in I_w}} opc_g S_{mgit} + \sum_{\substack{(a,m,i,j)\in NetP\\ a\in A_{truck}}} \left(\frac{avc_a}{100}\cdot fp + vmc\right)\cdot 2d_{ij}\cdot Q_{aijt} \\
& + \sum_{\substack{(a,m,i,j)\in NetP\\ a\in A_{boat}}} tc_a \cdot pw_m \cdot d_{ij}\cdot X_{maijt} \\
& + \sum_{\substack{(a,m,i,j)\in NetP\\ j\in I_{port}\wedge i\notin I_{port}}} hhc_j \cdot X_{maijt} \\
& + \sum_{i\in I_{port}} cfp_i \cdot Y_i + \sum_{i\in I_w} w_i \cdot lc_i \cdot wwh \cdot wpt \cdot Y_i \\
& + \sum_{i\in I_w} wpsq \cdot lc_i \cdot wwh \cdot wpt \cdot YC_i \\
& + \sum_{\substack{(m,g)\in H\\ i\in I_w}} w_g \cdot lc_i \cdot wwh \cdot wpt \cdot Z_{gmi} + \sum_{\substack{(a,i.j)\in Net\\ a\in A_{truck}}} w_a \cdot lc_i \cdot wwh \cdot wpt \cdot K_{ai} \Bigg) \Bigg] \\
& + tr \cdot DP_t
\end{aligned}
\tag{3}
$$

Firstly, the incomes are determined from sales through the multiplication of products' price per unit sold (psu_m) and the quantity that is delivered in markets in each time period t. The total cost terms include the following in the respective order: storage operating costs; transportation costs for road transportation; transportation costs for sea transportation; handling costs at the hub terminal; contracted costs with the freighter; and labour costs at entities, which include labour costs for storage and labour costs for owned transportation modes (road transportation).

Finally, the last term defines the depreciation of the capital invested (DP_t) and tr represents the tax rate. For the capital invested it was considered a depreciation linear method as presented in Eq. (4). The division of the fixed capital investment into equal parts for each time period is shown in Eq. (5). The fixed capital investment (FCI) is described in Eq. (6) and its terms include the investment in facilities, technologies and transportation vehicles, respectively.

$$DP_t = \frac{(1 - sv) \cdot FCI}{NT} \tag{4}$$

$$FDC_t = \frac{FCI}{NT} \tag{5}$$

$$FCI = \sum_{i \in I_w} sqmc_i \cdot YC_i + \sum_{\substack{(m,g) \in H \\ i \in I_w}} tec_g Z_{gmi} + \sum_{\substack{(a,i,j) \in Net \\ a \in A_{truck}}} ftc_a K_{ai} \tag{6}$$

4.4 Environmental Objective Function

As previously mentioned to model the environmental objective function, the ReCiPe method developed by Goedkoop et al. (2009) was applied as expressed in Eq. (7). The environmental impact of the three different SC activities is calculated for each midpoint category c. The activities considered are, in respective order, the environmental impact of storage, environmental impact of transportation and environmental impact of entities installation.

The final calculation of the environmental impact is given by the normalized sum of the impact of each individual activity described just now with the normalization factor η_c. The use of this normalisation factor is justifiable since the results of each impact category need to be in the same units.

$$\min EnvImpact = \sum_c \eta_c \left(\begin{array}{l} \displaystyle\sum_{\substack{t \in T \\ (m,g) \in H}} ei_{mgc} pw_m S_{mgit} \\ + \displaystyle\sum_{\substack{t \in T \\ (a,m,i,j) \in NetP}} ei_{ac} pw_m d_{ij} X_{maijt} + \sum_{i \in I_w} ei_{ic} YC_i \end{array} \right) \tag{7}$$

4.5 Social Objective Function

The objective of this function is the maximization of the social benefit, measured through an indicator developed by Mota et al. (2015) and presented in Eq. (8). This objective function relates the number of jobs created by the SC with the maximization of job creation in countries with lower economic development. The indicator selected to measure the economic development was the GDP, as this appears as quite adequate to measures such objective as stated in Mota et al. (2015). Based on the GDP per capita, a regional factor μ_i^{GDP} characterizes each region i.

The contribution of each different activity to the creation of jobs in that location is given by the following terms of Eq. (8), in respective order:

- Entity installation (warehouses), which considers the number of jobs created in each warehouse. The first two terms in Eq. (8) are part of this activity. It takes into account the minimum number of workers needed when a facility opens (w_i) and the workers that operate in warehouses with different capacities (w_{psq});
- Technology installation, which considers the number of jobs created with the operation of each technology (w_g);
- Transportation, which considers the number of workers per transportation mode (w_a) in the company's fleet, and the estimated number of jobs created per km through sea transportation,
  averaged in the number of years in the time horizon ($\frac{w_a}{yth}$). Transportation activity entails thus *yth*
  the last two terms in Eq. (8). The economic equivalent of the latter term is not present in the economic objective function because this service is included in the variable and fixed costs paid to freighters.

$$\max GDPInd = \sum_{i \in I_w} \mu_i^{GDP} w_i Y_i + \sum_{i \in I_w} \mu_i^{GDP} \cdot wpsq \cdot YC_i + \sum_{\substack{(m,g) \in H \\ i \in I_w}} \mu_i^{GDP} w_g Z_{gmi}$$
$$+ \sum_{\substack{(a,i,j) \in Net \\ a \in A_{truck}}} \mu_i^{GDP} w_a K_{ai} + \sum_{\substack{(a,m,i,j) \in NetP \\ a \in A_{boat} \\ t \in T}} \mu_i^{GDP} \frac{w_a}{yth} \cdot pw_m \cdot d_{ij} \cdot X_{maijt} \tag{8}$$

4.6 Constraints

The model constraints are grouped into four categories, namely: (1) material balances at factories, warehouses and seaports; (2) entity capacity constraints; (3) transportations constraints; and (4) technology constraints. The four constraints' categories are displayed in Appendix 1.

In terms of material balance at factories, the model ensures that all final products are moved out of factories to the warehouses or directly to the market. Secondly, as regards inventory kept in warehouses, the balance between the products kept in stock previously plus the inbound flow must equal the amount kept in stock currently plus the outbound product flow. In the case of seaports, an entity that operates solely in a cross docking, the inbound flow at each seaport equals the outbound flow. The last constraint associated to this category ensures that the demand at markets has to be completely satisfied.

The second category intends to set the capacity limits. Inequalities constraints the maximum and minimum supply of final products by factories to warehouses,

between each pair of entities, and limit the stock permitted at warehouses. The capacities in these constraints are pre-established; that is, before running the model these parameters are given, independently of the installed entities and technologies. In addition, these constraints function also as minimum flow constraints since they indicate that if an entity is installed then there are product flows going through it.

Regarding transportation, aspects as the necessary number of trips and trucks, type and capacity of the transportation mode selected are limited. The last category of constraints, concerning technologies, specifies the maximum storage capacity of each storing technology and the minimum storage level. For detail information on the model constraints see Mota et al. (2015).

5 Case Study Description

The developed model was applied for the creation of a European VSC, that due to confidentially reasons cannot be identified. Currently, the company owns two factories, which have sufficient capacity to meet the demand of their clients (21 cluster within all in Europe). The demand corresponds to the number of births multiplied by the number of doses of each vaccine recommended by the WHO. For the case under study, 4 types of entities are considered, namely, factories, warehouses, seaports and markets. Factories are regarded as suppliers of vaccines, considering that they are responsible for producing vaccines and afterward can ship them to warehouses or directly to markets. These entities are characterized by a maximum and minimum limit for supply capacity and order quantity.

Warehouses will be used to store vaccines and for that purpose, different storing technologies may be installed in these facilities. Warehouses locations as well as capacities and technology used are to be defined.

The company manufacturers and commercializes two types of products, one vaccine against poliomyelitis and another one against measles, mumps and rubella. The former is denoted by *rpIPV* while the latter is denoted by *fpMMR*. These two vaccines represent two different families of vaccines, one that is composed of vaccines that should be refrigerated and another one comprising vaccines that should be frozen. Product *rpIPV*, a SKU, is presented in a cardboard box with 10 vials, each containing 10 doses of vaccines, thus, each product SKU contains 100 doses of vaccines. On the other hand, product *fpMMR* is presented in a cardboard box with 10 vials as well; however, the vials only contain one dose of vaccine and, consequently, each product SKU contains 10 doses of vaccines. Both products described are stored in warehouses with the appropriate storing technologies. The proposed technologies differ in product stored, storage capacity and environmental impact. There are two technologies that adequately store refrigerated products Walk-In Cold Rooms (WICR) and refrigerators, and two others for frozen products, Walk-In Freezer Rooms (WIFR) and freezers.

In terms of transportation, two distinct ways, trucks or cargo ships may carry products. Transportation may be unimodal, performed only by trucks, or intermodal

occurs as a combination of both modes mentioned. As technologies, trucks are also characterized according to their capacity, variable costs, number of drivers and average vehicle consumption. The company may choose between two types of trucks, A or B, where B has a higher capacity and vehicle consumption. In relation to cargo ships and freighter's cost, they are also characterized by their capacity; hub fixed cost and hub variable cost.

The environmental impact of some SC activities is characterized using SimaPro Ecoinvent database version 8.01. By utilizing this database, data are extracted in order to characterize the four different storage technologies, three different transportation modes and the installation of entities.

To fully characterize the model, there is the need to detail the parameters that apply to the countries where the several entities are installed. For that reason, for each location variable costs, such as average labour cost and construction cost are considered, as well the GDP per capita, presented in the social objective function.

The company now intends to determine where are the best locations to locate warehouses, to which vaccines will flow after being produced at factories. This localization should account not only for an economic objective but also considering the environmental and social aspects. The superstructure considered, constituted by 2 factories, 7 possible warehouses and 5 seaports, is depicted in Fig. 3.

Fig. 3 Case-study superstructure

For the purpose of comprehending how each sustainability pillar, measured by each objective function defined, affects the VCS and planning modelled, three scenarios are considered:

- Scenario A: the optimum economic performance is prioritized, which implies that all the decisions regarding the design of the VSC are determined through NPV maximization of the entire SC;
- Scenario B: the optimum environmental performance is prioritized, which means that the environmental impact is minimized;
- Scenario C: the optimum social performance is prioritized, which means that the creation of jobs in countries with lower socio-economic conditions is maximized.

6 Results

6.1 Single Objective Optimization

Results obtained for the economic performance indicator across the different scenarios are presented in Table 1. One can observe that the most profitable solution (Scenario A) does not have the worst environmental performance when compared to the other two scenarios (B and C). However, scenario A has the worst social performance in comparison with the other two cases. The environmentally sustainable solution (Scenario B) is obtained at the cost of a 7% reduction in the profit over the 5-year time horizon, and the social performance increases by 24%, which translates in 186 more job opportunities. In its turn, the socially beneficial solution (Scenario C) is obtained through the maximization of job opportunities, at the expense of a 35% decline in the NPV. The environmental impact is also extremely affected (negatively), worsening around 1276% its performance, largely due to a massive usage of transportation. Nevertheless, this solution increases the social performance by 283% when compared with Scenario A, which corresponds to the creation of 1,246 additional job opportunities.

Table 2 summarizes further results for the model. As shown in Tables 1 and 2, the results returned from the execution of the model differ across the different optimization objectives both in terms of strategic and tactical decisions. Besides the differences, all the scenarios considered have in common two features: (1) two fac-

Table 1 Summary of performance indicator's values for scenarios A, B and C

Performance indicator	Units	Scenarios		
		A	B	C
Economic	€	1,817,029,498	1,696,733,844	1,183,138,668
Environmental		1,172,908	280,488	4,136,377.37
Social		386.18	478.38	1,476.73

Table 2 Decisions' results summary for scenarios A, B and C

	Scenarios		
	A	B	C
Warehouses	Madrid Prague	All installed	All installed with maximum capacity
Storage	Refrigerators and freezers are the preferred storage technologies used		
Inventory	More inventory of rpIPV is kept	More inventory of fpMMR is kept	More inventory of fpMMR is kept
Transportation	Most trucks purchased are big trucks	Most trucks purchased are big trucks	Most trucks purchased are small trucks
	Sea transportation is not used	Sea transportation is used in both scenarios	

tories operating, but not at maximum capacity and (2) storage done with refrigerators and freezers, since their ratio of capacity to price is greater when comparing with WIFR and WICR, respectively.

In the economic optimization scenario (scenario A), warehouses are only installed in two countries and Transportation Sea is not used, the company chose unimodal transportation with the acquisition of trucks of bigger capacity in higher quantity in comparison with smaller trucks.

When minimizing the environmental impact (scenario B), all the decisions were taken envisioning the reduction of the negative environmental impact of transportation, storing products in electricity consuming technologies and the installation of warehouses. All possible warehouses were installed in order to decrease the number of trips travelled by trucks, therefore decreasing the overall number of travelled kilometres. As for their capacity, all warehouses have the minimum capacity, except one. As can be seen in Table 2, all of trucks purchased have a big capacity to guarantee that the number of trips among entities is minimized, thus reducing the environmental impact associated with transportation. For the same reason, sea transportation is used in this scenario because even though the environmental impact of boats is greater than that of trucks, boats may carry more products per trip.

The last scenario (scenario C), aims to maximize the number of job opportunities created in the operation of storing technologies, warehouses and in driving the fleet of trucks owned by the company. In this case, the model returns a network where all warehouses were installed with maximum capacity, although their full capacity was not being reached, in order to increase the number of jobs available. The selection of refrigerators and freezers technologies, the acquisition of smaller trucks and the inclusion of intermodal transportation, were also considered in this model to increase even further the creation of jobs.

Comparing the fixed capital invested in the different scenarios and their distribution, as shown in Table 3, we see that the higher social benefit comes with the higher costs. This is due to the useless costs incurred by the company since the objective was to maximize the number of job opportunities without any economic restriction.

Table 3 Fixed capital invested in entities, trucks and technologies in scenarios A, B and C

	Units	Scenario A	Scenario B	Scenario C
Fixed capital invested in entities (warehouses)	€	362,727	558,180	2,614,500
Fixed capital invested in trucks	€	260,000	600,000	2,000,000
Fixed capital invested in technologies	€	213,151	213,151	1,062,450
Inventory holding costs	€	570,420	11,834,356	5,737,233

Table 4 Environmental impact of storage, transportation and facility installation in scenarios A, B and C

	Scenario A	Scenario B	Scenario C
Storage	26	26	159
Transportation	1,172,326	279,906	4,133,751
Facility installation	556	556	2,622
Total	1,172,908	280,448	4,136,532

Once the sum of the costs in C is greater in comparison with scenario A and B, the results from this scenario clearly show that it is not feasible. In this superstructure there are large quantities of resources not being used, which are only making the company incurring additional costs.

In parallel, scenario B have the higher value of all of fixed capital invested, has a result of his inventory profile. Once scenario B aims to minimize the environmental impact, efforts will be made to optimize the transportation routes, in terms of cargo and distance. Since the B trucks acquired are characterized by a higher transportation capacity, the transportation of vaccines to the markets will only occur when the maximum capacity is reached, thus increasing the costs of holding the vaccines inventory at warehouses.

On the environmental impact and as seen in Table 4, transportation is the greatest contributor to the total environmental impact and is the one that varies the most among scenarios. The results presented in Table 4 shows greatly reduced in scenario B due to the decline in the number of transportation trips. Transportation is thus the most important pinpoint to consider when crafting strategies to reduce environmental impact. In this study, intermodal solutions seem to be environmentally beneficial due to a higher transportation capacity of boats. Testing different warehouse locations and exploring rail options would be strategies worth following to further reduce environmental impact.

Proceeding with the analysis of Table 4, storage activities are the ones that contribute less to these SC environmental impacts. Nevertheless, there is an opportunity to improve the SC sustainability in terms of environmental impact when it comes to storage technologies. This may occur if fewer refrigerators and freezers are used; that is, the capacity of storage technologies should be completely used before purchasing more technologies. Furthermore, WICR and WIFR must be avoided if environmental impact is to be minimized.

6.2 Multi-objective Approach

As noticed before, some of the solutions through single objective optimization might not be viable to implement. Hence, it becomes necessary to analyse more than one objective simultaneously. To study better strategies on how to increase social benefit while preserving reasonable economic and environmental performances, new scenarios ought to be designed. In this case, the goal is to comprehend how to minimize the environmental impact or maximize social benefit with an additional economic constraint, which offers an overview of the necessary trade-offs. For this purpose, two scenarios are considered:

- Scenario D: In this scenario, the optimum environmental performance is prioritized with a maximum reduction of 5% in the NPV determined in scenario A. This results from the minimization of the environmental impact function with an additional constraint stating that the NPV must be at least 95% of the profit obtained in scenario A;
- Scenario E: In this scenario, the optimum social performance is prioritized with a maximum reduction of 5% in the NPV determined in scenario A. This results from the maximization of the social objective function with an additional constraint stating that the NPV must be at least 95% of the profit obtained in case A.

Table 5 shows the performance indicator's value for the new scenarios. With the additional economic constraint, the profit has not declined as much as expected when the environmental impact is being minimized. In fact, profit has increased by 2% when compared to scenario B. Yet, the environmental impact is significantly higher, approximately, 5% higher than that of scenario B. Hence, it is possible to conclude that a trade-off exists between the economic and the environmental indicators. Similarly, when the social performance indicator is maximized under the additional economic constraint, the same effect is observable. The social performance suffered a substantial decline so that the profit could be maintained at 95% of the original profit in scenario A. Consequently, 531 fewer job opportunities were created, but with a profit growth of 46% in comparison to scenario C.

When considering the prioritization of the optimum environmental performance, 5 warehouses operating at minimum capacity and 1 operating above it compose the resultant network. As seen in scenario B, the number of small trucks purchased was null and intermodal transportation is considered.

Table 5 Summary of performance indicator's values for scenarios D and E

Performance indicator	Units	Scenarios	
		D	E
Economic	€	1,726,000,000	1,726,000,000
Environmental		2684,593	1,083,437
Social		386.18	478.38

As an alternative, the outcome of the model in scenario E showed that all warehouses were installed but not at full capacity. Two of the seven warehouses were installed with maximum capacity, while the remaining warehouses were installed with, approximately, half of the maximum capacity. In this scenario 50 trucks A and 10 trucks B were acquired, thus maximizing the number of job opportunities created through transportation. Seaports were not used in this scenario, thus excluding intermodal transportation. In terms of fixed capital investments, the costs of this scenario were greatly reduced in comparison with scenario C.

Scenario E demonstrates an example of how social benefit may be created while decreasing negative environmental impact and generating a higher profit. It can be seen that if the social and economic objectives are analysed simultaneously, the model can decrease the environmental impact by 75% when compared to the scenario C (Table 6).

The outcome from the execution of the model in this scenario shows clear improvements for the economic and environmental performance indicators while maintaining the social performance indicator close to the one obtained from the scenario where the social indicator is maximized. In future improvements of the model, a multi-objective optimization method ought to be used in order to extract better conclusions on how the performance indicators interact.

In order to understand the impact of some critical parameters, a sensitivity analysis was carried out to investigate their impact on the SC network structure and planning. Two different analyses were conducted where changes in the following parameters were considered: demand values and investment costs.

Once demand uncertainty is a major problem that affects SC, uncertainty has been modelled through a variance of -5, -10, $+5$ and $+10\%$ in the demand value estimated initially. The investment costs, tested for a variation of $+5$ and $+10\%$, include costs incurred in the purchase of trucks, in the purchase of storage technologies, in the construction of warehouses and, finally, inventory holding costs.

Based on the results, 2 conclusions can be drawn. First, in terms of demand variation, one can conclude that the design of the SC is quite robust. The SC structure did not suffer any changes in terms of number and location of infrastructures in all runs; however, some differences in terms of flows of products are noticeable. Second, the variation of the investment costs does not have a great influence in the design and operations of the SC under study, since the major part of the total expenses incurred is included in the production costs.

Table 6 Environmental impact of storage, transportation and facility installation in scenarios D and E

	Scenario D	Scenario E
Storage	26	114
Transportation	284,011	1,036,592
Facility installation	566	1,731
Total	284,593	1,038,437

All in all the results of the case study show that depending on the performance objective that the company wants to prioritize, the company's decision-making will be more concerned with improving the activities and processes that drive that objective.

Therefore if the major concern is to improve the economic performance, efforts will be made to maximize the profits, satisfying the demand with the minimum possible quantity of resources. In the case of environmental impact, the major decision is related to the trade-off between having the company doing more transportation trips against keeping more inventories at the warehouse. Alternatively, environmental-friendly solutions may be procured to achieve sustainability while reducing inventories costs. Finally, from the usage of social indicators, it is possible to investigate socially responsible options while arranging compromises, either with the economic performance of the company, the environmental impact or both.

Ultimately, the goal is to design and plan the operations of the SC in order to maximize profits while ensuring that the company is embracing environmental sustainability in its operations and is demonstrating social responsibility.

7 Conclusions

The present paper aimed to develop a decision tool design and plan sustainable VSC, integrating the three dimensions of the TBL. The developed model provides support for strategic and tactical decisions at several levels of the SC. Specifically, it allows understanding the effect of these decisions on each one of the performance indicators (economic, environmental and social), thus enabling derivation of potential trade-off strategies to balance them. Moreover, the model also facilitates the comprehension of connections among different SC activities, giving an opportunity to better understand the performance of the combined indicators across the SC. From the usage of environmental indicators, it is possible to identify environmental sustainability foci and select actions to diminish environmental impact of SC activities. Similarly, from the usage of social indicators, it is possible to investigate socially responsible options while arranging compromises, either with the economic performance of the company, the environmental impact or both.

As future challenges, translating some of the limitations of the present work, numerous features ought to be included in the model. First and to further understand how to better plan inventory, other storing technologies such as solar refrigerators/freezers for zones with depleted electricity supply would also be useful and should be explored. Perishability is also a crucial characteristic of such products and should be modelled as this may influence the design and planning of the pharma supply chains.

On the objective functions namely on the social dimension modelling, health equity issues (in terms of the accessibility to vaccines) could also be addressed as to minimize the differences that exist among regions even inside the same country. However, to improve the social benefit in developing countries, the economic and environmental performance indicators would certainly be negatively impacted. Yet,

ultimately, the objective of immunization is to eradicate and prevent diseases in the world, which can arguably be classified as a social objective.

Finally, the presence of uncertainty such as on the vaccines demand should be also studied so as to build more robust supply chain networks that more easily would account for changes in the markets.

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Appendix 1. MILP Formulation Adapted from Mota et al. (2015)

1 **Sets**

i, j Entities or locations

$$I = I_f \cup I_d \cup I_c \cup I_{port} = I_{count1} \cup I_{count2} \cup \ldots$$

I_f—Factories; I_w—Warehouses; I_c—Markets (clients); I_{port}—Seaports

a Transport modes

$$A = A_{truck} \cup A_{boat}$$

A_{truck}—Truck; A_{boat}—Boat

g Technologies

$$G = G_{froz} \cup G_{refr}$$

G_{froz}—Freezing technologies; G_{refr}—Refrigerating technologies

m Products

$$M = M_{froz} \cup M_{refr}$$

M_{froz}—Frozen products; M_{refr}—Refrigerated products

t Time periods

2 Parameters

Entity-related parameters

hhc_i Handling costs at hub terminals
w_i Workers needed when entity i opens
lc_i Labour cost at location i
$wpsq_i$ Workers needed per square meter for entity i
$sqmc_i$ Construction cost of entity i per square meter
μ_i^{GDP} Social factor of location i based on GDP per capita

Product-related parameters

pus_m Price per unit sold of product m
pw_m Weight of each product unit

Technology-related parameters

w_g Fixed workers per technology g
tec_g Installation cost of technology g
opc_g Operating costs of technology g

Transportation-related parameters

ftc_a Fixed transportation cost for transportation mode a
avc_a Average fuel consumption ($L/100$ km) of transportation mode a
vmc Vehicle maintenance costs ($€/km$)
tc_a Variable transportation cost of transportation mode a per km
fp Fuel price ($€/L$)
cfp_i Contracted payment to the freighter for allocated capacity per time period and/or for hub terminal use
w_a Workers needed per transportation mode a for the case of road transportation. For the case of sea transportation, it represents the average number of jobs created in freighters per km

Environment-related parameters

ei_{mgc} Environmental impact characterisation factor of storing product m with technology g, at midpoint category c (per product unit)
ei_{ac} Environmental impact characterisation factor of transport mode a, at midpoint category c (per km)
ei_{ic} Environmental impact characterisation factor of installing entity i, at midpoint category c (per square meter)
η_c Normalisation factor for midpoint category

Others

d_{ij} Distance between entities i and j (km)
yth Number of periods in time horizon (e.g. years)
wpt Number of weeks per time period
ir Interest rate

sv Salvage value
tr Tax rate
wwh Weekly working hours

3 Variables

Continuous variables

S_{mit} Amount of inventory of product m stored in entity i in time period t
S_{mgit} Amount of product m stored with technology g at entity i in time period t
X_{maijt} Amount of product m transported by transport mode a between entities i and j in time period t
YC_i Necessary capacity of entity i
K_{ait} Necessary number of vehicles of transportation mode a entity i in time period t

Integer variables

K_{ai} Necessary number of vehicles of transportation modes a in entity i in all time horizons
Q_{aijt} Number of trips with transportation mode a between entities i and j in time period t
Z_{gi} Number of installed technologies g in entity i

Binary variables

Y_i 1 if entity i is installed

Auxiliary variables at objective functions

NPV Net Present Value
CF_t Cash flow in time period t
NE_t Net earnings in time period t
FDC_t Fraction of the total depreciation capital in time period t
FCI Fixed capital investment
DP_t Depreciation of the capital at time period t

4 Objective Functions

Economic Objective Function

$$\max NPV = \sum_{t \in T} \frac{CF_t}{(1+ir)^t}$$

Environmental Objective Function

$$\min EnvImpact = \sum_{c} \eta_c \left(\begin{array}{l} \sum\limits_{\substack{t \in T \\ (m,g) \in H}} ei_{mgc} pw_m S_{mgit} \\ + \sum\limits_{\substack{t \in T \\ (a,m,i,j) \in NetP}} ei_{ac} pw_m d_{ij} X_{maijt} + \sum\limits_{i \in I_w} ei_{ic} YC_i \end{array} \right)$$

Social Objective Function

$$\max GDPInd = \sum_{i \in I_w} \mu_i^{GDP} w_i Y_i + \sum_{i \in I_w} \mu_i^{GDP} \cdot wpsq \cdot YC_i + \sum_{\substack{(m,g) \in H \\ i \in I_w}} \mu_i^{GDP} w_g Z_{gmi}$$

$$+ \sum_{\substack{(a,i,j) \in Net \\ a \in A_{truck}}} \mu_i^{GDP} w_a K_{ai} +$$

$$\sum_{\substack{(a,m,i,j) \in NetP \\ a \in A_{boat} \\ t \in T}} \mu_i^{GDP} \frac{w_a}{yth} \cdot pw_m \cdot d_{ij} \cdot X_{maijt}$$

5 Constraints

Material balances

Material balance at factories:

$$\sum_{\substack{n,j:(n,i,j) \in F_{OUTF} \\ a:(a,n,i,j) \in NetP}} X_{naijt} = ins_{mi}, t = 1 \wedge m \in M \wedge i \in I_f$$

$$\sum_{\substack{n,j:(n,i,j) \in F_{OUTF} \\ a:(a,n,i,j) \in NetP}} X_{naijt} = P_{mit}, t \in T \backslash \{1\} \wedge m \in M \wedge i \in I_f$$

Material balance at warehouses:

$$\sum_{\substack{n,j:(n,j,i)\in F_{INW}\\ a:(a,n,j,i)\in NetP}} BOM_{mn}X_{najit} = S_{mit}$$

$$+ \sum_{\substack{n,j:(n,i,j)\in F_{OUTW}\\ a:(a,n,i,j)\in NetP}} BOM_{mn}X_{naijt}, t = 1 \wedge m \in M \wedge i \in I_w S_{mi(t-1)}$$

$$+ \sum_{\substack{n,j:(n,j,i)\in F_{INW}\\ a:(a,n,j,i)\in NetP}} BOM_{mn}X_{najit} = S_{mit}$$

$$+ \sum_{\substack{n,j:(n,i,j)\in F_{OUTW}\\ a:(a,n,i,j)\in NetP}} BOM_{mn}X_{naijt}, t \in T\backslash\{1\} \wedge m \in M \wedge i \in I_w$$

Cross-docking at seaports:

$$\sum_{\substack{n,j:(n,j,i)\in F_{INPort}\\ a:(a,n,j,i)\in NetP}} BOM_{mn}X_{najit}$$

$$= \sum_{\substack{n,j:(n,i,j)\in F_{OUTPort}\\ a:(a,n,i,j)\in NetP}} BOM_{mn}X_{naijt}, t \in T \wedge m \in M \wedge i \in I_{port}$$

Demand at markets:

$$\sum_{\substack{j:(m,j,i)\in F_{INC}\\ a:(a,m,i,j)\in NetP}} X_{najit} = d_{mit}, i \in I_c, t \in T$$

Entity capacity constraints

Supply capacity

$$P_{mit} \leq sq_{mi}^{max}, i \in I_f \wedge m \in M \wedge t \in T$$
$$P_{mit} \geq sq_{mi}^{min}, i \in I_f \wedge m \in M \wedge t \in T$$

Flow capacity

$$\sum_{a,m,j:(a,m,i,j)\in NetP} X_{maijt} \leq ec_i^{max} Y_i, i \in I \wedge t \in T$$

$$\sum_{a,m,i:(a,m,i,j)\in NetP} X_{maijt} \leq ec_j^{ma} Y_j, j \in I \wedge t \in T$$

Stock capacity

$$S_{mit} \leq il_{mi}^{max} Y_i, m \in M \wedge i \in I_w \wedge t \in T$$
$$S_{mit} \geq il_{mi}^{min} Y_i, m \in M \wedge i \in I_w \wedge t \in T$$

Entity capacity

$$YCT_{it} = \sum_{m,a,j:(m,a,j)\in NetP} vpu_m X_{majit} + \sum_{m:(m,i)\in V} vpu_m S_{mit}, i \in I_w \wedge t \in T$$
$$YC_i \geq YCT_{it}, i \in I_w$$
$$YC_i \leq ea_i^{max} Y_i, i \in I_w$$
$$YC_i \geq ea_i^{min} Y_i, i \in I_w$$

Entity existence constraints

$$\sum_{a,m,i,t:(am,i,j)\in NetP} X_{maijt} \geq Y_j$$
$$\sum_{a,m,j,t:(am,i,j)\in NetP} X_{maijt} \geq Y_i$$

Transportation constraints
Physical constraints

$$\sum_{\substack{a,j:(a,m,j,i)\in NetP \\ j\setminus(I_{port}\cup I_f)}} X_{majit} = \sum_{\substack{a,j:(a,m,i,j)\in NetP \\ j\in I_{port}}} X_{maijt}, m \in M \wedge i \in I_{port}$$

Necessary number of trips

$$\sum_{m:(a,m,i,j)\in NetP} X_{majit} \leq lt_a^{max} Q_{aijt}, (a,i,j) \in Net$$
$$\sum_{m:(a,m,i,j)\in NetP} X_{majit} \geq lt_a^{min} Q_{aijt}, (a,i,j) \in Net$$
$$Q_{aijt} \leq BigM \cdot Y_i$$
$$Q_{aijt} \leq BigM \cdot Y_j$$

Contracted capacity with sea carrier

$$\sum_{m:(a,m,i,j)\in NetP} X_{maijt} \leq cca_a^{max}, (a,i,j) \in Net \wedge a \in A_{boat}$$

Necessary number of transportation modes

$$KT_{ait} = \frac{\sum_j 2 \cdot dist_{ij} Q_{aijt}}{avs \cdot mhw \cdot wpt}, (a,i,j) \in Net \wedge a \in A_{truck}$$

$$K_{ai} \geq KT_{ait}, a \in A_{truck}$$

$$\sum_{a,i:a\in A_{truck}} ftc_a K_{ai} \leq inv$$

$$K_{ai} \leq BigM \cdot Y_i$$

$$K_{ai} \leq BigM \cdot \sum_{\substack{m,j:(a,m,i,j)\in NetP \\ t\in T}} X_{maijt}, a \in A_{truck}$$

Technology constraints

Technology capacity

$$S_{mgit} \leq sc_g^{max} Z_{gmi}, i \in I_w \wedge (m,g) \in H$$

$$S_{mgit} \geq sc_g^{min} Z_{gmi}, i \in I_w \wedge (m,g) \in H$$

$$S_{mgit}, X_{maijt}, YC_i, YCT_{it}, KT_{ait} \geq 0$$

$$K_{ai}, Q_{aijt}, Z_{gmi} \in \mathbb{N} \wedge \{0\}$$

$$Y_i \in \{0,1\}$$

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Drug Shortages and Their Impact on Patients and Health Care Systems—How Can Systemic and Organizational Frameworks Help to Prevent or Mitigate Them?

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Abstract Shortages of medicines have been reported worldwide, becoming a public health problem in many countries in recent years. They negatively impact on treatment outcomes, quality and efficiency of patient care, as well as that they pose organizational, managerial and financial burdens on health care facilities and generally—health care systems. Health and well-being of patients is and should always be the top priority for health care decision-makers; however, the variety of vested interests of different stakeholders of the pharmaceutical market makes coping with and preventing drug shortages a very difficult task. Characteristics of drug shortages vary across countries, but several lessons can be drawn based on a collective international experience. The complex nature of drug shortages necessitates an interdisciplinary approach, international collaboration and the application of experience from different scientific spheres. This chapter discusses dimensions of the impact that drug shortages have on patients' health and well-being, and health care systems. Various measures, systemic and organizational frameworks aimed to prevent or mitigate drug shortages are also discussed, as well as their role in diminishing the impact of drug shortages. The adopted methodology included a non-systematic review of the scientific literature and documents published by organizations active in the health care sector and pharmaceutical markets. This was supplemented by gathering additional information from selected health care system stakeholders and analysts who are dealing with the problem of drug shortages in different countries.

Keywords Drug shortages · Health care quality · Health care costs · Health care system · Health care impact · Financial impact

1 Introduction

Drug shortages (DS) have occurred more frequently over the past 20 years than before and have posed a threat to all stakeholders in global health systems (Dill and Ahn 2014; U.S. Food and Drug Administration 2011). Most probably, the problem

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of DS was described for the first time in a scientific journal in 1976 (Culliton 1976) and also when governmental bodies of the United States of America (USA) were urged to act on the problem (Stolar 1976) although the situation had arisen at least two or three years before (Culliton 1976). However, it was not until 1996 that the first database on DS, known as the University of Utah Drug Information Service (UUDIS), was established in Utah, the USA. This system, until today, records and provides information on the drugs out of stock within the University of Utah hospitals and clinics (Fox et al. 2003). UUDIS shows the number of new shortages per year fluctuating from 2001 to 2015 with an overall upward trend (Fox 2015). Considering that problem of shortages has remained unsolved over time; the burden of DS is clearly increasing.

The term "drug shortage" relates to situations in which patients do not receive the amount of medicines they need. However, defining this academically and systematically is not straightforward. One commonly-used definition has been coined by the American Society of Health-System Pharmacists (ASHP): *"A supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent"* (American Society of Health-System Pharmacists 2009). The American government regulatory authority for the pharmaceutical market, US FDA (Food and Drug Administration), has chosen to track only shortages of medically necessary drugs (American Society of Health-System Pharmacists 2009). Notably, De Weerdt et al. in 2015 found that there were 26 different ways worldwide of defining DS among governmental institutions, professional organizations, and individuals (De Weerdt et al. 2015). Those definitions can be divided into two types, (i) reporting and (ii) designating the drug shortage. The first determines when to report a shortage and the second confirms that it does occur (U.S. Food and Drug Administration 2011).

In 2017, the WHO has proposed a set of two co-existing definitions of DS. On the supply side: *"A 'shortage' occurs when the supply of medicines, health products and vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs. This definition refers only to products that have already been approved and marketed, in order to avoid conflicts with research and development agendas."* On the demand side: *"A 'shortage' will occur when demand exceeds supply at any point in the supply chain and may ultimately create a 'stockout' at the point of appropriate service delivery to the patient if the cause of the shortage cannot be resolved in a timely manner relative to the clinical needs of the patient."* (World Health Organisation (WHO) 2016). These WHO definitions can be seen as an effort to emphasize the needs of patients and the important role of essential medicines, while still taking into consideration the natural characteristics of the pharmaceutical market and the health care system's environment, where also non-essential, and sometimes even unnecessary medicines may be present.

Despite inconsistent views on the definitions of DS, the issue of shortages in the supply of medicines is undeniably increasingly common in the developed world (Dill and Ahn 2014; U.S. Food and Drug Administration 2011). There has been a

variety of articles raising concerns about the prevalence of DS in European countries (Casassus 2015; European Association of Hospital Pharmacists (EAHP) secretariat 2014), Canada (Morrison 2011), Australia (Tan et al. 2016) and, especially, in the USA (United States Government Accountability Office Report 2014; Ventola 2011). For example, the number of drugs listed as "active drug shortages" in 2012 by the UUDIS was 456, with 195 newly reported and 261 persisting from previous years, while these two indicators for 2007 were 114 and 40, respectively (United States Government Accountability Office Report 2014). The issue of supply disruption happens for different types of medicines, from basic products, like sodium (Dill and Ahn 2014) to hormones, anesthetics (Kaakeh et al. 2011) and even cancer treatment products (Murphy et al. 2014).

The causes of drugs falling short have also been investigated widely. At the production side, shortages of raw materials can greatly affect the industry's manufacturing capacity and supply chain (De Weerdt et al. 2015; Pauwels et al. 2014). The root cause of the ingredients' shortages may even be traced back to natural disasters (Pauwels et al. 2014). Poor manufacturing (e.g. inadequate quality, contamination or wrong packaging) can lead to a product recall which can adversely affect the market, especially if the alternatives are limited (Morrison 2011; Pauwels et al. 2014). In some cases, legal implications such as additional manufacturing quality requirements can reduce the profit resulting from a product line as manufacturing costs increase, which may reduce the market attractiveness. As profit is the key driver of the industry, legal actions may lead to the problem of production plants shutting down (Pauwels et al. 2014).

Interestingly, supply disruption happens only for a minority of drugs in the pharmaceutical market, affecting around 10%, or less, of the total volume of the medicines in use (Office of the Assistant Secretary for Planning and Evaluation; Office of Science and Data Policy—U.S. Department of Health and Human Service 2011). As mentioned above, DS is a fairly new and recent issue; however, a number of publications have shown its impacts and actions taken around the world to tackle it.

In this chapter, we aimed to provide an overview of different kinds of impacts of drug shortages, taking into consideration two major perspectives. The first one includes patients and pertains to issues of medical nature, while the second involves health care systems and pertains to issues of financial nature. Subsequently, we aimed also to provide an overview of systemic and organizational frameworks which could counteract drug shortages and counterweigh their impacts. The adopted methodology included a non-systematic review of the scientific literature and documents published by organizations active in the health care sector and pharmaceutical markets. In order to gather up-to-date and the most relevant information, we have also contacted several health care system stakeholders and analysts who are dealing with the problem of drug shortages in different countries.

2 Impact of Drug Shortages on Patients and Health Care Systems

2.1 Impacts on Patients and of Medical Nature

According to a survey, developed and deployed in 2011 by the Hematology/Oncology Pharmacy Association, aiming to characterize the impact of oncology DS in the USA, shortages led to delays in chemotherapy and therapy changes (McBride et al. 2013). They also increased the risk of medication errors and adverse outcomes, due to using less-familiar medicines. Near-miss medication errors (i.e. errors that did not reach the patients) were reported by 16% of survey participants, predominantly being associated with incorrect dosing conversions and using wrong concentrations. Adverse patient outcomes were believed to be related to DS by 16% of participants (McBride et al. 2013). The detrimental impact of DS on clinical trials was associated with suspending the enrollment of patients (44% of institutions), stopping the trials completely (67%), or the necessity to modify protocols. Other complications included changes to the medications used in trials, omission of some medicines from protocols, and stockpiling of medicines to secure the trials' completion (McBride et al. 2013).

Similarly, DS were revealed to evoke medication errors and adverse events, as well as to result in delayed or cancelled care, and patient complaints, in a survey carried out in 2012 among pharmacy directors in the USA (McLaughlin et al. 2013). At least one or more possible or probable adverse events were reported by 58% of respondents, while 1.1% of respondents reported patient deaths from DS; 1.7%—disabling events caused by shortages; and 19%—adverse events requiring intervention. From among the patient outcomes caused by DS, two were reported most numerously: alternative medication used (85.3% of individual reports) and therapy delay (70.8%). The others included the necessity of increased patient monitoring, suboptimal treatment and increased length of hospitalization (49.1%; 48.5% and 32.7% respectively), followed by: treatment failure, patient transfer to an institution with a supply of the needed medication, and re-admission caused by treatment failure, and death. Not surprisingly, 38% of respondents reported at least one patient complaint because of DS and 9% reported that patients provided their own supply of a medicine that was in shortage (McLaughlin et al. 2013).

Increasing error rates due to DS were also presented in 2015 within a report on a survey performed on the impact of DS in the Southeastern United States, where the majority of hospital pharmacy directors stated that shortages caused a 1–5% error rate in hospitals, given all the manipulation that pharmacists were required to perform to deliver the drug in the most appropriate form to patients. Another dangerous factor resulting from DS was specified as creating unsafe conditions for patients and staff 60% of the time (Caulder et al. 2015).

In order to provide insight into DS in Europe, a survey of hospital pharmacists was performed in 2013. The major clinical outcomes of DS, assessed by European hospital pharmacists as occurring "always or often" included substitution with equivalent drugs (46% of answers), rationing of the drug (23%), delay of therapy (9%) and

substitution with an inferior drug (7%) (Pauwels et al. 2015). Finnish community pharmacists, surveyed also in 2013, reported that problems of various kinds were caused by 33% of the DS cases and were predominantly associated with a lack of satisfaction among customers (54.1% of all problem-causing cases) (Heiskanen et al. 2015).

There is growing evidence on the impacts of DS in particular health care settings or medicine categories. A study performed in 2013, on the impact of DS on patients receiving parenteral nutrition after laparotomy in a 1242-bed medical center in the USA, revealed that shortages were associated with a statistically significant longer hospital stay. Another clinical impact was a longer stay on parenteral nutrition therapy which, although not statistically significant, was considered important due to clinical significance, suggesting a delay in return of bowel function (Bible et al. 2014).

When the impact of shortages of injectable oncology drugs was surveyed across the USA in 2013, 71% of responding hospital pharmacists reported that supplies were inadequate to treat patients and 64% reported that their facility completely ran out of at least one type of injectable oncology drug (Goldsack et al. 2014). Twenty five percent of respondents reported at least one drug safety event due to shortages and 25% of this group reported three or more safety events. Sixty percent of respondents perceived the risk of disease progression—attributable to oncology DS—to range from moderate to very high; while 51% of respondents perceived the risk level of an avoidable medical event due to a drug treatment delay or change to be in the same range. Similarly, the other types of risks were also assessed to range from moderate to very high. This included 40% of respondents perceiving a risk for patients to receive an incorrect dosage of a substitute drug, 46% perceiving the risk of the occurrence of an adverse drug reaction to a substitute drug, 29% perceiving the risk of incorrect drug substitute administration and 35% perceiving the risk of patient death due to drug treatment delay or change (Goldsack et al. 2014).

Managing injectable oncology DS was reported to be associated with other negative impacts, as well. According to 83% of respondents, providers may have changed treatment at their facilities and 62% of respondents reported the use of alternative drug regimens, 47%—dosage changes during treatment, 43%—treatment delays, 38%—prioritization of patients for treatment based on clinical factors, and 21%—patient referrals to or from other facilities (Goldsack et al. 2014).

2.2 Impacts on Health Care Systems and of Financial Nature

In an extensive study of the DS reported to have occurred between 2005 and 2016 in the USA, shortages were found to be associated with significant price increases of the affected medicines (Alevizakos et al. 2016). In majority, DS affected medications with apparently decreasing price trends, while after the shortages had happened, the resolution price growth rates remained still elevated.

Shortages of oncology medicines in the USA were found to have significant resource implications. Approximately 34% of pharmacists surveyed in 2011 reported that their facilities dedicated at least 1,000 personnel hours (i.e. 0.5 full-time equivalent staff resource units or 20 h weekly) to managing oncology DS (McBride et al. 2013). This resulted in an increased work burden of the already employed staff, rather than hiring additional personnel. Increased costs were reported from 85% of survey participants' institutions, while at 10% of the institutions the cost increases were associated with reimbursements of substitute products. Worryingly, as many as 28% of survey participants reported to purchase products in short supply from the gray market, at higher prices (McBride et al. 2013).

In a survey among pharmacy directors in the USA, 27% (51/185) reported that they measure costs arising from DS quarterly. Of all participants, 37 calculated quarterly costs from DS of greater than USD 100,000. Furthermore, to sustain the increased workload, 49 participants reported adding 0.6–1.0 full-time equivalents because of DS (McLaughlin et al. 2013).

A survey among European hospital pharmacists revealed that among financial impacts of DS occurring "always or often", there were the following components: increased hospital costs (39% of respondents' answers), using a more expensive alternative (37%), increased pharmacy and personnel costs (34%) and increased costs for patients (11%) (Pauwels et al. 2015).

Apparently, time spent by employees of pharmacies and health care facilities to handle DS is one of the major concerns, as far as the financial impacts are concerned. On the turn of 2015 and 2016, the Flemish community pharmacists in Belgium were spending a median of 25 min. per week, with a minimum of 14 min. and maximum of 38 min. per week (De Weerdt et al. 2017). The most time-consuming activity was gathering information on drug supply problems (45% of overall time spent on managing DS), which embraced checking the orders for missing products, contacting wholesalers and manufacturers, and collecting necessary information from the state's medicines agency website. It was followed by communication toward patients and colleagues (16%), mainly associated with explaining why their product was in shortage and thus the need to switch to a substitute. The next most time-consuming activities were ordering this substitute at another wholesaler or manufacturer (16%) and searching it (13%), as well as pharmaceutical compounding at the pharmacy or checking the stock to see whether a supply disruption can cause a drug shortage. Most of the time spent on these activities (95%) was executed by the pharmacists themselves (De Weerdt et al. 2017).

Another Belgian study, aiming to quantify and analyze time spent by Belgian hospital pharmacies' staff on DS problems, revealed that in 2015 the median time was 109 min per week, with a minimum of 40 min and a maximum of 216 min. One third of hospital pharmacists spent more than three hours a week on managing DS (De Weerdt et al. 2017). Most of the overall work (60%) to manage DS was performed by hospital pharmacists themselves, supplemented by the pharmacy technicians, logistics and administrative personnel. The most time-consuming activity associated with managing DS was gathering information about supply disruptions, which embraced contacting the supplier, the manufacturers or other hospitals to get more information

or to follow it up. The second activity was to check whether the supply disruptions will cause a DS, which was done through inspecting whether the remaining stock was sufficient to overcome the period of no delivery. Other labor-intensive activities included communication towards hospital employees and distribution of the alternative treatment, as well as distribution of the usual drug once back in stock (De Weerdt et al. 2017). The Finnish community pharmacists, surveyed in another study reported that DS result in increased time burden for serving customers (52.9%), additional work necessary for storage management (21.8%) and experiencing the working environment as more hasty (12.3%) (Heiskanen et al. 2015).

In the USA, a survey among pharmacy directors from all 50 states revealed that in 2010, the majority of time allocated on managing DS was spent by staff of pharmacy departments (pharmacists and pharmacy technicians—spending nine and eight hours a week, respectively), while physicians and nurses spent less than one hour per week performing this task (Kaakeh et al. 2011). Nationwide estimated annual labor costs amounted to USD 216 million. Reallocating existing staff to manage DS was a rather common practice (confirmed by 32% of respondents), while in some institutions hiring additional staff was also necessary (Kaakeh et al. 2011).

Increased time burden was also reported in a survey on the impact of DS in the Southeastern United States, where pharmacy directors were usually stating that additional 0.5 full-time equivalents were needed to manage DS in their institutions (Caulder et al. 2015). It was usually associated with managing orders and syringe preparations in alternative dosage forms. Syringe preparation, estimated for at least USD 2.0 per each prepackaged syringe (excluding drug costs), was associated with spending 10 additional pharmacy personnel hours per week. Increased drug costs due to DS were explained by charging extremely high (300–500%) mark-ups for hard-to-find drugs (Caulder et al. 2015). Time burden was increased not only due to managing orders and medicine preparations, but also due to communication—two to five hours per week in addition to regular therapeutic committee work and 10 additional staff hours per week to add for changing or updating hospital information systems (Caulder et al. 2015).

Studied across the USA in 2013, DS in the area of injectable oncology drugs were associated with increased costs (Goldsack et al. 2014). Receiving offers to purchase these drugs in short supply at a higher price was reported by 74% of surveyed hospital pharmacists. The increase in overall costs of treating patients was reported by 65% of respondents and within this price increase component, an increased labor spending related to managing DS was the most commonly reported cost driver (52% of respondents admitted that it had a considerable or major impact on costs at their facility). Other implications, associated with DS and reported to have considerable or major impacts on costs, included an expansion of inventory levels, purchasing more expensive substitute drugs, and purchasing a drug in short supply from an alternative supplier at a higher price (Goldsack et al. 2014).

An overview of types of impacts of drug shortages on patients and health care systems is presented in Table 1.

Table 1 Summary of impacts of drug shortages on patients and health care systems

Impact of drug shortages on patients and of medical nature	Impact of drug shortages on health care systems and of financial nature
• Increased risk of adverse outcomes, including deaths • Increased risk of disease progression • Increased risk of medication errors (including incorrect dosage and administration of a substitute drug, and adverse drug reactions) • Delayed or cancelled care • Suboptimal treatment • Delays of treatment • Problematic therapy changes • Increased length of hospitalization and longer stay on parenteral nutrition therapy • Rationing of medicines • Prioritization of patients for treatment • Substitution with inferior medicines • Patients' complaints • Negative impact on clinical trials (necessity to stop clinical trials, modify protocols, change or stockpile medications)	• Price increases of medicines in short supply • Increased costs due to reimbursement of more expensive substitute products • Necessity to purchase products in short supply even from the grey market • Increased costs for institutions and patients • Expansion of inventory levels • Increased workload and time burden for pharmacists, pharmacy technicians and administrative personnel (gathering information, checking the orders, contacting suppliers, communication with other staff)

3 Systemic and Organizational Frameworks Which Could Counteract DS and Counterweigh Impacts of DS

DS—appreciably experienced by patients, health care facilities and systems, raise questions on how to prevent or mitigate them. This section focuses on suggesting possible solutions to the described issues of DS.

Many governments have initiated actions to prevent DS, and when they happen to manage them and mitigate their harm. Apart from the US FDA, the Belgian, French, Dutch, Italian, Australian and Canadian governments have also officially defined DS in their legislations (De Weerdt et al. 2015). This can be considered as an important step in preparing and launching any further, well-organized and state-supported mitigative actions against drug shortages. One of the aims of the current national strategic plan of the Irish regulatory authority for health products is to maintain access to medicines at all times (Health Products Regulatory Authority 2016).

Establishing an information system to report on and warn against shortages is one of the most common responses among these national authorities. The US FDA has an open-access database to check for actual, potential or resolved shortages of drugs and other active ingredients and has a specialist unit named DS Staff to manage such information (U.S. Food and Drug Administration 2011). The United Kingdom (UK) and Canada target the private sector to gather information. Furthermore, whilst the UK's Department of Health targets pharmaceutical companies and recommends

them to exchange information (UK Department of Health et al. 2007), Health Canada, the Canadian governmental department for national public health, focuses on drug sellers and makes it mandatory to report discontinuations (Health Canada 2015). Health Canada also encourages communication between all stakeholders.

Other healthcare organisations, including professional health associations (American Society of Health-System Pharmacists 2009; European Association of Hospital Pharmacists (EAHP) secretariat 2014) and healthcare facilities (Fox et al. 2003) have also raised their voice and taken actions in relation to DS. For example, in addition to the University of Utah with the database mentioned above, the ASHP (American Society of Health-System Pharmacists) is another organization in the USA providing a gateway for any individual or organization to voluntarily and anonymously report a shortage (American Society of Health-System Pharmacists n.d.).

A favoured response of relevant authorities is to establish a system to report and track the drugs in or at risk of supply shortages, so as to support the wider health system to identify where, both geographically and clinically, the shortages occur or are likely to occur. However, for example the US FDA intervenes only if the drugs concerned are classified as 'medically necessary', i.e. they are only supplied through a single source or if they are used to treat serious diseases (American Society of Health-System Pharmacists 2009; Ventola 2011).

The analysis of DS cases described in the published literature can provide some guidance on possible solutions to prevent or combat DS. For example, conclusions of a study on the impact of fentanyl and benzodiazepine shortage on medication errors and clinical outcomes in the pediatric intensive care unit, in the USA, indicate that early awareness of DS, identification of potential therapeutic alternatives, and appropriate communication and education may mitigate the potential for increased prescribing errors that may be seen during shortages (Hughes et al. 2015). For combatting antimicrobial shortages, the implementation of aggressive alternative strategies to avoid inappropriate antimicrobial usage during shortages, was recommended by researchers analyzing the impact of piperacillin-tazobactam shortage on meropenem use and its implications for antimicrobial stewardship (ASP) programs (Barber et al. 2016). Although meropenem use increased dramatically during that shortage, ASP interventions and infectious disease consults increased, while mortality rates and therapy length remained unchanged, and interestingly, the average meropenem cost per course decreased.

In Table 2 a framework is proposed to counteract DS. It builds on synthesizing measures proposed and/or applied around the world to counteract DS and it distinguishes between: (a) measures for averting DS even from arising, (b) measures to be taken when a DS is arising or is present and (c) fundamental organizational principles to tackle the issue of DS.

Table 2 Framework of measures to counteract drug shortages (DS)

Measures aiming to	Avert DS even from arising	Tackle arising or present DS
Communication	• Adopting and using an official and uniformly interpreted definition of DS and unit of measurement • Using early warning systems with six-month advance notice, defining clearly for which type of medicines this is obligatory	• Informing and counselling patients and their care-givers (acknowledging that this is not a direct solution)
Organization	• Fostering the development of an environment in which medicines are manufactured and supplies are provided by more than one sole entity • Prescribing and importing an unlicensed medicine from other countries where it is licenced (although this is not a preferred option) • Not stockpiling drugs	• Applying new technologies such as Radio-Frequency Identification (RFID) and Quick Response (QR) codes • Shifting drug inventories between different health care facilities • Forecasting how long the DS will last • Identifying all patients in need of the drug in shortage and identifying alternative therapies • Offering and conducting training for the use of substitute treatments
Legislation	• Establishing applicable civil penalties and enforcing them for manufacturers that fail to notify the respective authority on time • Making use of Public Service Obligations (PSOs) • Banning parallel exports temporarily, when public health is threatened	• Creating additional clinical guidelines and other policies for dealing with a shortage situation of a critical drug obtained from a sole supplier • Creating criteria to determine which patients are eligible to be administered the remaining inventory of medicines in short supply
Fundamental organizational principles		
• Promoting the uptake of new technologies and advocating their application (e.g. RFID and QR codes) • Establishing monitoring systems to report DS • Establishing timely communication systems between pharmacists and prescribers to manage DS • Predetermining responsible stakeholders and tasks for every phase of the DS • Standardizing the reporting systems for DS at international level, using a mutually agreed definition of DS and unit of measure		

3.1 To Avert a Drug Shortage Even from Arising

Generally, DS can be averted by means of communication, organization and legislation. Firstly, communication is crucial in preventing DS. To facilitate a well-functioning reporting of DS an agreed definition for what constitutes a DS should clearly be formulated and applied (Bochenek et al. 2018). The European Medicines Agency (EMA) has created a shortages catalogue where ongoing and resolved shortages are reported (EMA 2018b). It is important to note that this is however no database. Some databases exist on national level though, for instance for Austria, which is publicly accessible (BASG 2018).

Next to an agreed definition, the EMA and Heads of Medicines Agencies (HMA) have urged a unit of measure for DS which would harmonize how DS are reported across the EU (EMA 2018a). Furthermore, an early warning system should be established in which either the manufacturer (Ventola 2011), or the Marketing Authorization Holder (MAH) (Schwartzberg et al. 2017) must notify an arising DS with at least six months in advance from when the DS is going to be present. The notification should be given to the Ministry of Health (MoH) or other applicable authority. To avoid malpractice, the MoH or another applicable organization should beforehand clearly define for which type of medicines such a notification is required.

Secondly, organizational efforts are essential. Having only a sole supplier might trigger a DS. Hence, manufacturing should be designed to incorporate several suppliers to not be dependent on a single one. An additional approach could consist in prescribing and importing medicines that are unlicensed in the country in need but are already licensed in other countries (Bochenek et al. 2018). However, this solution should not be the preferred one, to avoid any harm caused by administering an unlicensed medicine to patients.

Malpractices such as stockpiling drugs in anticipating a shortage should be avoided, since this might shift drugs away from other health care facilities with patients in need of these medicines (American Society of Health-System Pharmacists 2009). Besides, another consequence of storing excess inventory is unnecessary expenses (Ventola 2011).

Thirdly, legislative frameworks will be necessary to avoid DS from arising. For the case that the manufacturer fails to notify the respective authority on time, applicable civil law penalties should be established beforehand and then be enforced (Ventola 2011). Furthermore, for the situation in that a DS might pose a risk to patient health, the state could make use of Public Service Obligations (Bochenek et al. 2018) that should be referred to in the law in connection to solving public health challenges. Another measure could consist in banning parallel exports temporarily, when public health is threatened (Bochenek et al. 2018). This is to keep the respective medicines in the country from which medicines would be exported in a parallel export scenario and to hence, help avoiding a DS in that country.

3.2 To Tackle an Arising or Present Drug Shortage

To tackle an arising or present DS, again communicational, organizational and legislative efforts are crucial. To immediately respond to an arising or present DS, patients and their caregivers have the right to be informed about the situation. Although this does not present a direct solution to a DS, it is fundamental to keep this in mind. Furthermore, the patient and/or the care givers can once informed try to obtain this medicine by other means (i.e. outpatient care, increased out-of-pocket payments, reaching care abroad, etc.).

On the organizational scope, it should be taken advantage of existing medicine inventories of one health care facility that can be shifted to another healthcare facility with a high need of that particular medicine (Ventola 2011). This is to reallocate and align inventories to the actual demand in different places. Furthermore, how long a DS will last should be forecasted and regularly updated to facilitate planning (Ventola 2011). To facilitate this, it should be taken advantage of new technologies such as Radio-Frequency Identification (RFID) and Quick Response (QR) codes to have more precise knowledge of inventories and hence enable a more accurate forecasting. The European Commission (EC) is already aware of the potential of these new technologies, however mainly in the light of protecting intellectual property and fighting the problem of counterfeit medicines (EC 2017). In addition, a technical report of the Joint Research Centre of the European Commission's in-house science service describes various authentication technologies (Baldini et al. 2017). However, the implementation of such highly beneficial technology for enhancing the availability of medicines has not been pushed forward yet. These technologies are widely used in other sectors (Pejic Bach et al. 2016) and have already been put in relation to the healthcare sector and improving the stock control of medicines (Mehrjerdi 2015). However, more needs to be done to reach their implementation for reducing DS. Also further on the organizational scope, all patients who are in need of the medicine in shortage should be identified and provided with alternative therapies, if possible (Ventola 2011). Moreover, to keep the risk of medication errors and adverse events to a minimum, training for the use of substitute treatments should be offered to pharmacists and prescribers.

On the legislative scope, in the case of a sole supplier for an important medicine, additional clinical guidelines and other policies should be developed to respond to a DS situation (Jensen et al. 2002). Moreover, when it comes to the situation of a DS, doctors will have to prioritize who to administer the remaining medicines (Kempe et al. 2007; Kontturi et al. 2016). The latter should be based on a set of criteria reflecting ethical considerations that might require a guideline arising from a law that protects this priority-administering practice.

In this section the authors also like to point out that new DS might be arising across Europe due to the expected Brexit on 29th March 2019 (Coombes 2018; Mackey and Annaloro 2018). Challenges that might trigger additional DS post Brexit could encompass on the regulatory scope for instance, that the EU might not accept standards of the UK's Medicines & Healthcare products Regulatory Agency (MHRA)

regarding the efficacy, quality or safety of medicines (Mackey and Annaloro 2018). Furthermore, it is expected that the Brexit will have a significant impact on parallel trade amongst EU countries (Hakim et al. 2015). Actions should be taken to reduce the negative impacts of Brexit on the availability of medicines. Again, for this making use of the mentioned technologies will be essential and ease the challenges.

3.3 Fundamental Organizational Principles

To tackle the issue of DS there is an overarching principle that is promoting the uptake of new technologies and advocating their application (e.g. RFID and QR codes). Moreover, four fundamental organizational principles should be addressed. These are: (i) standardizing the reporting of DS for which an international agreement of what constitutes a DS will be essential, for instance, on EU level (Bochenek et al. 2018; De Weerdt et al. 2015; Pauwels et al. 2014); (ii) establishing monitoring systems to report DS (Fox et al. 2003); (iii) establishing timely information-sharing systems building on two-way communication flows between prescribers and pharmacists informing each other on the expected duration of the DS, alternative treatments and temporary therapeutic guidelines; and (iv) creating general guidelines and action plans for before, during and after a DS, determining the responsible stakeholders and their tasks (Ventola 2011).

4 Conclusions

DS exert significant impacts on patients and health care systems. Impacts on patients and of medical nature include delays and changes in treatment, increasing the risk of medication errors and adverse outcomes, detrimental impacts on clinical trials and patient complaints and decreased patient satisfaction with the provided treatment. The rationing and substitution of a drug in shortage with an equivalent or sometimes inferior drug are often required in case of DS. The impacts of DS on health care systems include increased labor burden and increased costs for pharmacies, hospital settings, but also for patients.

There need to be adopted systemic and organizational frameworks which could counteract DS and counterweigh impacts of DS. These include adopting widely agreed and uniformly interpreted definitions of DS, establishing information exchange and early warning systems, adopting new technologies and developing and enforcing applicable civil penalties. The proposed framework of measures to counteract DS includes measures which aim to avert shortages even from arising and measures to tackle arising or present shortages. These measures pertain to solutions associated with communication, organization and legislation.

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Patient Perspective: Reporting on Medicines Shortages—Hemophilia a Case in Latvia

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Abstract Following austerity measures in Latvia, the reimbursement system faced major changes. Coagulation factor concentrates (CFC) used for hemophilia A treatment were moved to a reference list. This meant that government would only pay for the cheapest treatment included in the reimbursement system. Prescription rules did not change, but hematologists could no longer choose the treatment for their patients. Patients continued to attended their hemophilia center every three months, where they received special prescriptions for treatment according to their condition in line with Baltic Hemophilia treatment guidelines. During 2011–2016, 13 shortages were registered for CFCs for hemophilia A (2 products). Patients were not aware that the system must provide them with necessary treatment within 2 days from request in the drugstore. It was pharmacies' responsibility to report shortages. Patients were instructed to report shortages to the Latvian Hemophilia Society, who, after verifying the fact with the respective pharmacy and wholesaler, reported the shortage to Health Inspection. Even when facts were confirmed by authorities, the reimbursement system did not react to shortages, and 11 times continued agreement with the distributor. In one case, the shortage was due to fact that the product was no longer produced, but no information was provided to the National Health Service of the Republic of Latvia (NHS). It took two months to exclude the product from the reimbursement system. In second case, the product was withdrawn from the system by the distributor, but immediately another product was provided for a similar price. The reimbursement system continued to function without patients' involvement, with processes only between the paying authority, industry, wholesalers, pharmacies and doctors.

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1 The Role of Treatment in Lives of People with Hemophilia

Hemophilia A is an inherited bleeding disorder in which blood plasma contains little or no coagulation factor VIII, therefore causing internal bleeding and long-term damage to joints (Franchini and Mannucci 2012). Portal for rare diseases and orphan drugs, Orphanet, defines hemophilia as a genetic disorder characterized by spontaneous hemorrhage or prolonged bleeding due to factor VIII or IX deficiency. Every year, 1 of 5,000 male babies are born with hemophilia A and 1 of 12,000 people live with hemophilia A globally (Orphanet 2009). According to unpublished data from the Latvian Hemophilia Society, hemophilia A affects 129 males in Latvia with a population of 1.96 million (Central Bureau of Statistics 2018). Due to the free movement of people in the European Union, it is very difficult to count the real number of patients in the country.

To stop and prevent internal bleeds that characterize hemophilia, patients use coagulation factor concentrates as replacement therapy (replacing the missing coagulation factor in the blood with intravenously injected coagulation factors) (Castaman and Linari 2018). With adequate treatment people with bleeding disorders can live a normal life. The consequences of lack of proper diagnostics and no treatment before 1950s is well documented as resulting in a shorter life expectancy, increased disability and other health problems.

Still today, 75% of the world's population face a lack of diagnosis and treatment as developed countries did 50 years ago (Skinner 2006). Unlike other rare diseases, for hemophilia many treatment options exist (Schrader et al. 2007; World Federation of Hemophilia 2012) and basic treatments are included in World Health Organization's (WHO) Essential Medicines List (World Health Organization 1977). It is the responsibility of every country to provide their patients with treatment. The price of medicines should never be the only selection criteria, but it often is (Johnson and Zhou 2011).

This is the first published evidence of cases where people with hemophilia A faced shortages of life-saving treatment that should be available for home use. Most of the provided information is compiled by the patient organization in an unstructured way over time from patient information, opinions and complaints, that were often later confirmed by authorities or other evidence.

2 Provision of Treatment to Patients

In Latvia, the government provides coagulation factor concentrates for people with hemophilia for home treatment and prophylaxis through the Reimbursement List (LR Cabinet of Ministers 2006). Before 2005, these medicines were purchased and provided to patients only through hospitals. In 2005, coagulation factors together with other specific treatments in oncology and hematology were included in the Reim-

bursement List (Ministry of Health 2005). The Reimbursement List is managed by the NHS and consists of Lists A, B and C. It also has other compensation mechanisms, such as Individual compensation and List M. Silins and Szkultecka-Dębek (2017) have described nuances of the Reimbursement system in Latvia.

Practically, the system can be described as follows:

- List A contains medicines with equal therapeutic efficacy and government pays only the cheapest,
- List B contains similar, but not interchangeable medicines and government pays for all of them,
- List C contains medicines that are used much more rarely and are more expensive than other treatments in List A or B and often have been reimbursed via individual compensations.

The price of coagulation factor concentrates for hemophilia in Latvia is fully reimbursed by the government (LR Cabinet of Ministers 2006). The amount of budget spent on hemophilia A treatment quadrupled between 2005 and 2017, growing from 621,000 EUR in 2005 to 2,546,000 EUR in 2017, including inhibitor patient treatment. The system served from 57 to 78 individual patients annually 2010–2017 (incl. patients with factor VIII inhibitors) (National Health Service 2018). In 2017, coagulation factor consumption finally reached the European Directorate for the Quality of Medicines (EDQM) recommended level (Council of Europe, Committee of Ministers 2017), namely 4.27 IU (international units) per capita, growing from 3.6 million IU in 2010 to 8.2 million IU in 2017. Table 1 summarizes available coagulation factor VIII brand names in Latvia 2010–2017 (National Health Service 2018).

The regulation is closely tied to Prescription rules, which are updated regularly and made public, as is the Reimbursement List itself (National Health Service 2018). For hemophilia A, the prescription limits are tied to Baltic Hemophilia Treatment Guidelines (2007). Hematologists use the same formula to calculate amounts of factor concentrates to prescribe to patients based on the severity of their disease or factor level in blood plasma, bleeding location and severity, body weight and treatment regimen as indicated in the Guidelines for Hemophilia Treatment (2012) (World Federation of Hemophilia 2012).

Table 1 Available coagulation factor VIII concentrates in Latvia, 2010–2017

No.	Brand name	Producer	Inclusion	Exclusion
1.	Immunate	Baxter	2008	2012
2.	Dried Factor 8Y	BPL	2009	2016
3.	Human Coagulation Factor	Baltic Therapeutic Service/Kedrion	2011	2014
4.	Recombinate	Baxter	2012	2018
5.	Octanate	Octapharma	2016	NA

Source Official gazette of the Republic of Latvia "Latvijas Vēstnesis"

The regulation stipulates that people with hemophilia visit hematologists in two university clinics (Children's Clinical University Hospital and Riga East University Hospital, both located in the capital city of Latvia, Riga) every three months to evaluate the progress of their disease and receive their special prescription for coagulation factor concentrates. Then with the special prescription they can receive the medicines in drugstores nearest to their home within 2 days from their request.

3 Limiting Access to Treatment

Since inclusion in the Reimbursement List, the consumption of coagulation factors grew in line with the economy in Latvia: the more money in the budget, the better patients were covered with medicines. As the starting point was close to zero in the beginning, expectations were high. In 2008–2009, the global economic crisis left deep marks in the economy of Latvia and tough austerity measures came into force. In 2009, public spending on health per capita dropped in Latvia (Thomson 2014). As Behmane and Innus wrote in 2011 (Behmane and Innus 2011), the government reduced the health care budget by 13% between 2008 and 2009 and by a further 14% in 2010—a total cut of 25% from 2008 to 2010. The budget was cut also for reimbursed medicines (Behmane and Innus 2011).

Since hemophilia treatment is one of the most expensive treatments the health system has to cover for chronic patients (O'Hara 2017), that was one of the target treatments to cut in Latvia to save money. In order to drive down spending for hemophilia treatment, the NHS chose to revise some of their previous decisions and moved the treatment of hemophilia from List B to List A in 2009. This decision was challenged by the Latvian Hemophilia Society in the Court in 2010, which proved that there was no legal basis to change evaluation outcomes in 2014 and thus change Reimbursement conditions (LR Administratīvā apgabaltiesa 2014). The Ministry's arguments to move coagulation factor concentrates from List B to List A ranged from naming considerably older and biological medicines "generic drugs", to speculating that there were no evidence various coagulation factors have different therapeutic efficacy and therefore basis to remain on List B. While Court reviewed the case, Ministry also changed the reimbursement regulations to suit the willingness to pay for only the cheapest coagulation factor for the disease. Although the need to push down prices, especially in such tough economic circumstances, is understandable, it should have happened in a way which does not impact patients negatively.

Due to the decision to change the Reimbursement List category, which meant covering expenses only for one—the cheapest—coagulation factor, patients suffered. From the product comparison, this was not the best option to choose from, since it had only one step viral inactivation and had comparatively lower level of specific activity (excluding albumin) for Factor VIII IU/mg protein (Brooker 2012). Most of patients had to switch treatment without prior notice and doctors were not well explained the details of the new reimbursement regulation version, for example, that they did not have to switch all patients, but only the new ones. The medicine

chosen by NHS needed three times bigger injections (up to 60 ml for an adult in one injection), it worked slower than the previous medicine and, in many cases, needed repeated injections in a few hours. It also created some minor side effects, that were never formally registered, because the medicine was used as home treatment. In some cases, patients refused to use the medicine, which they had to confirm with a signature in their medical records. Some parents were purchasing the previous treatment for their children for full price, after producers' discounts and support schemes had to end in 2011, just to avoid use of factor which they trusted less. The government is still not covering the costs of inhibitor testing, which is one of the obligatory tests to perform in case of a change of product.

4 Tackling Treatment Shortages

In the official procedure as described in the reimbursement regulation, a drugstore, which faces a shortage when a patient comes with a prescription for reimbursed medicine and cannot provide requested medicine in 2 days, is to confirm it with wholesalers and then report it to the Health Inspection for further investigation. Then the NHS decides upon exclusion of the medicine from the reimbursement list. In the case the reference (product with lowest price in List A) medicine was not available, the next cheapest option needed at least a month to be produced, labeled according to local laws and distributed to patients, so it never reached patients.

The decision to reimburse only the cheapest treatment option from 2009 meant also simple management and logistics errors. The distribution company, which had provided the cheapest price and thus won the government contract but was at no control of production, was not able to estimate the market demand and deliver medicines as defined in the reimbursement regulations.

Most of the shortages were reported to the Latvian Hemophilia Society by people with hemophilia, who could not wait for necessary treatment in the drugstore. Table 2 contains list of shortage events for hemophilia A treatment that were known to patient organization. During 2011–2016, 13 shortage events were registered for coagulation factor concentrates for hemophilia A in Latvia (2 products—"X" and "Y", both in List A as reference medicines—with the same indication, same route of administration and same price) by the Latvian Hemophilia Society. In some cases, shortages were longer than 2 weeks.

The first shortage, about which the patient organization was informed, was in 2011. This was reported when a patient lost patience after they were turned away to wait a few more days to receive delivery of medicines for more than two weeks. The Latvian Hemophilia Society reported the shortage to Health Inspection and the NHS to defend the interests of the patient they represent. The patient organization did so every time patients informed them about problems to receive prescribed medicines and monitored the outcomes closely. They also warned institutions that it was too risky to have only one product for a rare disease on the list, not only because of therapeutic limitations, but also because of risks with supply.

Table 2 List of coagulation factor VIII concentrate shortage events in Latvia, 2011–2016

No.	Year	Month	Shortage for medicine X or Y
1	2011	1	X
2, 3	2011	2	X, Y
4	2011	3	Y
5	2011	8	X
6	2011	12	Y
7	2012	2	X
8	2012	3	X
9	2012	6	X
10, 11	2014	2	X, Y
12	2016	6	X
13	2016	7	X

Data source Latvian Hemophilia Society

In 2011 and 2014 there were two plasma-derived coagulation factor products in the reimbursement system, both distributed by the same company. At some points, both products were not available in drugstores simultaneously. In 2014, the production of product Y (see Table 2) was stopped due to the renovation of the factory, but no information was provided to authorities in Latvia for 4 months.

The NHS also sometimes lingered with decisions to exclude products from the list due to shortages, because no alternatives were available for the same price (in this case—information about production stop was provided in May, but product was excluded from the list only in July 2014).

When limited access to treatments occurred several times in 2011, the patient organization won an "Advocacy in Action" grant from the World Federation of Hemophilia and developed an information toolbox for patients about their rights in the healthcare system in Latvia (Clarke 2011). In 2012, a brochure was published and distributed among patients, healthcare professionals and other patient organizations. Materials were also presented at patient meetings. The goal of the project was to provide patients with informative material on patient rights, the basics of the reimbursement system, their treatment options and other key information for everyday use.

Over the period, patients reported privately and anonymously various situations of shortages in the drugstores to the patient organization. In some cases, too few packs of medicines were provided to patients in the drugstores. In one case, the drugstore provided a letter to the hematologist, explaining that the small proportion of the prescribed medicine that they can provide was given to patient and the rest would be delivered later. In another case, Health Inspection carried out an investigation and found some packs of medicines in one of the wholesaler's stock and therefore dismissed the shortage. In another case journalists reported that hospitals can always use fresh frozen plasma as option to stop bleeding in emergency cases. In one case

the company blamed patients for stockpiling and taking out all the stock from pharmacies, which was not true: instead, pharmacies just could not calculate the demand properly. In one case the supply chain suffered because of volcano eruption in Iceland. In another case, product package labeling had to be changed and confirmation with National Medicines agency did not go as smooth as expected. In a third case, production of a product was stopped.

To provide children with better treatment options, generation I recombinant coagulation factor VIII was included in the Reimbursement system in 2012. Unfortunately, the company and institutions had agreed to cover the costs of this medicine only for children, thus no adults were eligible for this treatment. Also, children who turned 18 and switched to the adult hospital, had to switch treatment as well–not because medical need, but because of the age limit. Out of the 57–78 patients with hemophilia A who received treatment from reimbursement system, 1–3 turned 18 each year and went from the Children to the Adult Hemophilia Treatment Center. The patient organization together with doctors asked the Ministry of Health several times to abolish this discriminative condition to continue the treatment, but it was only allowed when the Cabinet of Ministers approved the Rare Disease Plan II (Cabinet of Ministers 2017) and provided additional budget for it. This needed another 6 months to execute.

Another consequence of repeated shortages was worsening adherence to prescribed regimens. Patients were afraid that in the case of an emergency there would be another shortage and they would not be able to treat a bleed. They therefore saved some doses of treatment for worse days. They also saved medicine for other patients with more bleeding episodes and for those who needed surgery. During this period, 3 patients were refused necessary surgery in hospital if they could not provide blood coagulation factor concentrates themselves. Although hospitals had to purchase coagulation factors for these surgeries, they could not do so because of limited resources. It was very difficult for the patient organization and treating doctors to convince patients to use medicines as prescribed.

Because of uncertain circumstances in the economy and health care, some people and families with hemophilia emigrated from Latvia in hope to improve their economic and treatment conditions abroad. They moved to the UK, Ireland and Germany for work and medical care. They have never returned to Latvia.

In 2014 when a shortage of both reference medicines occurred again, the majority of people with severe hemophilia A did not hesitate to agree to participate in a clinical trial with a new extended half-life recombinant coagulation factor. This trial provided unlimited amounts of the newest, yet not registered, coagulation factor and they could, for the first time in their life, have proper dental care and do necessary surgery (such as joint replacements). The clinical trial ended in mid-2016, but the NHS was unable to negotiate the price with the company at a level Latvia could afford to pay, and the decision was made not to include the medicine in the Reimbursement List. All patients, who participated in the clinical trial, had to switch back to previous treatment. Some patients informed the patient organization, that their bleeding episodes had vastly increased and an immediate solution was necessary.

At the same time, a new announcement of a shortage came (this time not from patients, but from healthcare professionals), and in few weeks the company which

distributed the reference medicine previously, had signed an agreement with the NHS about delivery of another product. This new product was immediately included in the Reimbursement List as reference medicine in List A for hemophilia A for a price that was not much different from the price for previously reimbursed treatments.

There has been no information about shortages since mid-2016. This is a product that several countries in Europe used and therefore the supply chain was able to cater demand in Latvia on time. The distribution company was also gaining experience with the market and more data on total factor consumption were available. The patient organization collected and analyzed the government data and then provided summaries to authorities and anyone interested.

5 Conclusions

Inclusion of only one treatment option in the reimbursement system when other treatment options existed was very risky for all involved stakeholders. Shortages, although foreseen in respective regulations as a finable event that may result in exclusion from the Reimbursement List, were difficult to define and tackle from a supply-chain perspective.

For patients, who are not very well aware of the operations of reimbursement system and drugstores, limited access to life-saving treatment may mean serious consequences to adherence to treatment, and undermined trust in doctors and the health care system.

The reimbursement system continued to function without patients' involvement, with engagement only between the paying authority, industry, wholesalers, pharmacies and doctors. The patient organization was always monitoring the situation, but not officially included as a stakeholder in the process.

Although patients can provide meaningful information and help authorities avoid bureaucracy, they are included in the overall system only as end customers without rights to improve or interfere with the system.

The role of the patient organization, even if not formally recognized, can be major. As non-profit organizations that are established to promote and advocate for needs of their target groups: they have possibilities and rights to provide insights and improve processes in many ways.

By the time of finishing this article, major changes in the provision of coagulation factor concentrates for people with hemophilia A occurred, coming into effect from July 1, 2018. All coagulation factors were moved back to List B, providing three different treatment types (plasma-derived factor VIII (continued from 2016), plasma derived factor VIII with von Willebrand factor, and III generation recombinant factor VIII (replacing I generation recombinant factor)). They are now available for all patients without discrimination by age (Nacionālā veselības dienesta rīkojums Nr. 16-2/137 2018). Extended half-life products are also promised to appear in the List

B, after the company confirms the price. The possibility to prescribe individually tailored treatment regimens is closer than ever. All the suffering and efforts over the past decade have resulted in a better future for people with hemophilia A in Latvia.

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Shortages of Medicines Originating from Manufacturing

Maurizio Battistini

Abstract The shortages of medicines in certain markets, and therefore the difficulty of patients to access to them, is a serious and recurrent issue that has its roots in several factors, including manufacturing, considered as the set of activities that begin from the procurement of the starting materials until the delivery of the finished product to the hospitals or the intermediate distributors or wholesalers. The main purpose of the content is to investigate what are the different factors, individual or combined, related to the production steps of the final dosage forms, which may be the source of shortages on the market. From the analysis of the risks' factors, and their likelihood of occurrence and severity, born a series of considerations necessary to understand how the risk, associated with each element, can be reduced and made acceptable with mitigation measures. The risk reduction and the management of the emergency situations are the critical aspects that need to be controlled, especially for those medicines whose supply is critical for the patients. The author tries to propose a systematic approach to the management of the situations that generates shortages, independently from market drivers or dystonias, related to specific events connected to the manufacturing chain, whose occurrence can't be neglected for the health impact that could result. The author, with a significant experience in the pharmaceutical field, intends to bring to the attention of the readers, his knowledge of the practical aspects governing the analysis and risk containment of the shortages originating from manufacturing in order to proactively react to their occurrence.

1 Introduction

This article analyzes the main aspects that are at the origin of medicines' shortages related to manufacturing issues. The text shows the analysis of the causes associated with the possible corrective and preventive actions to be implemented to mitigate the effects. The reader will find in the contents a useful guide to understand the

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phenomenon and a key to understand the main reasons and potential remedies so as to investigate aspects that may be unknown to him. The manufacturing and control of medicines are in fact the basis of the continuity of supply of the market and the examination of the problems that may hinder the implementation allow the reader to deepen the concrete problems related to the sourcing of the markets (in this specific case intended as the patient). The author has the sole ambition to illustrate the main elements that characterize the phenomenon, conscious that deepening the issue deserves a degree of expertise that may not be typical of those who read the article and approach the problem for the first time. Please note that some opinions in the text are based in the personal background and professional experience of the author.

Shortages of medicines have been a global problem for the past decade and have also increasingly affected the European Union (EU) with significant impact on patient care. The causes of medicine shortages are varied and include economic, business, political, manufacturing and distribution issues.

There are a series of factors that can affect the supply chain performances on which we can intervene to control the safe and prompt delivery to the patient; one of the main of them is related to the manufacturing being the origin of the goods.

The Fig. 1 shows the complexity of the supply chain and the several aspects impacting on its security (the toolkit covers the entire supply chain and lifecycle of medical products from raw materials to use by patients). Supply continuity is one of the main aspects to insure in order to avoid medicines shortages on the markets. Good Manufacturing Practices, and related aspects, are highlighted in the picture to show their criticality in the entire process and as a principle aspect treated in this chapter. Comprehensive product quality and supply chain security requires a multi-layer approach that includes prevention, detection, and response strategies and actions. The toolkit is a comprehensive resource that addresses areas of vulnerability in the medical product supply chain. *The toolkit will be used by industry stakeholders and regulators from around the globe to adopt best practices, for training purposes, and to strengthen laws and regulations to protect consumers from unsafe and substandard drug products* (Food and Drug Administration, https://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/ucm559053.htm).

The report from a stakeholder meeting at the European Medicines Agency (EMA) in October of 2015 underlined the need: *"Developing a proactive approach to the prevention of medicines shortages due to manufacturing and quality problems"*. To insure the supply chain continuity we must distinguish mitigation activities from the long term strategies as actions to put in place in order to react to shortages occurrence. Mitigation activities are directed at preventing supply disruptions from turning into actual shortages. Long-term Prevention strategies are intended to address the underlying causes of shortages to prevent supply disruptions from occurring in the first place (Fig. 2).

Mitigation and Prevention have two different goals:

- Strengthen the mitigation response—Improve and streamline mitigation activities once the Agency is notified of a supply disruption or shortage.

Fig. 1 Supply chain security toolkit (*Source* Food and Drugs Administration and Asia Pacific Economic Cooperation)

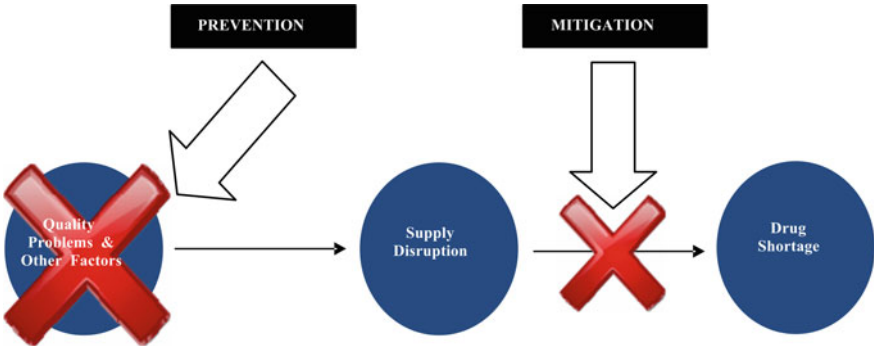

Fig. 2 Addressing drug shortages: mitigation activities and long-term prevention (*Source* Strategic Plan for Preventing and Mitigating Shortages—Food and Drugs Administration October 2013)

- Develop long term prevention strategies—Develop prevention strategies to address the underlying causes of production disruptions to prevent drug shortages.

A mitigation example follows.

- When particulate matter (including glass and metal particles) was found in an injectable drug product that was medically necessary and vulnerable to shortage, FDA (Food and Drug Administration) exercised discretion to allow distribution of the product along with a letter, included in the drug's packaging, warning health care professionals to use a filter when administering the drug. The exercise of discretion was temporary, and was conditioned on the manufacturer's ability to demonstrate to FDA that the filter did not affect the way the drug works and could successfully remove the particulate. FDA also worked with the manufacturer while the manufacturer identified and addressed the root cause of the problem, so that it could resume producing a drug product that did not need the work-around involving the filter.
- In contrast, a drug that is contaminated with bacteria or fungi presents a more extreme risk to patients, one that cannot be mitigated through a work-around such as the one described above. In such cases, the manufacturer must correct the conditions leading to the contamination before the product is safe for use, even if correcting the conditions ultimately leads to a shortage.
- Each situation must be carefully evaluated to determine the public health impact, keeping in mind that a given action may have unintended, and potentially long-term, consequences.

2 Initiatives Promoted to Examine and to Contrast Medicines' Shortages

Conscious of the shortages impact on patient healthcare continuity, several European initiatives has been promoted in order to mitigate or prevent the problem. The recent history and background should help to better understand.

2.1 Main Initiatives Promoted by EMA Regarding Medicines' Shortages

EMA is mainly involved with shortages due to manufacturing or Good Manufacturing Practice (GMP) compliance problems. In 2012, the Agency published a reflection paper concerning public health incidents arising from manufacturing disruptions linked to problems such as quality defects or GMP compliance issues. The paper summarises the lessons learned from previous crises and presents short and mid-term actions that may allow the EU regulatory network to prevent, mitigate and manage

shortages of important medicinal products In 2013, EMA organised an initial public workshop on product shortages due to manufacturing and quality problems in order to raise awareness of the impact of shortages and to promote better and proactive risk management by companies.

Based on the implementation plan and input gathered at the October 2013 workshop, EMA developed a set of documents to support medicines regulators involved in the EU-level coordination of shortage situations due to GMP non-compliance/quality defects:

- Criteria for classification of critical medicines;
- Facilitation of benefit-risk assessment through a defined common assessment report;
- Points to consider for the overall assessment of a medicine shortage due to GMP noncompliance, quality defects;
- Identification of risk indicators for shortages;
- Decision tree to help decide whether a particular national shortage should be escalated to European level;
- Information sources for issuing treatment recommendations during medicines' shortages;
- Public catalogue of shortages.

In October-2015, EMA convened a second stakeholder meeting bringing together national competent authorities, industry, patient and healthcare professional representatives to discuss recent initiatives and to reflect on possible further actions to proactively manage shortages. The workshop was divided into three parts. The first part was only attended by representatives from national competent authorities and was used to provide an overview on the way shortages are managed across the EU regulatory network. The second part included representatives from industry associations (professional and trade) and patient/healthcare professional associations in addition to representatives from national competent authorities. During this part speakers gave short presentations on the impact of shortages and approaches to their management.

Break-out individual sessions:

- Definition of shortage and possible metrics;
- Causes of supply chain disruptions (related to good distribution practice);
- Implementation of inter-association tools by industry;
- Communication of shortages (between industry and regulators and between regulators, and to healthcare professions and patients).

Feedback of the break-out sessions would be used to update the shortage implementation plan. The third part with representatives from national competent authorities was used to agree on a common approach amongst regulators.

2.2 *Initiatives Promoted by Independent Associations to Face up to Medicines Shortages*

PDA (Parenteral Drugs Association) and ISPE (International Society for Pharmaceutical Engineering) also worked together "to deliver a proposal and plan that address the prevention of drug shortages due to manufacturing Quality Issues".

- ISPE developed the "Drug Shortages Assessment and Prevention Plan" [Drug Shortage Prevention Plan 2014 and Drug Shortage Assessment and Prevention Tool—2015—ISPE] to aid manufacturers in assessing their preparedness for preventing or managing a supply disruption. ISPE's systems based approach is responsive to the root causes of manufacturing and quality issues and is founded on the six dimensions necessary to obtain operational success and avoid shortages. It contains recommendations for each dimension: corporate quality culture, robust quality system, metrics, business continuity planning, communication with authorities and building capability and helps to address shortages on a global basis.
- PDA developed a complementary "Risk-Based Approach for Prevention and Management of Drug Shortages" [Technical Report No. 68 Risk-Based Approach for Prevention and Management of Drug Shortages—2014—PDA], which provides a holistic risk-based framework at a product level for prevention of shortages, a risk triage model that can be used to assess drug shortage risks and implement appropriate controls, as well as templates for a Drug Shortage Risk Register and a Drug Shortage Prevention and Response Plan. The templates provided help to systematically and, proactively identify potential risks to product supply in the end-to-end value chain for a product, prioritize risk mitigation activities and use the outputs to engage in proactive dialogue with health authorities.

3 Medicines' Shortages—Overview of the Phenomenon

The complex scenario of the supply chain requires identifying the information sources in order to collect data available to proactively or promptly react to a disruption or shortage of medicines. For that, we mainly focus on supplier and manufacturer.

However, although extremely useful, the information sources shown in Fig. 3 produce only part of the aspect. For example, some key drivers of drug manufacture and distribution are not transparent, such as production schedules, distribution of production volume across various contract manufacturing facilities, the amount of inventory stored by a manufacturer, and wholesaler and pharmacy/hospital supply and purchasing practices. Additionally, the role that other sources of products (e.g., gray market distribution, compounding, unapproved drugs) play in contributing to shortages or in the reactions to shortages is not already clearly understood.

One of the key elements to manage shortages of medicines is to find a clear definition of critical medicinal product. When defining a product as critical, two

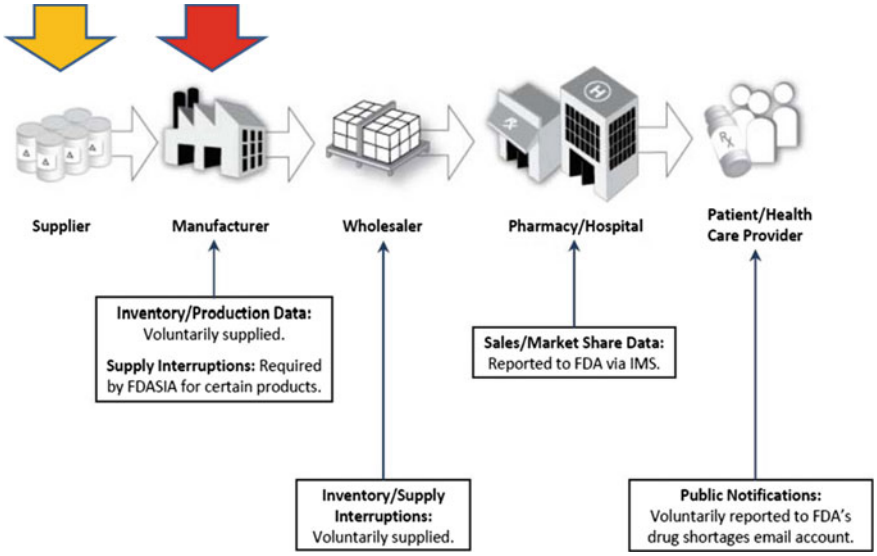

Fig. 3 FDA's key supply chain information sources (*Source* Strategic Plan for Preventing and Mitigating Shortages—Food and Drugs Administration October 2013)

criteria are of importance: the therapeutic use and the availability of alternatives. The definition of the previous concepts should help to better understand.

- Therapeutic use—The medicinal product is an integral part of the treatment for a disease, which is life-threatening or irreversibly progressive, or without which the patient could be severely harmed. This could be in acute situations (e.g. emergency situations), or chronic situations/maintenance of stable conditions, or disease with a fatal outcome where the product has been shown to affect the progression of the disease or survival.
- Availability of alternatives—Even if the product would be used in the situation defined above, it would not be classified as being critical in case appropriate alternatives are available. These could be:
  - Alternative manufacturing site for the same product; *bottle neck*—manufacturing capacity and technical and regulatory times to switch.
  - Different strength/formulations of the same product; *bottle neck*—need for formulations suitable for use in special populations.
  - Alternative dosing (lower dose/temporary break from drug treatment) or limiting the use to high risk patients could be explored; *bottle neck*—this might depend on the expected duration.
  - Generics; *bottle neck*—the availability and volume should be checked.
  - Other products in the same class or even other classes; *bottle neck*—adverse events.

These criteria seem reasonable and easy to apply but there are many particular situations that must be carefully managed. For example, GMP non-compliance or quality defects may lead to shortage of a product, if it is decided not to release a batch or even to withdraw batches from the market; this is good precautionary practice but there might be situations where withdrawing a product or not releasing it might do more harm to a patient than allowing a product to remain or to be released on the market. On this particular case the Chap. 8 of the EU Guidelines (Vol. 4) on Complaints, Quality Defects and Product Recalls at the point 8.27 declares: *It should also be considered whether the proposed recall action may affect different markets in different ways, and if this is the case, appropriate market-specific risk-reducing actions should be developed and discussed with the concerned competent authorities. The risk of shortage of an essential medicinal product which has no authorised alternative should be considered before deciding on a risk-reducing action such as a recall. Any decisions not to execute a risk-reducing action which would otherwise be required should be agreed with the competent authority in advance.*

3.1 Supply Shortages Due to a Inadequate Manufacturing Approach or Quality Defects

As the reader can understand, there are many aspects to consider for the overall assessment of a supply shortage of a medicinal product due to GMP Noncompliance or to quality defects. Focusing on product and manufacturing the related questions are many:

- Which batches, pharmaceutical forms, strengths, pack sizes are affected by the supply problem?
- Which countries are experiencing supply interruption?
- Is it likely that the supply problem will affect other countries in the near future?
- Is a stock-out, or near stock-out situation likely to occur? If so, in which countries?
- Provide a technical report of the problems in the manufacturing or quality area that means that has given rise to the possibility of a shortage. The Manufacturing Authorization Holder (MAH) should be asked to provide analytical data and should discuss the relevance of the data. What is the root cause of the supply interruption and where in the manufacturing process does it occur?
- What preventive and/or corrective actions has the company taken to avoid and/or resolve the deviation and the shortage?
- Member State to countries where shortage is evident? If so, how would this be handled?
- Have all alternatives of improving the supply chain been explored? E.g. modification of manufacturing process, use of alternate manufacturers, etc.
- What is the stock situation for other strengths or formulations of the medicinal product that could compensation for the supply interruption?

- What is the current stock situation/member state? Are there any buffer stocks at distributor or hospital sites? Forecasted demand rates and estimated stock out dates should be provided. Discussion on the feasibility of stock rotation between member states to cover and any other measure to prevent the shortage should be requested.

  a. What is the estimated lead-time before the product reaches out of stock level? Provide lead times and a timetable for (a) manufacture and supply utilizing the batches in question and (b) manufacture and supply utilizing new batches.
  b. Considering the nature of the defect, what is the level of risk of the use of a defected product from the quality point of view? What is the threshold beyond which the quality defect has harmful effect on the patient and clinical use would deem inappropriate?
  c. Is it possible to import the medicinal product (re-packaging and re-labeling) from other EU member state to countries where shortage is evident? If so, how would this be handled?
  d. Have all alternatives of improving the supply chain been explored? E.g. modification of manufacturing process, use of alternate manufacturers, etc.
  e. What is the stock situation for other strengths or formulations of the medicinal product that could compensation for the supply interruption?

3.2 Risk Indicators for Shortages Related to Manufacturing and Quality Aspects

To properly answer or react to several of the above questions, the identification of Risk Indicators for Shortages related to manufacturing and quality aspects is requested. Supply Chain Risk Factors evaluation should be the key point to start the assessment.

1. There is only a single manufacturer of the API registered;
2. There is only a single manufacturer of Finished Product registered;
3. Location of the Manufacturing Site(s) cause any concern?
   This may be based on a general concern that there is a potential for future disruption in the supply due to the geographical location of the manufacturing facility, or source of plant or animal materials;
4. One or more manufacturing sites have a marginal level of GMP compliance or are subject to increased inspection surveillance (note EudraGMDP (1) and potentially risk based classification). This should be based on what is in the marketing authorization application and checking EudraGMDP during the assessment and ideally liaising with the inspectorate;

   (1) Directives 2004/27/EC on human medicinal products and 2004/28/EC on veterinary medicinal products introduce the legal framework for the Community database. The concept of a European Inspections database is included in the above specified legislation to provide EEA National Competent

Authorities and the European Medicines Agency (EMA) with an overview of the status of pharmaceutical manufacturers. The legislation provides for an electronic tool containing complete information on all pharmaceutical manufacturers. This includes information on Manufacturing and Importation Authorisations (MIA) and Good Manufacturing Practice (GMP) Certificates for authorised sites in the EEA and information on GMP certificates for manufacturers in third countries.

5. There is a high product concentration at the finished product manufacturing site;
6. End to End Manufacturing process has long lead/holding times and/or extended supply chain;
7. Manufacturing methods are complex, with capacity bottle necks in production;
8. The manufacturer has had previous problems with quality defects and/or recalls;
9. The manufacturer has had previous problems with supply;
10. The medicinal product would meet the criteria of critical;
    Based on classification criteria for critical medicinal product agreed by Committee for Medicinal Products for Human Use (CHMP)
11. Design/device feature of the medicinal product could potentially prohibit switching patients.

Main supports from EudraGMDP Database

- Compliance with Good Manufacturing Practice—A certificate of Good Manufacturing Practice (GMP) is issued to a manufacturer by the national competent authority that carried out an inspection if the outcome of the inspection confirms that the manufacturer complies with the GMP principles, as provided by EU legislation. If the outcome of the inspection is that the manufacturer does not comply a statement of non-compliance may be entered into EudraGMDP. Certificates and statements of non-compliance may be issued to manufacturers of medicinal products and manufacturers of active substances located inside and outside EU.
- Manufacturing and Importation Authorization—Manufacture of medicinal products in the EU or importation from a third country is subject to the holding of a Manufacturing and Importation Authorization. The National Competent Authority of the Member State in which the manufacturer or importer operates issues these Authorizations.
- Compliance with Good Distribution Practice—A certificate of Good Distribution Practice (GDP) is issued to a wholesale distributor by the national competent authority that carried out an inspection if the outcome of the inspection confirms that the wholesale distributor complies with GDP, as provided by EU legislation. If the outcome of the inspection is that the wholesale Distributor does not comply a statement of non-compliance may be entered into EudraGMDP. GDP certificates and statements of non-compliance may be issued to wholesale distributors of medicinal products and distributors of active substances.
- Wholesale Distribution Authorization—The wholesale distribution of medicinal products is subject to the holding of a Wholesale Distribution Authorization. The

National Competent Authority of the Member State in which the wholesale distributor operates these Authorizations.

- Registration of Active Substance manufacturers, Importers and Distributors—-Manufacturers, importers and distributors of active substances are required to register their activities with the National Competent Authority of the Member State in which they operate.
- Defined the frame of work and its complexity, for a full understanding of the issue it is also requested to know the principle manufacturing and quality constraints that could lead to a shortage or disruption situation.

  – Reliability of suppliers of critical starting materials (mainly manufacturers of API outside Europe);
  – Discontinuations (sometimes older drugs are discontinued in favor of newer, more profitable drugs). *With fewer firms making older sterile injectable drugs, there are a limited number of production lines that can make these drugs. The raw material suppliers that the firms use are also limited in the amount they can make due to capacity issues at their facilities. This small number of manufacturers and limited production capacity for older sterile injectables, combined with the long lead times and complexity of the manufacturing process for injectable drugs, results in these drugs being vulnerable to shortage. When one company has a problem or discontinues, it is difficult for the remaining firms to increase production quickly and a shortage occurs.*
  – Just in Time inventory practices that result in minimal product stock being on hand at any given time;
  – Globalization of manufacturers;
  – Concentration of production sites;
  – Production issues;
  – Complexity of the products;
  – Increasing Regulatory requirements.

In a similar scenario building redundancy, holding spare capacity, and increasing inventory levels could lower the risks of shortages; but what should be the main preventive and corrective actions that should be put in place to allow the risk mitigation:

- Guaranteed utilization orders—Many companies think that guaranteed utilization orders (a commitment to order a specific amount annually) to manufacture lower-margin, lower volume products, could reduce shortages of those products, especially those without predictable demand. Guaranteed orders could provide the proper incentives to the companies in order to invest in backup facilities or new manufacturing lines as a way to protect against potential shortages.
- Regulatory expectations and legacy products—Increasing regulatory expectations for legacy products is one of the obstacle to prevent shortages. Unfortunately many companies not want to either incur the costs of submitting new or supplemental filings or to risk current regulatory scrutiny, and associated delays, for taking actions required to upgrade a facility or the equipment. Investments in facilities that manufacture legacy products are lower due to challenges in assur-

ing regulatory compliance of legacy products for which development histories are often not available, either because of multiple company acquisitions or because the products were developed many years ago. The time required to get an application approved also contributed to their decisions not to invest in the facilities or equipment that could prevent a shortage. Shortages of legacy products can be also connected with analytic methods used for detecting impurities for which the revalidation requests high costs associated to concerns over the potential rejection of a re submitted regulatory application. It's a big challenge to improve analytical methods when the development histories for legacy products are not as robust as those of more recently developed products. Some form of regulatory discretion and increased collaboration with the involved Authorities would enable to reduce the risk of supplies interruption by building more resilient supply chains (including upgrading facilities, building new manufacturing lines, or adding new contract manufacturers in a more efficient manner), in particular for legacy products.

3.3 Main Reasons of Medicines' Shortages Related to Manufacturing and Quality Issues

In 2012, for example, based on information collected from manufacturers, FDA determined that the majority of production disruptions (66%) resulted from either:

- Efforts to address product-specific quality failures (31%, labeled Quality: Manufacturing Issues).
- Broader efforts to remediate or improve a problematic manufacturing facility (35%, labeled Quality: Remediation Efforts).

Quality or manufacturing concerns can involve compromised sterility, such as roof leakage; mold in manufacturing areas; or unsterilized vials or containers to hold the product issues that could pose extreme safety risks to patients (Fig. 4).

The majority of the shortages, more than 72%, were in the sterile injectable category, and the affected product categories or therapeutic classes ranged from anti-infective and anesthetic drugs to cardiovascular and oncology treatments.

The International Society for Pharmaceutical Engineering (ISPE) conducted a survey of its membership and found that compliance, together with manufacturing and product quality issues, represented the single most important factor leading to drug shortages.

There are many shortages that are not influenced by correlations with quality and manufacturing factors, like: market uncertainties and product margins; supply chain network design; demand forecasting; relationships between manufacturers and key stakeholders, including purchasing organizations and regulators.

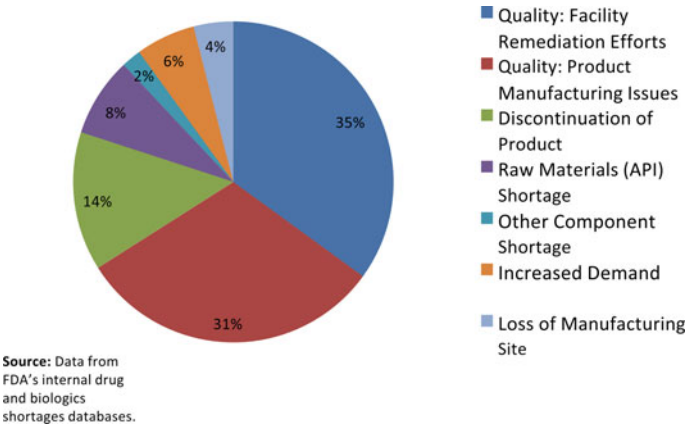

Fig. 4 Drug shortages by primary reason for disruption in supply in 2012 (*Source* Strategic Plan for Preventing and Mitigating Shortages—Food and Drugs Administration October 2013)

3.4 Medicines' Shortages Risk Reduction Starting from the Analysis of the Main Manufacturing Reasons

A deep analysis of the entire manufacturing and control flow is requested to identify the critical steps in a production process that could lead to a shortage or disruption; an example, coming from the experience of the author in the aseptic manufacturing of medicines is shown here below (Fig. 5).

Considering an overview approach what could be the manufacturing and control aspects that could be the main causes of potential shortages of medicines and what could be the overall strategies for their reduction.

(1) **Manufacturing and Control—Main Causes of potential Shortages**

- Unexpected shortages of Starting Materials, Intermediates, Auxiliary Materials (including laboratories supply and spare parts).
- Starting materials (Active Principle Ingredient, Excipients, Primary and Secondary Packaging Materials, Printed Packaging Materials) affected by unexpected defects of non compliance.
- Intermediates produced far away from final product assembling.
- Contaminations, impurities happen, due to significant quality assurance issues during manufacturing steps.
- Occurrence of a quality defect, despite all measures were taken according to quality standards.
- Unforeseen results of environmental monitoring in routine manufacturing (especially in the aseptic process manufacturing) but also in the periodic process simulation trials (media fill performed in the shutdown period).

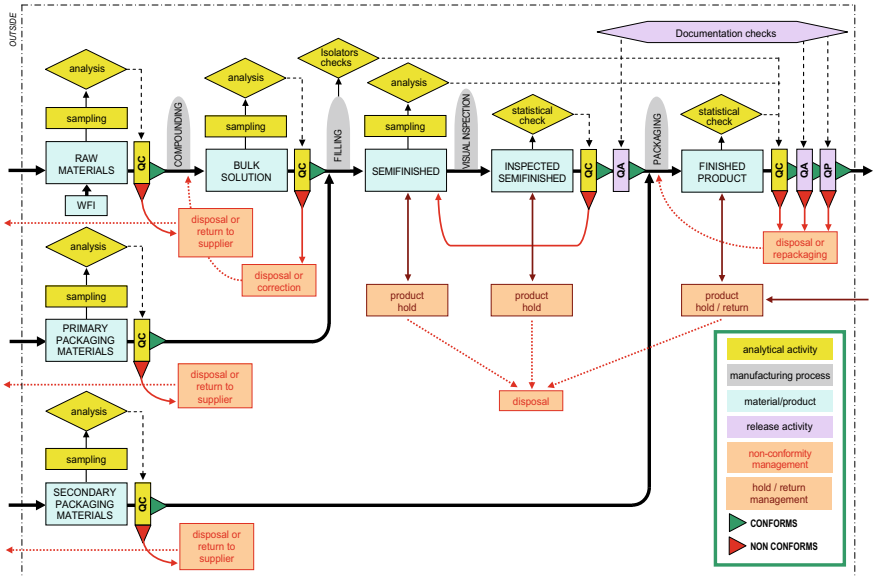

Fig. 5 Critical steps of a manufacturing process that could lead to a shortage or disruption (Own source)

(2) Overall strategies for shortages risk reduction

Business Continuity Elements—Reviewed gaps across the supply chain management processes allow to identify areas for prevention of future shortages. There are some business continuity elements involved in protecting against a sudden and unexpected demand for a product. Namely:

- **Business continuity planning**—Decisions and plans that drive the ways companies design and structure their manufacturing networks to reduce the risk of supply interruptions by identifying backup manufacturing facilities, building new manufacturing lines within existing facilities, and/or establishing dual-source suppliers to react quickly to sudden, unexpected spikes in demand.
- **Supply chain management**—Capability of a company's inventory management, demand planning, and forecasting accuracy to enhance the organization's ability to proactively avoid a supply interruption by aligning the predicted demand volumes with the material inventory levels needed.
- **Safety stock of raw materials**—Maintain buffer or extra stocks of raw materials needed to meet rapid and unexpected increases in product demand.
- **Safety stock of intermediates and finished products**—Store backup inventory of finished products in order to protect against unexpected product demand. Maintaining backup inventory of key drug intermediates is an additional strategy.
- **Backup internal and external manufacturing facilities**—Additional facilities in place to manufacture same finished products. Backup manufacturing for products

that required dedicated facilities is mainly limited by the fact that the expected rate of return is low due to the reduced sales volume anticipated for the products.
- **Dual-source suppliers**—Second source suppliers in place to provide the components needed to manufacture finished products. Despite this safeguard in place there are residual risks related to supply interruptions due to quality issues.
- **Ability to add a shift to an existing manufacturing line**—Processes in place to swap the manufacturing of one product with one at risk of shortage. This strategy risks to create a shortage for the product that was replaced.
- **Warm starts**—Ramp up operations at a contract manufacturer to help meet unexpected and sudden surges in demand. The resources needed required significant investment and for that reason is limited to products having relevant annual sales or percentage of market shares.

But also they are of consideration:

- Periodic risk assessment reviews—Reports that identify the potential compliance risks across a company's manufacturing supply chain.
- Periodic assessment of the supply chain performances—Assess supply chain resilience and shortages in the annual product quality review.
- Trending reports—Studies that review past supply chain data trends to forecast potential issues and trigger additional risk assessments.
- Issue management communication system—A method that communicates the potential compliance risks across an organization's functional groups and external partners.
- Improvement of processes and analytical standards—Improve processes and analytical methods development programs in order to ensure more robust technology transfers to commercial facilities, which improve the opportunity to consistently demonstrate conformance to the established product specifications.

There are other sources to understand and prevent potential risk of shortages and disruption, but mainly for issuing treatment recommendation during shortages of medicinal products, that are:

- GMP inspection report identifying or investigating a shortage;
- Outcome of an GMP inspection and regulatory assessment;
- Quality defect reports and assessment;
- Manufacturing problem report and assessment;
- Availability of other strengths or pharmaceutical forms of the same product;
- The MAH risk assessment of the clinical use of the medicinal product with a defect/GMP non compliance;
- Information on the status of the remaining stock of the affected medicinal product;
- Distribution plans of the remaining product in the EU and world wide;
- Regular updates on the stock situation of the affected medicinal product (per country);
- Reports on the progress of the corrective actions taken to revert the shortage cause;
- Information on the estimated timing of the return to normal production levels;
- The MAH's risk assessment of switching patients to other alternatives;

- Relevant clinical information: experience from previous drug shortage(s) (contingency plan on how to deal with a shortage or experience with amended dosing, e.g. lower dose or experience with other medicinal product within the same indication or unpublished clinical data; on-going investigations and clinical trials).

4 Medicines Shortages Escalation from National to European Level

Another important aspect not to be overlooked in the shortages management is the decision tree on escalation from National to European level. The decision tree would facilitate the chose on when such escalation to a European level could be considered.

The GMP non-compliance/quality defects may lead to a shortage of a medicinal product, if it is decided that it is necessary to prohibit importation and/or release of a batch or to withdraw batches from the market. Though in general such action based on GMP non-compliance/quality defects is good precautionary practice and at the discretion of the Member States when products are authorized nationally, there might be incidents where it is necessary to elevate the discussion to agree on a harmonized risk management strategy at a Union level in order to protect public health.

In details:

No escalation to the European level is required if:

a. shortages are limited to a single Member State (although noted that this situation may change over time);
b. the shortage duration is limited and not considered relevant from a clinical point of view (e.g. for vaccines, vaccination may be postponed for a few weeks), although this situation may evolve over time.

Escalation to a European level may be considered if:

a. the product is considered to be a critical medicinal product in a Member State and there is evidence that indicates that the shortage will affect more than one Member State. It is possible that there may be differential supply of GMP compliant/GMP non-compliant product between Member States;
b. a decision to keep a suspected defective product on the market may have possible safety implications (e.g. sterility is not guaranteed) that may indicate the need for Union advice on appropriate risk minimization measures to be taken to allow continued use of the suspected defective product;
c. the product at issue is considered to be non-critical but the concern is due to critical GMP non-compliance/quality defects which may affect other products on the Union market;
d. the product is considered to be non-critical but shortages may have an impact on public health (e.g. owing to the number of users or the characteristics of the patient population).

Once a Member State or several Member States have decided that an escalation to Union level is necessary, the following principles should be followed in determining which Committee at the Agency should take the lead in the assessment and communication strategy. It is proposed that shortages only affecting Centrally Authorised Products (CAPs) as well as shortages affecting both CAPs and non-CAPs are subject to the CHMP's review. Should more than one Rapporteurship be affected, a lead Rapporteur will be nominated by the Committee. Should a shortage only affect non-CAPs, the Member State(s) should escalate the issue to the Heads of Medicines Agencies CMD (HMA) for an harmonized response at Union level.

Quite relevant to understand the status of the shortages at the European level is the *Shortages Catalogue* available on internet (*EMA webpage*). The *Shortages Catalogue* contains information on medicine shortages that affect or are likely to affect more than one Member State, where EMA has assessed the shortage and provided recommendations to patients and healthcare professionals across the EU. Unfortunately it does not give a complete overview of all medicine shortages occurring in the EU, as most shortages are dealt with at a national level.

5 Conclusions

The chapter provides readers with an overview of the aspects that may compromise the continuity of supply of medicines on the market (patients). Once the potential origins of medicines-related shortages are understood, the reader is given the possible ways to prevent it from happening or to mitigate deficiencies. These are obviously analyzes and tools that require a fair degree of expertise to be implemented.

No single predictor identified whether a product was at risk of a shortage. There is a set of issues outside of quality that contributed to drug shortages, including the inability to ramp up production when a competitor leaves the market. Among the causes there is also the lack of incentives that would benefit manufacturers when they could produce the product needed to meet demand and prevent a shortage. There are also operational-related elements such as the ability to design predictable, flexible, and redundant supply chains that react quickly to changing demands and/or problems with specific manufacturing sites; predict future demands by improving market insights and navigate regulatory expectations.

Multiple factors outside of quality are contributing to drug shortages. From a deep analysis of the issue result that some product classes, such as antibiotics, hormones, and/or cytotoxic drugs, are mainly affected by the shortages because may require dedicated manufacturing facilities, an added challenge for these products. Manufacturing facilities requiring segregated, self-contained, or specialized lines indeed prevented the establishment of redundant capacity due to the investments that would be required for products where demand might not be stable on an annual basis and have low margins.

The existence of multiple suppliers does not negate the potential of a shortage, since each manufacturer could experience difficulties in ramping up operations when

a competitor withdrew from the market. The new paradigm has shifted from dual sourcing and backup manufacturing options for products to a network with limited sourcing and fewer manufacturing options when products went off patent.

Strengthening quality and the development and implementation of systems that proactively identify, measure, and monitor risks across the manufacturer's overall supply chain are the main points to take in proper consideration. This includes GMP compliance risks as well as issues that may develop when there are no robust development and/or manufacturing processes in place. Manufacturers should be diligent in selecting suppliers and, when necessary, partner with them to help improve their quality systems. As a result, a well performed risk analysis of the production and control flow, including supply of certain starting materials, will be helpful to identify the main critical points affecting the manufacturing continuity and the supply of the finished product on the market.

The author leaves the readers with some strategic questions to answer; many of that queries should help to understand and sizing the shortages causes, to perform a gap analysis, and to define a preventive and corrective actions plan to control and mitigate the impact of shortages having as principle origin quality and manufacturing problems.

- What are the five main topics of your business continuity plan?
- What are the connection and the key factors between: production plan—inventory plan—sales plan—financial plan—sales forecast periodic review?
- What elements are considered for sourcing from suppliers? Critical material, high-volume, …?
- Are contract manufacturers and critical suppliers involved in production planning?
- Are suppliers and contract manufacturers expected to timely notify you in case supply issues are expected?
- Does your contracts with suppliers establish volume purchase guarantees?
- Do these contracts have failure-to-supply clauses/penalties? If yes, can you provide details of the penalties enforceable in case of supply defaults?
- Percent orders to be delivered on-time and full quantity? Percent of rejections?
- In terms of overall capacity strategy, does your company adopt flexible manufacturing and what levers are used to meet sudden or unexpected increase in demand?
- Does your company maintain registered spare capacity or strategic inventory of key intermediates and finished products?
- Does your facility operate on a single, double or tree shifts basis for the drug product that was short?
- Is your manufacturing line approved for multiple products or dedicated?
- How ease is the change-over in your manufacturing facility? High, medium or low?
- Do you measure overall equipment effectiveness (OEE)? What are the usual OEE levels?
- Rank the following quality issues in causing supply interruptions based on the occurrence and likely impact: Rejection due to poor tech transfer process (method);

Rejection due to operator error (man); Rejection due to machine error (machinery); and Rejection due to outsourced material (material).

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Risk Mitigation and Preventing Medicines Shortages

João Roque, João Luís de Miranda and Pál Fehér-Polgár

Abstract The main attributes of Supply Chain (SC) operations within AbbVie, a global pharmaceutical company, are presented, as well as the key factors for risk mitigation within the deliverance of AbbVie products and services are introduced. We focus both the management of external risks and the management of product supply risks, properly pondering the key risks and additional mitigation strategies in both cases. At AbbVie, the Sales and Operations Planning (S&OP) and demand forecasting are jointly addressed, being the S&OP involvement, the key elements within S&OP, and the global S&OP process contributing all together for the successful prevention of medicines shortages. In this way, Key Performance Indicators (KPI) were defined to adequately measure AbbVie performance, and SC operations are evaluated through the customer satisfaction, the operational excellence, and the assurance of supply during a three-years period.

1 Introduction

AbbVie is a research-driven biopharmaceutical company, with sites located all around the world, and about 29,000 employees including scientists, researchers, communicators, manufacturing specialists, and regulatory experts. AbbVie is discovering, developing, and delivering drugs in therapeutic areas of proven expertise, such as

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immunology, oncology, neuroscience, virology, and general medicine. AbbVie is thus committed to improving health outcomes, operating responsibly, contributing to communities where it can make an impact, and finding better solutions for patients (Roque 2017).

Research and innovation are the cornerstones of AbbVie, for that collaborating with peers, universities, clinical experts, governments, and advocacy groups. Through a dynamic and collaborative approach that is addressing the most challenging diseases, recent advances in leading-edge science are being allowed, and thus new solutions for patients are achieved worldwide.

Delivering products and services for AbbVie is a large and complex mission. The related SC operations are tightly inter-connected, and small disturbances in one single stage can imply large perturbations at a later stage, or even products penury and shortages. For that, the entire pipeline is considered, from the active drug until the final distribution, and also including the drug product, the packaging, and the patient services.

The structure of this chapter considers the following parts: in Sect. 2, the main subjects of risk mitigation in the pharmaceutical SC are presented; in Sect. 3, the S&OP activities at AbbVie are described; in Sect. 4, S&OP as a key success factor to prevent medicines shortages is addressed; and finally in Sect. 5, the conclusions are discussed.

2 Risk Mitigation in Pharmaceutical SC

In this section, the key factors for risk mitigation within the deliverance of AbbVie products and services are introduced. We present both the Management of External Risks and the Management of Product Supply Risks, and also in both cases properly pondering the key risks and additional mitigation strategies.

The **Management of External Risks** considers the key risks related with the natural disasters, the geopolitical challenges, the cargo theft, the product diversion, and the counterfeit products. Additional mitigation strategies are put in place, such as risk strategy and external monitoring. In more detail:

- The risk strategy addresses the redundancy of supplies, the global inventory management, the business continuity plans (e.g., local and global teams deployed, employee protection plans), the 'person in plant' approach for Third Party Manufacturer (TPM), the external benchmarking, and the implementation of improvement programs (Shen 2015);
- The external monitoring includes the monitoring of ongoing distribution (e.g., "track and trace" activities), agency actions, ongoing monitoring of global landscape, audits for distribution security, and anti-theft programs.

When addressing the **Management of Product Supply Risks**, the key risks are the misalignment between market demand and supply, the regulatory agency actions, and the supplier performance challenges. Additional mitigation strategies are also

implemented, such as risk strategy, proactive monitoring, and process governance as described in below:

- The risk strategy ponders the technology, capacity and capability investments to support the pipeline, the planned redundancies aligned with pipeline over the long range planning, the optimization of capacity through short term contract manufacturing; and the elimination of long term capacity excess;
- The proactive monitoring considers the assess impact of external agency actions on peers and suppliers, the benchmark performance and technology, the performance monitoring through functional KPIs, the program for effective internal audit, and the reviews of quality management;
- The process governance verifies the S&OP alignment of commercial demands and supplies, the program reviews for pipeline leadership, and the functional reviews for all cost improvement programs.

Additionally with the AbbVie suppliers, the dual sourcing plans face the inventory management within the review of "suppliers" and the related potential risks. Both the financial watch-list is proactively reviewed and the quality and delivery performance is tracked within the supplier audit program; and finally, the overall reviews for supplier risk management are also treated.

3 Sales and Operations Planning (S&OP)

In this section, the Sales and Operations Planning (S&OP) and demand forecasting at AbbVie are jointly addressed, being the S&OP involvement, the S&OP key elements, and the global S&OP process contributing all together for the successful prevention of medicines shortages. The purpose is to improve forecasting and communication across the network of affiliates, as well as the global SC. In addition, S&OP is also addressing the forecast accuracy, the demand processes, and the management of culture change.

As regarded in AbbVie, S&OP is a routine business process to proactively align supply and demand while identifying and mitigating risks. This business process is treated as a behavior, and not just a series of meetings. For that, some key questions shall be pondered:

Do we understand the demand and its inherent risks?

Do we understand the supply and its inherent risks?

Have we tested the SC and know what to produce?

Do we agree that we have a good plan?

About the S&OP involvement, a wide network is involved in the monthly S&OP cadence, while different areas such as commercial, finance, purchasing, SC, Manufacturing, and the senior leadership are important, thus requiring additional monitoring:

- COMMERCIAL—by providing Approved Demand Statement (ADS), indicating scenarios with respective probability, communicating risks and challenges, and explaining the business impact;
- FINANCE—by collating the outcome of S&OP cycle into the latest best estimate;
- PURCHASING—by translating supply requirements to in-coming material purchases. Ensuring sufficient capacity with the suppliers;
- SUPPLY CHAINS—by translating commercial demands into manufacturing volumes, and ensuring overall balance;
- MANUFACTURING—by assessing internal capacity, absorption, and impact to schedule;
- SENIOR LEADERSHIP—by reviewing the output of monthly S&OP cycle, resolving elevations or conflicts, and making decisions where needed.

In plus, the key elements for the local affiliate S&OP are presented in below. The forecast on patients' products and services is providing S&OP with the necessary data and information. Beyond the needs both for financial reconciliation and supply reconciliation, including the typical reviews on assumptions, demands, and commercial subjects, also the business intelligence, the historical data, and the KPI review are taken in account.

Concerning the global S&OP process, the information-feedback cycle considers the affiliate procedures, planning, and manufacturing in each area and also globally. Each one of the three referred topics is related to its own time-scale (Hillier and Liebermann 2015), being this global process largely mirroring a well-known classification that is utilized in many cases (see, for example, Barbosa-Póvoa et al. 2016).

- AFFILIATE—long-term or strategic approach, concerning the long-term SC evolution over the course of several years, and incremental changes like expected variation in goods and materials (demand, availability, pricing) need to be assessed beforehand to ensure stability and efficiency for the entire SC pipeline; it includes a 28 months forecast (the commercial ADS), financial projections, and the commercial strategies for sales.
- PLANNING—mid-term or tactical approach, usually concerning plans ranging from one week to one year, mostly addressing the optimal usage of the existing SC infrastructure and allocation of scarce resources, the downtime in equipment maintenance, and capacities or availability under existing contracts. due to the different time scale, financial aspects and uncertainties (regarding both the future external and internal state of the SC pipeline) are considered in more detail; it integrates the replenishment plan, related financial projections, and supply tactics for replenishment.

- MANUFACTURING—short-term or operational approach, typically addressing decision-making that affects a time span variable from the minutes to the days/weeks/few months range; a detailed knowledge of the pipeline is assumed and technical issues are focused (e.g., production and/or distribution constraints); it completes the master production schedule, the planned orders, and the manufacturing tactics.

Finally, closing the information-feedback cycle, the financial projections and the division strategies for sales, replenishment, and manufacturing are all integrated, both by local area and globally.

4 S&OP as a Key Success Factor to Prevent Medicines Shortages

In this section, KPI are defined to adequately measure AbbVie performance within the proper time horizon, Therefore, SC operations are evaluated through the customer satisfaction, the operational excellence, and the assurance of supply during a three years period.

The importance of measuring is based in that measurement is the first step that leads to control, and then to process improvements. In fact, it is widely known (Harrington and Voehl 2012) that:

> ***"If you can't measure something, you can't understand it."***
>
> ***"If you can't understand it, you can't control it."***
>
> ***"If you can't control it, you can't improve it."***
>
> ***"What gets measured gets done!"***

In this way, the KPI main purpose is to identify issues that contribute to better understand the current situation, and then to improve the existing situation in the future. For that, AbbVie performance integrates a three year operations performance, and the main KPIs in this time horizon are:

- **Customer Satisfaction**—it is predetermined by how the expectations of the customer are met, because customer satisfaction is directly connected to the customer's needs (Kotler et al. 2017); in plus, the degree to which these needs are fulfilled determines either enjoyment in the case of conformity or disappointment from discrepancy (Hill et al. 2007); in the past three years, the *AbbVie* mark for customer service is about 98.3%;
- **Assurance of Supply**—it is commonly stated as *the right goods/services at the right time and place*; in the last time horizon, the AbbVie mark for the monthly patient impact backorder is about 0.001% of sales;

- **Operational Excellence**—it is the typically regarded as the execution of the business strategy more consistently and reliably than the competition; in the past three years, the AbbVie inventory turns 3.2 while the related peer group average mark is 1.9, spanning from 1.7 (Amgen) to 2.8 (BMY).

5 Conclusions

AbbVie is a global pharmaceutical company with more than six thousand employees working in Supply Chain and Operations with strong presence in dozens of countries, thus the deliverance of products and services to patients is dealt with due diligence, by using risk mitigation measures, improving SC operations, and identifying and addressing the related KPI.

The key risks at AbbVie, considering also the additional mitigation strategies, are both the Management of External Risks and the Management of Product Supply Risks. In plus, the S&OP and demand forecasting are jointly addressed within the following topics: the S&OP involvement; the S&OP key elements; and the global S&OP process.

Then, adequate and tuned KPI are implemented to evaluate the entire SC operations at AbbVie and, in a three-years period, it is observed high level of customer satisfaction (98.3%), assurance of supply with backorder impact of about 0.001% of sales, and operational excellence with inventory turns 3.2 while the average mark for the related peer group is 1.9.

In this way, AbbVie is improving forecasts, demand processes, and communication procedures, integrating all the referred factors and indicators properly, and contributing for the successful prevention of medicines shortages across all the national and European affiliates, as well to the global pipeline.

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An Exploratory Assessment of Risk and Resilience in Pharmaceutical Supply Chains

Rachel Ward and Vincent Hargaden

Abstract With medicines shortages becoming an increasingly prevalent issue, it is necessary to carry out an assessment of the resilience of pharmaceutical supply chains, to determine where vulnerabilities exist which may be contributing to the shortages problem. This chapter describes an initial exploratory assessment of supply chain resilience in the downstream section of pharmaceutical supply chains. Using a previously validated approach (the Supply Chain Risk Assessment Method—SCRAM^{TM}), survey data was collected from a number of supply chain managers dedicated to pharmaceutical sector. The findings suggest a number of areas in which supply chain capabilities require improvement in order to develop more resilience supply chains, particularly flexibility in sourcing; flexibility in order fulfilment; visibility and collaboration.

Keywords Supply chain resilience · Pharmaceutical supply chains · Medicines shortages

1 Introduction

Medicine shortages are an increasingly prevalent issue in pharmaceutical supply chains (Ward 2018). Shortages have an impact on stakeholders at all levels in the supply chain resulting in additional cost and stress for stakeholders, wasted time, and affecting patients by providing inadequate access to medicines resulting in subpar treatment and in rare cases, death (Ward 2018). The increase in incidents of medicine shortages is due to a number of reasons including globalisation, just-in-time inventories and the increasing number of natural disasters causing disruption to the supply chain (Wagner and Neshat 2009). In addition, the ageing European population is set to exacerbate the problem. It is expected that by 2020, 25% of the European population will be 60 years and over European Commission (2014). As the population

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ages, the need for medicines increases due to the fact that the number of conditions experienced by an individual tends to increase with age. The focus of this chapter is to outline the approaches for assessing supply chain risk and resilience; select an appropriate method to measure the resilience of the pharmaceutical supply chain; to use this approach to carry out an initial exploratory analysis of the resilience of medicines supply chains in Europe. The scope of the initial assessment is limited to the downstream members of the pharmaceutical supply chain, that is, investigating the resilience of at the manufacturer and wholesaler levels. It is limited to the investigation of supply chain partners dealing with small molecule drugs as the complexity of large molecule drugs leads to additional complications with regards to managing the supply chain.

2 Literature Review

2.1 Supply Chain Disruption and Risk

Supply chain disruptions are defined as "random events that cause a supplier or other element of the supply chain to stop functioning, either completely or partially, for a (typically random) amount of time" (Snyder et al. 2016). Supply chain disruptions can be broadly allocated into three categories: Random disruptions (e.g. as a result of natural disasters), accidental, and intentional (e.g. terrorist attacks) (Sheffi and Rice 2005). The former two categories are most applicable to the pharmaceutical supply chain. Disruptions not only impact on the company performance in the short term, through lost earnings, or additional costs, but can have lasting impacts. It was found that the announcement of a supply chain disruption caused a decrease in equity risk in the subsequent year for companies surveyed between 1989 and 2000 (Hendricks and Singhal 2005). Supply chain managers must attempt to avoid supply chain disruptions and recover from them. A key way in which supply chain managers can and have attempted to avoid supply chain disruptions is through risk assessment, mitigation and to design resilient supply chains.

Literature about disruptions and risk management is at a relatively nascent stage with the research area gaining much traction in the early 2000s following a number of high-profile supply chain disruptions including those caused by the 9/11 terrorist attacks in 2001 and the Severe Acute Respiratory Syndrome (SARS) epidemic between 2002 and 2003. Supply chain risk management is primarily focused on identifying and mitigating two types of risk: supply/demand risk and disruption risk (Kleindorfer and Saad 2005). Risk mitigation can take the form of reserve-holding such as excess capacity, inventory, and redundant suppliers (Chopra and Sodhi 2004). Supply chain risk management requires the quantification and identification of risks, but this is not always possible (Pettit et al. 2013). Another issue is that risk management tends to disregard low-probability, high-impact events (Pettit et al. 2010). There is also a focus on profit-maximisation and operational risk rather than upstream and

downstream supply chain risk (Tang 2006). It has also been argued that there should be a focus on total time to recovery (Tang 2006) as there can be an assumption a supply chain will return to prior level of performance post-disruption (Fiksel 2006).

2.2 Supply Chain Resilience

Resilience is "*the ability to survive, adapt, and grow in the face of turbulent change*" (Pettit et al. 2013). A number of definitions have been proposed for resilience however, the key idea of resilience is the ability to learn from disruptions and to grow. Supply chain network design has long ignored the dynamic nature of supply chains and the need to constantly adapt and grow with disruptions. Supply chain disruptions are unavoidable (Peck 2005; Craighead et al. 2007). Supply chain managers must accept these two key characteristics of supply chains and adapt and grow. The best way in which this can be achieved is through resilience measurement and improvement efforts. Resilience is about adaptability, flexibility, maintenance, and recovery (Ponomarov and Holcomb 2009). The key difference between resilience management techniques and risk management techniques centres around the ability to learn and grow following supply chain disruption. This is the fundamental advantage of resilience management efforts. It has been proposed that resilience can be broadly achieved through either building in redundancy or increasing flexibility (Sheffi and Rice 2005). Redundancy-augmentation includes strategies such as holding additional inventory, multi-sourcing strategies, and having low capacity utilisation rates (Sheffi and Rice 2005). However, excessive inventory is not only expensive, but also can be detrimental to lean operations and product quality. Thus, increasing flexibility is often hailed a more appropriate resilience improvement strategy. Increasing the flexibility of the supply chain requires initiatives such as increasing the number of suppliers, developing stronger relationships with existing suppliers, and generally increased collaboration between stakeholders, an endeavour which is often considered the greatest strength in supply chain design. However, despite the difference between risk and resilience management, one is not recommended solely over the other, but rather to be used in conjunction with each other as there are specific advantages to both techniques (Pettit et al. 2010).

2.3 Resilience Measurement Methods

Resilience measurement methods are limited due to the nascent nature of the research area. The research conducted to date has been largely qualitative rather than quantitative (Hohenstein et al. 2014). At a high level, there are four general approaches to measuring supply chain resilience: case methods, modelling methods, simulation methods and survey based methods. There are different benefits and purposes for each of the methods. For example, mathematical modelling methods are appropriate

for more tightly defined problems, whereas, simulation methods are better for more dynamic behavioural-based problems. Some of the different methods of calculating resilience are outlined in Hohenstein et al. (2014), Tukamuhabwa et al. (2015).

2.3.1 Case Study Based Methods

A vulnerability framework was developed which posed three critical questions: "What can go wrong? What is the likelihood of that happening? What are the consequences if it does happen?" (Sheffi and Rice 2005). Here, disruptions are categorised as a function of their likelihood of occurrence compared to the consequences of occurrence. However, this vulnerability framework is unique to an individual company due to the differing consequences. The tool can be used by management to prioritise planning. It is a case by case analysis of the resilience of a supply chain. Companies can then use the resilience framework which measures resilience as a function of company position and responsiveness. A method called the BCFI method (balanced critical factor index) was developed which identified the most critical practices leading to a more resilient supply chain (Nikookar et al. 2014). However, this method was disregarded due to the limitations in the sample used to validate the method; just five companies within the automotive industry were tested.

2.3.2 Mathematical Modelling Methods

The measurement of supply chain resilience using a hybrid fuzzy probabilistic method was proposed (Pavlov et al. 2017). The method expanded on existing methods of assessment "by incorporating ripple effect and structure reconfiguration". However, this approach was limited by the fact that it was based under the assumption that supply chain failure only results from supplier disruption.

Modelling techniques have been used to determine the resilience of distinct supply chains (Tomlin 2006). A single-product setting with two suppliers is modelled (Tomlin 2006): a reliable supplier, and an unreliable supplier. A mitigation and contingency framework was implemented. The focus was on supply-side tactics of sourcing mitigation, inventory mitigation, and contingent rerouting. It was found that the length of the disruption impacts the appropriate contingency strategy.

A model which focuses on the potential impact of a disruption rather than the cause was developed, in which it was found that "the greatest exposures often lie in unlikely places" (Simchi-Levi et al. 2014). Traditional risk management practices focus on identifying the probability of an event and its likelihood of occurrence. Using linear optimisation and Markov modelling, the impact of a disruption was analysed using time- to-recovery (TTR) and time-to-survive (TTS) as key inputs (Simchi-Levi et al. 2014). Time-to-recovery is the time it takes to recover from a disruption. Time-to-survive is the amount of time before the performance of a node decreases. The model focuses on evaluating supply chain vulnerability given the occurrence of a disruption "regardless of their cause and where they strike" (Simchi-Levi et al. 2014).

It provides a quantitative risk exposure model to allow for the easy identification of risks in the supply chain. The impact of a disruption could be assessed using the model rather than quantifying the likelihood of occurrence (Simchi-Levi et al. 2015). The model was applied to the automotive industry to identify risks and mitigate disruptions. It allowed for the identification of previously unrecognised risks. A key obstacle to using traditional methods of evaluation surrounds data availability; in particular, it is often difficult to predict and quantify high-impact low-probability events. Transparency is noted to be low in the pharmaceutical industry and thus would prohibit the availability of data. The focus of the proposed method is on the impact of a disruption regardless of the cause as it is suggested that mitigation efforts are typically similar regardless of the cause of disruption (Simchi-Levi et al. 2015).

The vulnerability of supply chains was assessed using graph theory (Wagner and Neshat 2012). Here is was proposed the measurement of supply chain vulnerabilities using the supply chain vulnerability index (SCVI). It was claimed that vulnerabilities could not be measured or observed directly but could be determined by "drivers of vulnerability" (Wagner and Neshat 2012). The vulnerabilities investigated were performance-based, structural (number of employees, sales revenue, production type), and managerial (logistics importance, supply chain risk planning, supply chain risk management). The SCVI uses graph modelling to assign a score to each vulnerability; a high score indicates poor performance, and a low score indicates high performance. This measurement tool was designed to help direct the efforts of management to make appropriate changes by justifying costly measures by evaluating the risk position before and after implementation of risk mitigation efforts (Wagner and Neshat 2012). It is suggested that a measurement tool and a better understanding of supply chain vulnerability is required in order to impact the decisions of policy makers with respect to an economy's supply chain vulnerability (Wagner and Neshat 2012). While the proposed method was useful, it failed to measure supply chain resilience, the purpose of this research. Graph theory was also proposed as a method of determining a supply chain resilience index (SCRI) (Soni et al. 2014). This method "considers all the major enablers of resilience and their interrelationships for analysis using an Interpretive Structural Modelling approach" (Soni et al. 2014). The method entails the use of surveys to identify the enablers of resilience and their interdependencies, the representation of this information on a diagraph, the translation of this visual representation into a matrix, and the ultimate calculation of the supply chain resilience index (SCRI). The surveys were limited to companies in India and as such, the results are suitable for use in countries with similar geographic, political and economic characteristics. In this regard, caution is advised against the use of measures created in a Western context in different contexts as there may be discrepancies in the wording and meaning of terms (Singhal et al. 2008). The number of survey questions was limited and as such the method was disregarded. A modelling method employing the resilience triangle, developed in civil engineering (Bevilacqua et al. 2017), was combined with the disruption profile plotted by Sheffi and Rice (2005). The resilience triangle models the loss of resilience of a structure during and after a disruption. The basic idea is to reduce the size of the triangle by increasing performance (reducing the impact of the disruption and thus the vertical

depression following disruption), and the reduction of recovery time (shortening of the horizontal axis). Supply chain resilience is also analysed using a survey using structural equation modelling (Wieland and Wallenburg 2013).

2.3.3 Simulation Methods

Simulation models can be used to "stress test" a system (Schmitt and Singh 2009). One of the first simulation-based frameworks in the area of supply chain risk and resilience was developed to assess supply chain resilience to disasters [30]. This assessed the vulnerability of a consumer products company to disruption risk and was used to quantity the impact on customer service. Monte Carlo and discrete-event simulation were used to develop the risk profiles for the supply chain locations and connections and to simulate the network interactions and risk management methods respectively (Schmitt and Singh 2009). Following on from discussion of loss in market share as a measure of disruption impact (Sheffi and Rice 2005), the measurement of market share before and after an event as a method of determining resilience was proposed and the impact of retail stock-outs analysed (Wu et al. 2013). The measurement was undertaken using an agent-based simulation model whereby two manufacturers produced two different products (A and B) to two different shops. One of the key benefits of agent-based simulations is that individual agents have the ability to make autonomous decisions. The agents have the ability to adapt and learn over time which allows for the modelling of the dynamic nature of resilient supply chains (Wu et al. 2013). This method encompasses consumer decisions to delay product purchase, substitute the product, or not purchase. These options are not always available to those purchasing medicines due to the fact that there may only be one manufacturer of a specific product and as such the luxury of product substitution does not exist. A multi-dimensional and hierarchical supply chain resilience measurement model which characterises the readiness, response and recovery of a supply chain is proposed (Chowdhury and Quaddus 2016). The model is cross-sectional in nature and as such investigates supply chain resilience at a particular point in time for a specific industry in a specific country. Using this model, they found flexibility and disaster preparedness to be the most crucial elements in creating effective supply chain resilience for an apparel manufacturer in Bangladesh (Chowdhury and Quaddus 2016).

2.3.4 Survey Based Methods

One of the first comprehensive approaches to assess and measure supply chain risk and resilience is the SCRAM™ (Supply Chain Resilience Assessment and Measurement) methodology developed in 2013 (Pettit et al. 2013). The methodology builds upon the conceptual framework first proposed in 2010 (Pettit et al. 2010). The basic premise of the method involves the investigation and measurement of the supply chain vulnerabilities and measuring the extent to which the stakeholder

has capabilities to overcome these vulnerabilities. Seven vulnerabilities were determined: turbulence, deliberate threats, external pressures, resource limits, sensitivity, and supplier/customer disruption, and 40 corresponding vulnerability sub-factors (outlined in Pettit et al. 2013). The fourteen capabilities to overcome these vulnerabilities are: flexibility in sourcing, flexibility in order fulfilment, capacity, efficiency, visibility, adaptability, anticipation, recovery, dispersion, collaboration, organisation, market position, security, financial strength. There are 71 capability sub-factors which are outlined in Pettit et al. (2013). The SCRAM™ methodology is a survey-based method which involves asking respondents a number of questions to be rated on a Likert scale. Respondents were encouraged to answer to the best of their ability, however a response option of "Don't Know" is available in the case that respondents were unsure. Each question was equally weighted. A value was assigned to each response on the Likert scale: 1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree. A value of 0 was assigned to "Don't Know".

The resilience score can be calculated as a function of the average vulnerability and capability scores. The aim is to tend towards higher resilience scores, as high resilience scores are related to higher performance (Pettit et al. 2013). However, a resilience score of 100% is not the precise aim as it could correspond to an over-investment in capabilities. The true aim is to lie in the 'Zone of Balanced Resilience' (Pettit et al. 2010). The 'Zone of Balanced Resilience' is the state at which the company is neither exposed to disruption, nor experiences erosion of profits. The specific areas to be improved are identified by calculating the resilience gaps: the percentage distance a point lies from the 'Zone of Balanced Resilience' (Pettit et al. 2013).

3 Exploratory Assessment of Supply Chain Resilience

An initial exploratory assessment of the resilience of medicines supply chains was conducted using the SCRAM™ methodology (Pettit et al. 2013). As the research described here is exploratory in nature, the survey was distributed via email to a small number (n = 9) stakeholders in the downstream pharmaceutical supply chain (i.e. manufacturers and wholesalers), based in Western Europe. Respondents held mid-senior level supply chain management roles, including procurement, production, planning and distribution. Respondents were contacted in advance to assess their willingness to participate in this early stage research. The completed survey data from the nine respondents was then used to calculate the average vulnerability, capability and resilience scores. The following numerical analysis of the survey data is based on a previously developed method (Pettit et al. 2013).

The overall supply chain vulnerability score (V) is calculated using Eq. (1) as the average of the vulnerability factor scores (V_i), where there are seven (n_V) vulnerability factors. Vulnerability factors are assumed to be equally weighted.

$$V = \frac{\sum_{i=1}^{n_V} V_i}{n_V}, n_V = 7 \tag{1}$$

Similarly, the overall supply chain capability score (C) is calculated using Eq. (2) as the average of the capability factors scores (C_j), where there are fourteen capability factors. Capability factors are assumed to be equally weighted.

$$C = \frac{\sum_{j=1}^{n_C} C_j}{n_C}, n_C = 14 \tag{2}$$

Vulnerability and capability factor scores are calculated using Eqs. (3) and (4) respectively. These formulae calculate the average of the associated sub-factors (which are assumed to be equally weighted).

$$V_i = \frac{\sum_{k=1}^{n_{V_i}} V_{i,k}}{n_{V_i}}, i = 1 \rightarrow n_V \tag{3}$$

$$C_j = \frac{\sum_{k=1}^{n_{C_j}} C_{j,k}}{n_{C_j}}, j = 1 \rightarrow n_C \tag{4}$$

$$R = \frac{C - V + 4}{8} \tag{5}$$

The resilience score (R), which an range from 0 to 100%, was calculated as a function of the average vulnerability and capability scores using Eq. (5). Based on the data gathered from the nine respondent companies, the overall resilience score was found to be 52%. While the objective is not necessarily to achieve a resilience score of 100%, which would indicate over-investment in capabilities, there are opportunities for improvement efforts.

It was found that connectivity and sensitivity were the greatest vulnerabilities exhibited based on the data collected in this exploratory analysis of the pharmaceutical supply chain. The weakest capabilities, those lacking attention and investment, included flexibility in sourcing, collaboration, dispersion, and flexibility in order fulfilment.

Vulnerabilities and capabilities were then ranked both in terms of factor score and in terms of importance. The average rank was calculated as a function of the rank of the factor score ranking and the ranking due to importance.

Connectivity was found to be the greatest vulnerability. Connectivity is "the degree of interdependence and reliance on outside entities" (Pettit et al. 2013). The medicines supply chain is highly dependent on outside entities due to the fact that there are typically a limited number of suppliers and stakeholders with the relevant specialist

capabilities. Improvement of this vulnerability could not occur without possible compromise of the safety of the product.

Sensitivity is defined as "the importance of carefully controlled conditions for product and process integrity" (Pettit et al. 2013). It is almost impossible to reduce this vulnerability due to the nature of the products in the medicines supply chain. It is possible to increase attention towards the linked capabilities in order to overcome this vulnerability. The linked capabilities include efficiency, adaptability, and dispersion.

The strongest capabilities were found to be recovery and anticipation; the ability to recover from and predict supply chain disruptions (Ward 2018). Fundamental to a highly resilient supply chain, attention should continue to be directed towards these capabilities. No further investment appears to be necessary however.

Designing resilient supply chains can be a costly procedure. This is one of the key motivations behind the calculation of resilience gaps, i.e. determining the gap between each vulnerability/capability linkage (Pettit et al. 2013). This is carried out using Eq. (6). Where there are negative gaps, i.e. the particular vulnerability is greater than the its corresponding capability, targeted improvement can be put in place to address this gap.

$$R_{GAP_{i,j}} = \frac{C_i - V_j}{4} \tag{6}$$

Resilience gaps above +15% are highlighted in yellow Table 1 and correspond to an over-investment in capabilities, i.e. a possible erosion of profits. Resilience gaps between +15% and −15% are highlighted in green and lie in the 'Zone of Balanced Resilience' (Pettit et al. 2013). Resilience gaps below −15% are highlighted in red and indicate an over-exposure to vulnerabilities and provide supply chain managers with areas to priorities in order to design more resilient supply chains.

As highlighted in Table 1, there are specific areas for improvement including: flexibility in sourcing; flexibility in order fulfilment; visibility; and collaboration. The results provide the insight that there is possible over-investment in certain capabilities which are attributable to the relatively high resilience score obtained. There appears to have been significant investment in defending against deliberate threats. Specifically there has been significant investment in security, anticipation, adaptability, and recovery. While there do not appear to be any particularly malicious intentions towards the pharmaceutical supply chain, there have been issues recently with regards to counterfeit medicines entering the supply chain. Therefore, while defence against deliberate threats may not appear to be directly necessary for dealing with medicine shortages, it is necessary for dealing with other issues faced by the pharmaceutical supply chain. There has been significant investment to counteract turbulence and supplier/customer disruptions. This appears to be appropriate due to the past experiences of demand fluctuations. The largest resilience gaps appear to be between connectivity and flexibility in sourcing and order fulfilment. Due to the nature of the products in the supply chain, the complexity in manufacturing, and strict quality standards, this is unsurprising. It has been suggested that some of the key issues surrounding this lack of flexibility in sourcing and order fulfilment are due to industry consolidation,

Table 1 Results from medicines supply chain SCRAM™ (Ward 2018)

	V1	V2	V3	V4	V5	V6	V7
C1	-0.15%			-10.22%		-30.07%	4.65%
C2	6.93%			-3.14%		-22.99%	11.73%
C3	8.04%			-2.03%			
C4				2.07%	-10.68%		
C5	13.62%					-16.29%	18.43%
C6	18.63%	21.53%	-6.77%	8.56%	-4.19%	-11.28%	
C7	20.31%	23.20%		10.24%		-9.61%	
C8	24.67%	27.57%					29.48%
C9	16.49%			6.42%	-6.33%		21.29%
C10	9.15%					-20.77%	13.95%
C11						-11.92%	
C12				11.67%		-8.18%	26.54%
C13		34.86%					
C14				4.57%		-15.28%	19.44%

where: V1 = Turbulence; V2 = Deliberate Threats; V3 = External Pressures; V4 = Resource Limits; V5 = Sensitivity; V6 = Connectivity; V7 = Supplier/Customer Disruptions; C1 = Flexibility in Sourcing; C2 = Flexibility in Order Fulfilment; C3 = Capacity; C4 = Efficiency; C5 = Visibility; C6 = Adaptability; C7 = Anticipation; C8 = Recovery; C9 = Dispersion; C10 = Collaboration; C11 = Organisation; C12 = Market Position; C13 = Security; C14 = Financial Strength

pricing pressures, and strict regulations (Ward 2018). Economic incentives such as price floors on generic medicines, and increased regulation regarding cessation of production have been proposed as potential strategies to improve the situation (Ward 2018). The allowance of temporary importation of products from other countries is another suggested method through which flexibility in sourcing could be improved (Ward 2018). There must be a minimum of three manufacturers to have a viable market model. It is encouraged that stakeholders collaborate to alleviate the issue of medicine shortages. There are few opportunities towards improving flexibility in order fulfilment as production is planned in advance. Change to this capability could result in unnecessarily large costs and it is recommended that no action be taken to invest further in this capability (Ward 2018). Collaboration and visibility were two of the weaker capabilities demonstrated by the pharmaceutical supply chain (Ward 2018). Supply chain collaboration is a necessary antecedent to successful supply chain functioning. It is recommended that stakeholders work together towards the common goal of improving patient lives. A key way in which supply chain visibility and collaboration can be achieved is through better reporting systems. Country specific reporting systems should be easily integrated with a central European reporting database, monitored by the European Medicines Agency (EMA). Increased visibility

and collaboration through better and more timely reporting will allow for earlier identification of shortages and the issues causing shortages. This early identification will allow for improved response to shortages. The pharmaceutical industry is suggested to have limited capabilities with regards to data analytics. There are opportunities for the pharmaceutical industry to utilise technology towards improving the situation. For example, data analytics could be used in order to better forecast demand with the ultimate aim of reducing the occurrence of shortages, and cloud-based technology could be used to improve information-sharing between supply chain partners (Ward 2018). Continuous measurement of the resilience is recommended. The interconnectedness of risks must not be ignored. Improvement efforts in one area may exacerbate the situation in others (Chopra and Sodhi 2004). This is a key motivation behind continuous resilience measurement.

4 Conclusion

Medicine shortages are increasing in prevalence. Action must be taken now to alleviate the issue. The resilience of European pharmaceutical supply chains was investigated and it was found that there are opportunities for improvement. It was found that increasing attention should be awarded towards increasing flexibility in sourcing and collaboration (Ward 2018). It is necessary that stakeholders collaborate towards the common goal of improving patients lives. The first step in achieving this goal is to determine a harmonised definition of medicine shortages to allow for better reporting of shortages. The next step is to create a centralised reporting system which allows for the accurate tracking of causes and predicted length of shortages. Stakeholders must collaborate in order to benefit patients. Timely reporting of shortages is necessary in order to allow for better response efforts. Flexibility in sourcing could be improved by allowing temporary sourcing alternatives, in particular in cases of shortages. Combining these two capabilities will allow for better response to disruptions and will allow for better identification of the key issues causing shortages, allowing for learning and growth opportunities, thus resulting in a more resilient supply chain.

The research described in this chapter was exploratory in nature, with larger numbers of respondents required to fully generalise the findings. Downstream supply chain entities were the focus of this research, however upstream entities could be surveyed to provide additional insights into the resilience of the supply chain as a whole and allow for additional opportunities for collaboration. Resilience is dynamic in nature. Future research could involve longitudinal studies of the changes in resilience over time. Triangulation of methods is an effective way by which research is validated. Validation of the results obtained could be further achieved by measuring the resilience using different methods such as simulation methods.

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Review of Pharmaceutical Sea Freight and Malaysian Third-Party Logistics Service Providers—A Supply Chain Perspective

Wai-Peng Wong and Keng-Lin Soh

Abstract Logistics is the backbone of trade because it integrates the supply chain for trade facilitation of all businesses including pharmaceuticals. The objective of this article is to review pharmaceutical ocean logistics trends and issues, and four Malaysian third-party logistics (3PL) research publications consisting of service quality, cost and service differentiation, integration and information system of freight-forwarding and container freight. The publication review is to ascertain if third-party logistics are potentially capable of supporting ocean pharma non-cold chain freight to pre-empt medicine shortages and identify challenges of the logistics supply chain. The research showed logistics service quality impacts customers' satisfaction, low costs and service differentiation influence firms' sustainable financial competitiveness, integration of depot and hauliers enhances national logistics performance, information system affects supply chain integration (SCI), and SCI affects operational and environmental performance. These studies involved third-party logistics service providers (LSP) along the supply chain which were freight-forwarding companies and their customers, and the container depots and hauliers. The review provides research evidence of logistics service quality potentially capable of meeting the requirements of conventional ocean-going non-cold chain pharma container freight as featured in professional logistics publications. Medicine shortages attributed to freight forwarders are unlikely noting their agility and robustness in the face of economic uncertainties. They are agile enough to manage factors internal and external to the firms. The research also provides suggestions to the SCI challenges confronting the conventional ocean container freight supply chain at the depot-haulier interface to forestall delays. This article reviews relate to research investigations of 3PL in Malaysia, a country sitting in the heart of Southeast Asia.

Keywords Pharmaceutical sea freight · Malaysia · Third-party logistics · 3PL · Logistics · Southeast Asia

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List of Abbreviations

AOA	Availability of Alternatives
AVE	Average Variance Extracted
CFAI	Cross Functional Application Integration
CR	Composite Reliability
DC	Data Consistency
EP	Environmental Performance
FTQ	Functional logistics service quality
GDP	Gross Domestic Product
HTMT	Heterotrait-monotrait ratio of correlations
IF	Integration factors between Depots and Hauliers
II	Information Integration
IS	Information System
LPI	Logistics Performance Index
LSP	Logistics Service Providers
LSQ	Logistics Service Quality
MBV	Market-based View
OE	Operational Efficiency
OI	Operational Integration
OP	Organizational Performance
PDSQ	Physical Distribution Service Quality
RBV	Resource-based View
SAT	Satisfaction
SC	Supply Complexity
SCI	Supply Chain Integration
SD	Supply Dynamism
SE	Supply Environment
SI	Supply Importance
SQ	Service Quality of Depot
TNQ	Technical logistics service quality
3PL	Third Party Logistics

1 Introduction

Southeast Asia comprises 10 ASEAN countries and East Timur. The 10 ASEAN countries are Brunei Darussalam which is ranked 70 of 160 countries in the 2016 Logistics Performance Index (LPI), Cambodia 73, Indonesia 63, Laos 152, Malaysia 32, Myanmar 113, the Philippines 71, Singapore 5, Thailand 45 and Vietnam 64 (World Bank 2016). These countries ranked within the top three quintiles except for Myanmar and Laos in the fifth quintile. Hence, Southeast Asian countries were among the best and poorest logistics performing countries. These countries are trading countries and therefore would have logistics as their backbones to their economies. The

more developed trading countries would have in place relatively better logistics infrastructures. This explains 5 of the Southeast Asian countries found their rankings in the top two quintiles in the Logistics Performance Index (LPI) for 2016 (World Bank 2016). The generics in these countries stood at 63% of total medicine spend in 2017 (Henry 2018). By 2020, these countries are expected to generate $40 billion in pharmaceutical sales (Munir and Hong 2016). The pharma market sizes for Indonesia, Thailand and Vietnam are forecasted at $12.6 billion, $9.47 billion and $6.6 billion respectively (Henry 2018). These expanding market sizes are fuelled by an expanding middle class, a rise in personal income, and a surge in private insurance coverage (Munir and Hong 2016). With these increases, the vital associated services to support deliveries are logistics services. This is particularly so especially for the developing countries with complex geography and underdeveloped transportation system (Munir and Hong 2016).

Logistics is the management of acquisition, storage, transportation, and delivery of goods through supply chain (Hamilton 2004; Bowersox 2013). They are the activities or processes for the effective and efficient movements of raw materials, semi-finished and finished goods from business to businesses along the supply chain to end customers (Srivastava et al. 2008). Logistics strategically allows companies to keep pace with market changes and forge supply chain integration (Meade and Sarkis 1998) to sustain competitive advantages for financial profitability (Vasiliauskas and Jakubauskas 2007; Wong et al. 2015).

The 1960 s' saw logistics concept appearing in physical distribution of the outbound side of logistics system (Coyle et al. 2002). They relate to consumer non-durable goods and finished goods physical distribution (Coyle et al. 2002). Beginning 1970 s through 1980 s, businesses and commercial logistics providers introduced inbound logistics to support manufacturing or operations. Logistics in a service enterprise is the acquisition, scheduling, and management of the facilities or assets, personnel, and materials to support and sustain service operations or business (Coyle et al. 2002).

Logistics service offerings or logistics activities have terms which are used interchangeably such as "logistics alliances" (Bowersox 1990), "contract distribution" (Aertsen 1993), "logistics outsourcing" and "contract logistics" (Sink et al. 1996; Leahy et al. 1995; Lewis and Talalayevsky 2000), "freight forwarder" (Sgouridis 2003; Vasiliauskas and Jakubauskas 2007), "integrated service provider" (Bowersox et al. 2007), "logistics service provider" (LSP) (Sauvage 2003; Sum and Teo 1999; Stefansson 2006; Salleh 2009) and "third party logistics (3PL)" (Lieb 1992; Berglund et al. 1999; Bask 2001; Stefansson 2006; Vasiliauskas and Jakubauskas 2007; Liu and Lyons 2011). Generally, 3PL is a broader term that is frequently used to cover businesses in freight forwarding or contract logistics (Vasiliauskas and Jakubauskas 2007). In other words, 3PL performs all or a large portion of a client's supply chain logistics activities and its value adding is based on information and knowledge at the lowest cost (Bowersox et al. 2013)

3PL assumes multiple distribution activities but no ownership of inventory (Sink et al. 1996). They are LSP(s) delivering, managing and controlling logistics activities on behalf of their users (Laarhoven et al. 2000). They are companies that provide

logistics services such as transportation, warehousing and forwarding (Wu and Liu 2008). As such, logistics users find outsourcing to 3PL advantageous in driving down their inventory investment and costs while improving delivery reliability and speed (Heizer and Render 2014). The outsourcing of 3PL services is popular and allows companies to develop its core competencies to maintain competitive advantage (Bowersox and Daugherty 1995) critical to the survival of business (Bhatnagar et al. 1999; Shang 2009; Zhao and Tang 2009). Over the passage of time, 3PL then developed rapidly to fulfil the demands of logistics services such as transportation, warehousing, freight consolidation, inventory management, labelling and packaging (Wu and Liu 2008).

Containers facilitates world trade growth (The Economist 2013) and drives economic globalization of 20th century (Bernhofen et al. 2012; World Economic Forum 2013). Goods are efficiently moved and transferred in containers because they facilitate inter-modal transport between sea, air and land (World Shipping Council, History of Containerization). Containers have a very important role to move containerized goods for economic value-adding processes along the supply chain. This increases business opportunities and the GDP to benefit the national economy (Hanouz et al. 2014).

This article first describes the pharma logistics development and issues of ocean freight supply chain. It includes the sea shift from pharma air freight. Second, it reviews 3PL studies of Malaysia which is in the LPI second quintile. These studies researched Malaysian 3PL for service quality (Soh et al. 2015), cost and service differentiation (Wong et al. 2015), and integration (Wong et al. 2016; Sinnandavar et al. 2018). Thirdly, this review provides discussions and recommendations with empirical based evidence to support pharma logistics and to assist in overcoming some problems encountered in logistics supply chain in conventional ocean container freight. These relate particularly to costs and quality, sustainability and SCI in Malaysia, a country which is ranked 32 in the LPI (World Bank 2016). It shows the conventional logistics capabilities of Malaysia and the 3PL practices and their impact on the companies and economy.

The organization of this article is as follows. The next section describes logistics development and issues based on professional pharma sea logistics publications. It is followed by the review of 4 Malaysian 3PL studies. Conclusion contains the applications of the research to support ocean going container logistics development and to resolve some pertinent issues in the latter.

2 Pharmaceutical Sea Freight

The pharmaceutical industry which traditionally uses air freight is turning to sea freight because of pressure to reduce prices, increasing generic competition and elusiveness of "blockbuster" drug for profit growth (Edwards 2017). For example, the movement of goods in Europe and US, Baxter International uses intermodal services (Pharma Logistics IQ 2018a). These transportation services are more energy-

efficient. The shipping containers are now moved from manufacturing facilities by truck, switched to rail or barge for longer distances and then shifted back to truck to complete the delivery. It partners with FedEx in the US to transport products with prescribed temperature requirements (Pharma Logistics IQ 2018a). These are practised despite ocean-freight challenges. Another case in point is AstraZeneca which has recorded success because of its quality focus. Its sea freight has yielded cost improvements, lower emissions and more accuracy to prevent temperature control lapses (Pharma Logistics IQ 2018b). Over the past five years, ocean transport has taken on much greater visibility in the pharma industry with Kato et al. (2014) calling it the sea shift. Cost competitiveness is one factor driving sea freight acceptance since it is up to 80% less expensive than air transport. In addition, although it takes much longer than air travel it is often more reliable, because there are far fewer product handoffs. The drawback of pharmaceutical air freight is it accounted for 80% of all reported temperature excursions compared with 1% for sea journeys (Shanley 2018). Cumulatively, lower costs, fewer opportunities for temperature excursions, and a smaller carbon footprint are making ocean transport more attractive for pharmaceuticals (Shanley 2018). Similarly, Eli Lilly which has been conducting studies of ocean transport of biologicals has found transporting products by sea saves 80% in costs, reduces carbon footprint, staffing requirement, packing, and storage needs, and reduces vibration and shock to materials during transport (Shanley 2018). A key driver behind the sea shift was the economic downturn, which prompted traders to find ways to cut their supply chain costs while maintaining their efficiency (World Bank 2016). For these reasons, more pharmaceutical shippers are looking to ocean freight as an alternative to the more expensive air freight (Pharma Logistics IQ 2018b) and increasing the deployment of 3PL services (Douglas 2018).

However, logistics supply chain has its vagaries especially for ocean shipping with the stringent cold-chain requirements of temperature-sensitive pharmaceuticals even as cold-chain technology evolves (Biopharma Cold Chain Sourcebook 2017; iContainers 2017; Pharma Logistics Summit 2017; Pharma Logistics IQ 2018b) to meet the increasing stringent regulations and quality control for pharmaceutical logistics (Edwards 2017; Douglas 2018). Generally, ocean freight takes time and coordination to efficiently move a shipment, and every delay can have negative consequences, notably if its cargo is perishable (Rodrigue and Notteboom 2017). Though temperature-sensitive pharmaceuticals are often transported in reefer containers with required temperature zones (Pharmaceuticals reefers cargo handbook 2018), just three per cent of reefers presented for shipment contain drug products (Pharma Logistics IQ 2018a). The International Institute of Refrigeration (IIR) states that 'heat-sensitive health products, kept at a controlled temperature (particularly between 2 and 8 °C) represent only 2% of the total volume of medicines with their value approaching 15% globally (Pharma Logistics IQ 2018a). Moreover, a large portion of the pharmaceutical products that move along the cold chain are in the experiment or developmental phase (Rodrigue and Notteboom 2017). In these development, many temperature-controlled shipments still follow traditional practice where some manufacturers continue to employ conventional logistics services (The Biopharma Cold Chain Sourcebook 2017). The 2017 edition of Pharmaceutical

Commerce's Annual Biopharma Cold Chain Sourcebook estimates non-cold-chain pharma logistics costs $66.5 billion rising at a 4–5% growth rate. By 2021, pharma non-cold chain logistics are estimated at $76.5 billion (Pharmaceutical Commerce 2017). On this premise of logistics value, this article dwells on conventional ocean-going non-cold and non-biological container freight which involves 3PL along the supply chain such as freight-forwarding companies, depots and hauliers. Pharma raw materials shipped using normal temperature include ascorbic acid, fluconazole, betamethasone dipropionate (M), diclofenac sodium and erythromycin estolate to name a few. This study focuses on logistics service quality and customers satisfaction; low costs, service differentiation and firms' competitiveness; integration and national logistics performance; and information system, supply chain integration (SCI), operational and environmental performance to highlight their relevance to pharma logistics development.

3 Review of Malaysian Third-Party Logistics Service Providers

The following sections contain reviews of 4 articles about Malaysian freight-forwarding and container haulage of third-party logistics providers. They provide descriptions and discussions of the research output especially the significance of their support and challenges that are encountered by ocean-going freight supply chain. They are divided into (1) Logistics Service Quality, (2) Paths to Sustainable Financial Performance, (3) Supply Chain Integration and National Logistics Performance, and (4) Supply Environment and Organizational Performance.

3.1 Logistics Service Quality

This section reviews two documents. They are: Chin (2014). *Third party logistics service quality and the moderating effect of switching costs between customer satisfaction and behavioural loyalty*. Thesis. Universiti Sains Malaysia, and Soh et al. (2015). A theoretical model to investigate customer loyalty on logistics service providers for sustainable business performance, *Int. J. Business Performance and Supply Chain Modelling*, 7(3), 212–232. They address logistics service quality, customer satisfaction and behavioural loyalty in the context of freight-forwarding companies and their customers.

This research was undertaken during the period between 2011 through 2014. Data collection was done between June through August 2013. Logistics service quality (LSQ) provides a competitive advantage since it could sustain businesses (Wong et al. 2015, 2016; Mentzer et al. 2001; Mentzer and William 2001; Morash et al. 1996; Bowersox et al. 1995). Porter (1980) noted that customers come with different

demands making them relatively costly to meet. Even so, Malaysian freight forwarders could fulfil the myriad customer demands across its industries. This tension between quality and costs is resolved by the theory of cumulative capabilities by Ferdows and De Meyer (1990) which suggest cost focus comes after the achievement of product and service quality. This is attested to when AstraZeneca saw success due to its emphasis on quality for its sea freight. Sea freight has rewarded them with cost improvements, lower emissions and greater accuracy to prevent temperature deviations as mentioned earlier (Pharma Logistics IQ (2018b). This shows quality dimensions are pre-eminently important before yielding profits.

The development of LSQ followed the work of Bienstock et al. (1997) who developed and refined physical distribution service quality (PDSQ). Several literature (Kyj and Kyj 1994; Bowersox et al. 1995; Morash et al. 1996; Mentzer and William 2001; Mentzer et al. 2001; Wong et al. 2015, 2016) suggest logistics excellence could create competitive advantage for logistics service providers. Other researchers (Kahn and Mentzer 1996; Murphy and Poist 1996; Mentzer et al. 2001) suggest logisticians and marketing should work together to create a competitive advantage to customers through logistics excellence. With excellent quality of logistics service performances, companies could create customer satisfaction (Mentzer et al. 1989; Bienstock et al. 1997; Mentzer et al. 2001; Soh et al. 2015).

Chin (2014) shows the effectiveness and validity of functional quality (personnel contact quality, ordering procedures, order discrepancy handling and information quality) and technical quality (order release quantities, order accuracy, order condition, order quality and timeliness) in third-party logistics. This research had freight-forwarders as respondents across 10 industries (chemical, wood-based, metals, paper, printing and publishing, rubber products, food and beverage, transport equipment, machinery and equipment, textiles and apparel, and electrical and electronics) and data collected was tested on the conceptual framework Fig. 1.

Data analysis showed the nine first level constructs are valid and their internal consistency reliability ranging from 0.896 to 0.968 which are well beyond the threshold value of 0.70 (Hair et al. 2011). The mean values of the construct were personnel contact quality 5.168 out of a Likert scale of 7 with 1 as "strongly disagree" to 7 "strongly agree". Ordering procedures 4.931, order discrepancy handling 4.290,

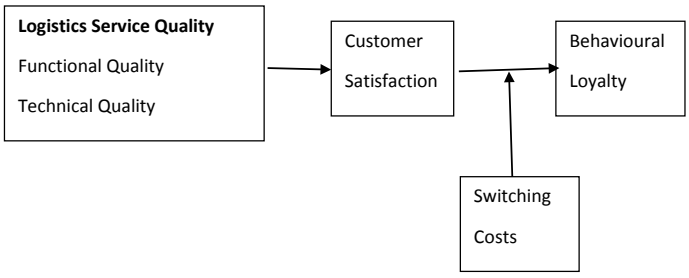

Fig. 1 The conceptual framework. Adapted from Chin (2014)

information quality 4.874, order release quantities 4.290, order accuracy 3.920, order condition 4.529, order quality 5.043 and timeliness 5.166 (Chin 2014). Further analysis showed statistically significant results from functional and technical quality mediated by customer satisfaction to customer loyalty. The results are tabulated in Tables 1 and 2.

Data analysis in Soh et al. (2015) also showed the R^2 of 0.479 suggesting 47.9% of the variance in customer satisfaction could be described by the functional logistics service quality (FTQ) and technical logistics service quality (TNQ). Since the R^2 value of satisfaction (SAT) is 0.479, the explanatory power of the variables is substantial (Cohen 1988). The second order technical logistics service quality also has a positive relationship with customer satisfaction ($\beta = 0.238$; $p < 0.01$) and the functional logistics service quality has a positive relationship with customer satisfaction ($\beta = 0.514$; $p < 0.01$). The R^2 of the variance of customer loyalty is 0.662 and explained by customer satisfaction. The $R^2 = 0.662$ is also considered substantial. There is a positive relationship between customer satisfaction and customer loyalty ($\beta = 0.774$; $p < 0.01$).

Based on these results, the nine LSQ dimensions of freight-forwarders were above average. The second order factor of technical logistics service quality and functional logistics service quality provided customer satisfaction which were translated into customer loyalty. These are indicative of a supportive third-party logistics in freight-forwarding. In the context of container shipping and last mile delivery, the pharma

Table 1 Hypotheses result of Chin's (2014)—relationships between service quality, customer satisfaction and customer loyalty

Relationship	Path coefficient	Decision
Technical logistics service quality → customer satisfaction	0.238	Supported**
Functional logistics service quality → customer satisfaction	0.514	Supported**
Customer satisfaction → customer loyalty	0.774	Supported**
Functional logistics service quality → customer satisfaction → customer loyalty	0.467	Supported**
Technical logistics service quality → customer satisfaction → customer loyalty	0.212	Supported**

**$p < 0.01$
Source Chin (2014)

Table 2 Hypotheses testing—high order or second order factor—depicting the relationship between service quality and satisfaction

Relationship	Path coefficient	*t*-value	Decision
FTQ → SAT	0.514	4.735**	Supported**
TNQ → SAT	0.238	2.256*	Supported**

Note **$p < 0.01$ ($t > 2.33$), *$p < 0.05$ ($t > 1.645$)
Source Chin (2014)

non-cold chain industry could safely rely on the freight-forwarders to provide above average logistics service quality (Chin 2014) for customer satisfaction. Additionally, the research also showed behavioural loyalty was derived directly from logistics service quality. A very important research evidence proved customer loyalty was non-spurious when the switching costs failed to negatively moderate the relationship between customer satisfaction and behavioural loyalty (Chin 2014). Therefore, pharma non-cold chain could safely rely on the logistics service quality of freight-forwarders in Malaysia especially on inland transport. The customers' non-spurious loyalty proved their freight-forwarders' LSQ could generate true satisfaction. The quality of Malaysian 3PL logistics services is therefore reliable.

In order to fulfil customer logistics service requirements, one important factor could be the relaying of accurate and timely information to LSP(s) and the latter's logistics capabilities. Accurate and timely information relay is mutually important to LSP and customers which is fundamental to supply chain integration effectiveness. Information sharing must be in place to support logistics transactions. While information sharing suffers from leakages, the empirical evidence renders support it is shared via human commitment to both technical and functional service quality, and efficient use of reliable communication technologies and transport.

3.2 Paths to Sustainable Financial Performance

This section reviews two documents, namely, Chong (2014). *3PL financial performance in Malaysia—internal and external drivers*. Thesis. Universiti Sains Malaysia, and Wong et al. (2015). Differentiated service consumption and low cost production: Striking a balance for a sustainable competitive advantage. *International Journal of Production Economics* in the context of freight-forwarding companies. They contain environmental forces, strategic emphases, operational performance and financial performance.

This research was undertaken during the period between 2011 and 2014 in a time of global economic uncertainties, and data was collected in June through August 2012. It set out to determine if the Market-based View (MBV) or the Resource-based View (RBV) would impact strategic choices of low cost and differentiation and how these would impact cost performance and service performance and if these two performances would affect financial performance. For differentiation, innovation is the engine that improves efficiency, reduces costs and generates competitive advantage (DSV Market Monitor 2017). The lowering of costs and the focus on core competencies are reasons for logistics outsourcing. The former would motivate pharmaceutical companies solicit LSPs such as freight forwarders which have a continuous focus on cost improvements. The risk of complacency without innovation would cause LSPs service offerings become commodities rendering outsourcing to them a non-competitive advantage. Therefore, LSP(s) must maintain long-term profitable relationships with lower costs and differentiation as competitive drivers. The research framework is depicted in Fig. 2.

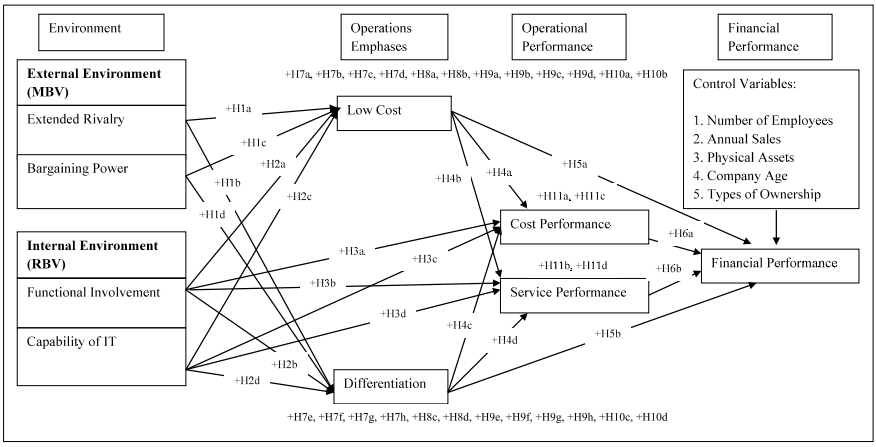

Fig. 2 The conceptual framework. *Source* Chong (2014)

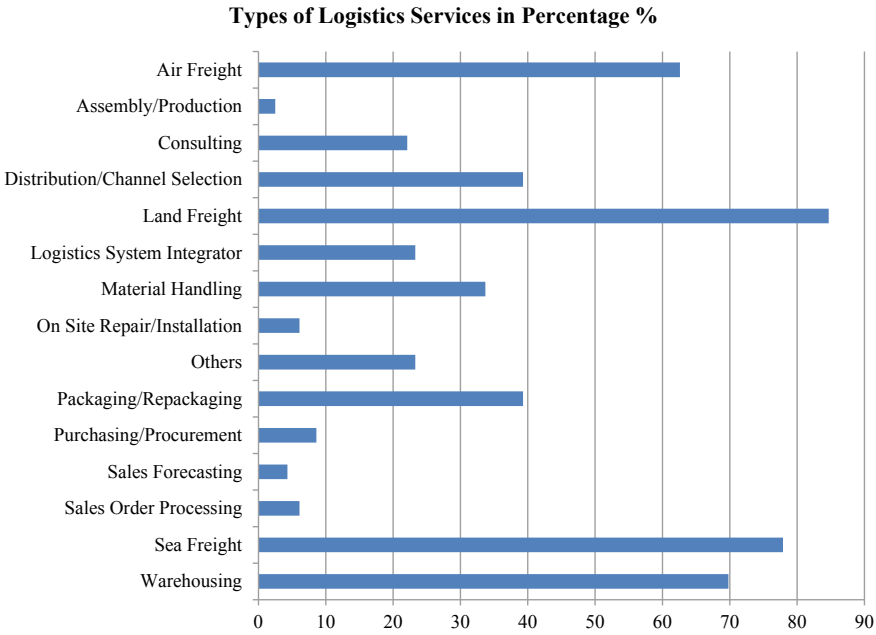

Fig. 3 Logistics services of 3PL companies. *Source* Chong (2014)

Questionnaire survey was used to collect data. The sampling frame was the freight forwarders from members of the Federation of Malaysian Freight Forwarders (FMFF) (Wong et al. 2015). Altogether 164 respondents participated. Figure 3 shows the breakdown of the composition of the respondents, and it shows 80% of the sea freight forwarders in Malaysia participated in the survey (Chong 2014).

Data analysis showed all constructs carry means of above average values on a Likert scale of 7. Functional involvement has a mean of 4.4545, capability of IT 3.6117, extended rivalry 5.2212, bargaining power 5.0248, cost emphases 5.6989, service emphasis 5.9798, cost performance 5.2782, service performance 5.6307 and financial performance 4.8826 (Chong 2014). Data was purified for convergent and discriminant validity. All AVEs of the latent construct were in the range of 0.558 to 0.738 which exceeded the good rule of thumb of 0.5 meaning 50% or more variance of the indicators should be accounted for suggesting adequate convergence (Henseler et al. 2009; Chin 2010; Hair et al. 2010). The reliability scores for all constructs were also satisfactory as well with values above 0.70 meeting the recommended value by Hair et al. (2010). Data analysis also showed evidence of discriminant validity at the indicator level, as each item loaded or correlated more highly on their construct than on other constructs (Wong et al. 2015). Hypothesis testing results are tabulated in Table 3 Summary of Research Findings.

Though not all hypotheses are significant, the results offer important commercial conclusions. The results provided several pathways for companies patronising either MBV or RBV to attain financial performance. The authors noted that sustainable financial performance provides continuity of business which is sustainable cash flow to say the least. This could only be derived from the cost and service performance testifying to the 3PL(s) competitiveness. Altogether there were 10 pathways with 6 pathways attributed to MBV and 4 pathways to RBV. These results also mean freight forwarding companies were agile and could easily navigate their way in times of apparent economic uncertainties using cost and differentiation strategies. Two internal resources, cross-functional involvement and IT capability could also help freight forwarders weather economic storms. This strategic agility reflected the Malaysian freight forwarders' robustness.

The services of pharma supply chain freight forwarders are required frequently since medical supplies are needed continually and sometimes urgently. In times of economic uncertainties, hospitals and clinics are assured their pharma supplies will not be disrupted logistically. This is because the research model proved the robustness of the freight forwarders could still support delivery in economic uncertainties. This is consistent with the findings in Chin (2014) and Soh et al. (2015). Such 3PL robustness and agility would prevent any shortages of medical supplies which otherwise could compromise patients' well-being or putting their lives in jeopardy. In addition, with a robust supply chain, pharma companies need not stock up unnecessarily thereby lowering inventory holding costs. Hence, warehousing costs could be reduced. Pilferage losses and expired supplies could also be avoided. Therefore, medicines and medical device importers and exporters could rely on the third-party logistics providers in Malaysia to meet their demand. All these could only be achieved with proper SCI. Information flow and material flow must co-exist to ensure customer satisfaction and financial performance. Information must be obtained and coordinated from within (RBV) and external to the company (MBV). Two important external information sources are customers and suppliers. Both these stakeholders provide information such as value and quantity of goods (raw, semi- and finished goods) transported. The identity of recipients of these goods reveals important information of their produc-

Table 3 Summary of research findings

Hypothesis		Beta	Std error	*t*-value	Decision
H1a	Extended rivalry → low cost	0.258**	0.072	3.582	Supported
H1b	Extended rivalry → differentiation	0.223**	0.088	2.529	Supported
H1c	Bargaining power → low cost	−0.092	0.068	1.347	Not supported
H1d	Bargaining power → differentiation	0.222**	0.051	4.331	Supported
H2a	Functional involvement → low cost	0.617**	0.082	7.490	Supported
H2b	Functional involvement → differentiation	0.175	0.110	1.588	Not supported
H2c	Capability of IT → low cost	−0.272	0.093	2.928	Not supported
H2d	Capability of IT → differentiation	0.168	0.116	1.448	Not supported
H3a	Functional involvement → cost performance	0.046	0.081	0.566	Not supported
H3b	Functional involvement → service performance	−0.178	0.113	1.570	Not supported
H3c	Capability of IT → cost performance	0.283**	0.073	3.893	Supported
H3d	Capability of IT → service performance	0.587**	0.101	5.806	Supported
H4a	Low cost → cost performance	0.295**	0.057	5.182	Supported

Note $^{**}p < 0.01$, $p < 0.05$
Source Chong (2014)

tion planning, capabilities and capacity. Noting this importance, information leakages should be prevented because freight-forwarders have the fiduciary responsibilities to not share or reveal proprietary and commercially valuable information they have come to possess from supply chain partners.

3.3 Supply Chain Integration and National Logistics Performance

This section reviews Wong et al. (2016). Could the service consumption-production interface lift national logistics performance? *Resources, Conservation Recycling*. 128: 222–239. It consists of integration factors, depot service quality, haulier firms'

sustainable performance and national logistics performance in the context of container depots and hauliers.

This research was undertaken between 2013 and 2016, and data collection was made in September through November 2015. It aimed to resolve the queuing at the depot-haulier interface. The research attempted to answer two questions. First, what integration factors could influence depot service quality? Second, could depot service quality affect haulier firms' sustainable performance and together lift the national logistics performance? At centre stage is the conceptual framework in Fig. 4. This is dominated by two theories—the stakeholders theory and the agency theory.

The questionnaire survey consisted of 13 Integration Factors questionnaire items having a mean of only 3.3 out of a 7 point Likert scale with 1 as "strongly disagree" to 7 "strongly agree". This hovered below the average of 4 indicating poor integration, a situation which is much undesired in international supply chain competitiveness. The means of the depot service quality questionnaire items were personnel contact quality 3.5, order discrepancy handling 3.5, information quality 3.6, order release quantities 3.1, order accuracy 4.2, order condition 3.8, order quality 4.3, timeliness 2.7 (Wong et al. 2016). Obviously, timeliness which was the issue at hand (Wong et al. 2016) had the lowest score. Order quality has the highest score. Overall, depot service quality could be improved. The means for hauliers firms' sustainable performance was 4.9 which is at the higher end of the average (Wong et al. 2016).

Data purification was carried out using a series of tests. Loadings of all items were greater than 0.5. Convergent validity, factor loadings, composite reliability (CR) and average variance extracted (AVE) were also determined (Wong et al. 2016). Convergent validity showed all item loadings exceeded the recommended value of 0.5 (Hair et al. 2010). Composite reliability was in the range of 0.856 and 0.969 and exceeded the recommended value of 0.7 (Hair et al. 2010). AVE measures were greater than 0.5. They ranged between 0.641 and 0.891. No multicollinearity issues were encountered as all the VIF values were below the minimum threshold level of 5 (Hair et al. 2011).

The hypothesis testing bore the following results in Table 4 while Table 5 summarizes results of mediation analysis.

The statistical results allow the conclusions of the following:

1. That integration factors could influence national logistics performance only via the consecutive mediation of depot service quality and haulier firms' sustainable performance. Consequently, integration factors (between depot and hauliers)

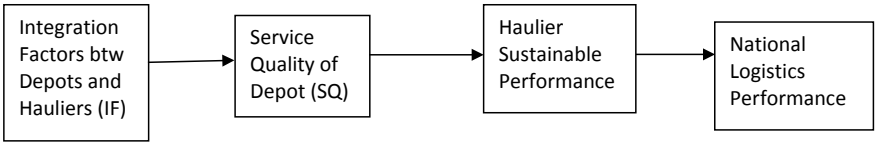

Fig. 4 Conceptual framework. Adapted from Wong et al. (2016)

Table 4 Results of hypotheses tests

Path	β	T statistics (|O/STDEV|)	*P* values	Hypothesis
Hauliers sustainable performance to national logistics performance	0.337	1.713	0.087	Accepted
IF to hauliers sustainable performance	0.437	3.270	0.001	Accepted
IF to national logistics performance	−0.037	0.170	0.863	Rejected
IF to SQ	0.502	4.538	0.001	Accepted
SQ to hauliers sustainable performance	0.429	3.599	0.001	Accepted
SQ to national logistics performance	0.131	0.681	0.496	Rejected

Adapted from Wong et al. (2016)

Table 5 Results of mediation hypotheses

Path	β	T Statistics (|O/STDEV|)	*P* values	
IF to hauliers sustainable performance	0.651	8.397	0.000	Accepted
IF to national logistics performance	0.291	1.791	0.07	Accepted
SQ to national logistics performance	0.334	3.094	0.002	Accepted

Adapted from Wong et al. (2016)

should reduce unnecessary container transaction delays at depot-hauliers interface. This would reduce cycle time, idling emission, and fuel wastage.

2. That integration is achievable with close coordination of depot-hauliers, efficient loading and offloading of empty containers, excellent yard facilities in the depot, shared performance data, shared schedule, shared demand forecast, and shared container inventory/container availability status. These would forestall logistics supply chain problems.
3. That depot service quality could contribute to national logistics performance via haulier firms' sustainable performance.
4. That haulier firms' sustainable performance could contribute to national logistics performance.
5. That the ripple effect of supply chain actions and actors were effected via the logistics supply chain.

Noting the above, it augurs well for the pharma ocean freight which is dependent upon the containers to take note of the service quality on inland transportation. The interface of depot-hauliers should be attended to for two reasons. One, the perceived lower service quality of the depot could affect container transaction cycle time, and

the less than satisfactory haulier firms' sustainable performance could have rippled time delay downstream and adversely affect especially the economic, environmental and social aspects along the logistics supply chain (Wong et al. 2016). In response, the pharma manufacturers and transport providers could exert pressure on the principals of the depots and the shipping lines to improve depot service quality. This could be effected because pharma logistics value was on the increase and shipping lines would necessarily pay heed to such concerns because of pharma sea shift growth (World Bank 2016; Stanton 2015; Kato et al. 2014) and the competitiveness of the ocean freight industry (Jacques 2017).

Apart from the encouraging findings in the logistics supply chain, pharma manufacturers and third-party logistics providers should have the confidence in Malaysia's trade facilitation in logistics as it ranks 32 out of 160 in the Logistics Performance Index (World Bank 2016). Malaysia is among the 5 Southeast Asian countries whose rankings are within the top 2 quintiles of the Logistics Performance Index (World Bank 2016).

The poor logistics service quality at depot-hauliers interface should be seriously further studied for supply chain integration especially for information sharing. The information to the hauliers to pick up or return empty containers should be accurate to avoid unnecessary waiting in the long queue. Any explanation for the lack of information sharing because of the fear of information leakage cannot be sustained because the depot-haulier business transactions are only operational and non-financial. They transact empty containers. There are no financial transactions between the depot-hauliers because the hauliers are agents acting on behalf of their principals, the manufacturers.

3.4 Supply Environment and Organizational Performance

This section reviews Sinnandavar et al. (2018). Dynamics of supply environment and information system: integration, green economy and performance. *Transportation Research Part D: Transport and Environment*, 62: 536–550 in the context of the container depots and hauliers.

The research was undertaken between 2013 and 2017. Data collection was done in January through March 2017. Usable responses numbered 110 from a total of 119 received. This research involved supply environment, supply chain integration and organizational performance with information system as the moderator. It answered three research questions. They were (1) Does the supply environment of the depots affect SCI between depots and hauliers? (2) Does SCI between hauliers and depots affect the haulier's organizational performance? and (3) Does information system interface between transacting organizations moderate the effect of supply environment on SCI? (Sinnandavar et al. 2018). The answers to these questions would suggest the value and importance of supply environment, supply chain integration and information system in achieving organizational performance of haulier companies.

Haulier companies are omnipresent actors along the inland-port oriented container haulage and the delivery supply chain. Haulage companies are the respondents in this research. With pharma sea freight on the increase (World Bank 2016; Stanton 2015; Kato et al. 2014), container haulage would become increasingly important bringing into focus their sustainability performance—time, cost, vehicular emissions reduction, and social commitment—because of the environmental commitment by signatories to the 1997 Kyoto Protocol.

The research is staged using the following theoretical framework, Fig. 5.

Data collected was purified before hypothesis testing. As the results (Table 6 CR, AVE and loadings for measurement model and Table 7 HTMT for measurement model) indicate, the CR and AVE are above the threshold of 0.70 and 0.50 respectively making the measurement model reliable. The HTMT results show the ratios of below 0.85 level which is deemed to be the strictest level to assess discriminant validity (Henseler et al. 2015). The results confirmed the indicators represent distinct constructs. Convergent validity of the measurement model is strong evidenced by the loadings of indicators to the principle construct of more than 0.50 and weaker cross loadings of indicators to other non-principle constructs. Altogether 8 indicators were eliminated during the assessment for construct reliability and construct validity in achieving the required threshold.

Hypothesis testing yielded the results in Table 8.

Noting the above results, pharma sea freight logistics management could expect a conducive supply environment to promote supply chain integration (SCI) since at least 2 of the 4 first-order factors which are the availability of alternatives (AOA) and supply complexity (SC) could influence SCI positively. Ocean liners should provide alternative accessibility to containers to reduce the adverse effects of oligopolistic practices and to increase speed in container transactions and lowering costs to benefit pharma logistics. Interestingly, supply complexity could yield a better SCI despite the oligopolistic industry. It is consistent with the above average freight forwarders logistics service quality in Chin (2014) which satisfies customers. It suggests customers satisfaction was met through the international shipping supply chain though it was complex. Further, the freight forwarders seemed to have handled these complexities well enough to foster SCI. The hypothesis results showed SCI efforts would result in improved operational performance. Therefore, SCI efforts should be stepped up to improve operational performance. This is an unenviable task because supply chain

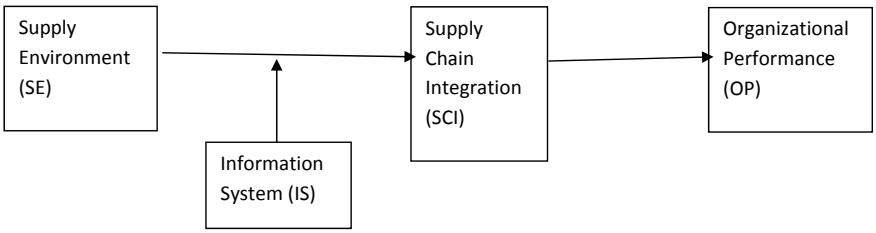

Fig. 5 Theoretical framework. Adapted from Sinnandavar et al. (2018)

Table 6 CR, AVE and loadings for measurement model

Constructs	Factor loadings	Composite reliability (CR)	Average variance extracted (AVE)
IS—Data Consistency (DC)	0.909	0.909	0.833
IS—Cross Functional Application Integration (CFAI)	0.971	0.971	0.944
SE—Supply Dynamism (SD)	0.896	0.964	0.842
SE—Availability of Alternatives (AOA)	0.917	0.915	0.844
SE—Supply Importance (SI)	0.887	0.955	0.840
SE—Supply Complexity (SC)	0.683	0.824	0.707
SCI—Information Integration (II)	0.899	0.942	0.804
SCI—Operational Integration (OI)	0.858	0.935	0.743
OP—Operational Efficiency (OE)	0.680	0.855	0.598
OP—Environmental Performance (EP)	0.927	0.967	0.854

Adapted from Sinnandavar et al. (2018)

Table 7 HTMT for measurement model

Construct	AOA	CFAI	DC	EP	II	OE	OI	SC	SD	SI
AOA										
CFAI	0.442									
DC	0.466	0.831								
EP	0.334	0.329	0.350							
II	0.646	0.683	0.625	0.475						
OE	0.590	0.342	0.368	0.693	0.583					
OI	0.683	0.582	0.570	0.498	0.849	0.757				
SC	0.595	0.247	0.258	0.284	0.486	0.382	0.510			
SD	0.730	0.453	0.396	0.512	0.584	0.534	0.597	0.650		
SI	0.231	0.088	0.176	0.046	0.090	0.098	0.087	0.215	0.057	

Source Sinnandavar et al. (2018)

Table 8 Numerical presentation of the structural model

Relationship	Path coefficient	*R* square	*t*-value	Decision
SD → SCI	0.119		1.051	Not supported
SC → SCI	0.257*		3.131	Supported
AOA → SCI	−0.238*		2.204	Supported
SI → SCI	−0.053		0.987	Not supported
SCI → OP	0.620*		10.329	Supported
SCI		0.612		
OP		0.382		

*Two tailed test type at significance level of 0.05 ($t > 1.960$)
Source Sinnandavar et al. (2018)

actors usually fall short of collaboration for various reasons. One such reason is the fear of information leakage to third party actors. Even direct recipients of information could use trade information to their unfair and unethical advantage. Noting leakages compromise the competitiveness of a company, the SCI is a minefield to supply chain actors. Therefore, studies on SCI-Information Sharing-Leakage are recommended.

4 Conclusion

The across-the-board development in pharma container shipping represents the ushering in of sea shift for both cold- and non-cold chain pharmaceutical logistics. In total, this sees a greater number of manufacturers shipping pharmaceutical products by ocean container freighters. Factors which encouraged the sea shift are cost competitiveness, the introduction of generics which takes away the profits of blockbuster drugs which are nearing their patent protection period. Ocean pharma container freight also enjoys quality and integrity required of pharma goods through less handling and less temperature excursions outside the strict temperature range. In addition, the reduction of emissions by sea vessels serves to protect the environment. The pharma ocean cold-chain technology is developing and intensifying while a large part of pharma sea freight is still non-cold chain using conventional container facilities.

The above pharma logistics concerns are assuaged by the capabilities of conventional non-cold chain container logistics evidenced in the preceding 4 journal articles. The articles support LSQ which includes proper handling (Chin 2014; Wong et al. 2016) which are important in pharma transport. Cost reduction could be derived from the strategic paths of MBV and RBV through both low costs and differentiation to achieve cost performance and service performance for sustainable financial competitiveness (Wong et al. 2016). The Malaysian LSP(s) could ensure the availability of pharmaceuticals as they are both agile and therefore robust even in varying economic

conditions. Though ocean going freight experiences longer sea journey, it benefits from the economy of weight and distance (Bowersox 2013). The perennial depot-haulier transaction delays could be mitigated by a more effective SCI (Wong et al 2016; Sinnandavar et al. Sinnandavar et al. 2018) since SCI is statistically significantly affecting company performance. Both the economy of weight and distance, and the effectiveness of SCI would lead to lower emissions to support the increasing consciousness of a cleaner environment by major global logistics companies and signatories to the Kyoto Protocol. This means the Malaysian third-party logistics service providers could mitigate the concerns of pharma sea freight cited in professional online publications.

Future research should be widened to include other actors along the pharma supply chain such as manufacturers, ocean liners, port authorities, customs, operators and retailers. The last mile delivery performances should also be given deeper consideration as well. The study could be extended to include the pharma cold-chain transport and facilities and their current performances. The SCI-Information Sharing-Leakage is another area to prioritise.

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The Needs and Barriers Within the Supply Chain Actors—Hospital Pharmacy Needs

Aida Batista, João Luís de Miranda and Ana Paula Teixeira

Abstract In this chapter, the roles and daily practice of a Hospital Pharmacist are revisited, as well as the needs related with medicines shortages are addressed. The outcomes and the prevalence of shortages are also discussed, in a way to better contribute for enhancing the European pharmacy practice. Medicine shortages may result from single or multiple causes, from problems at the production level, to issues on the supply chains that prevent medicines from reaching points of care. Regardless the causes, shortages potentially increase costs for health systems, including higher prices of substitute medicines, costs related to treatment of adverse reactions, medication errors, and also the consequences of delayed therapy. But there are also the invisible costs for healthcare system that include time spent on solving the shortages, changes in management procedures, communication and the additional risks to patients caused by shortages. The conclusions point for in-depth collaboration with the health professionals, the pharmaceutical supply chain stakeholders, and the effective usage of databases on medicine shortages.

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1 Introduction

Medicines are not simple items of commerce, they are an essential component of patient care and in the hospital sector they must be administered to the patient in a timely manner. This is particularly the case for patients taking medicines which have a significant clinical consequence when doses are missed, such as anti-psychotics, anti-epileptics, immunosuppressive and anti-cancer drugs. Thus, a medicine shortage is an unwelcome event in any hospital pharmacy, added by the fact that pharmacists often learn about the shortage at the moment they fail to receive an ordered product from the wholesaler or manufacturer, due to lack of information.

The unpredictability of shortages and lack of information provided to healthcare professionals make it quite difficult to plan effective strategies to provide medication to patients. The communication challenges posed by medicines shortages imply that pharmacists must give the right information to prescribers, nurses, patients and others, but they also have to receive the right information to pass on. For example, why the shortage is in occurrence, how long it may last, and what alternatives are available.

The problems caused by medicines shortages are serious, threaten patient care in hospitals and require urgent action. Managing medicines shortages and ensuring continuity of supply can also cause the diversion of significant amounts of the time and attention of a hospital pharmacist from other tasks important in the provision of high quality, safe and efficacious care.

The European Association of Hospital Pharmacists (EAHP) also considers that due to the scale of the problem, its cross-border nature, its impacts on patient care and its relationship to European Union law, a European investigation of the problem involving the European Commission, European Medicines Agency (EMA), and European Heads of Medicines Agencies (HMA), is required.

In this chapter the following topics are addressed: in Sect. 2, the roles of hospital pharmacists and the daily life in the pharmacy; in Sect. 3, the outcomes of shortages: in Sect. 4, the prevalence and nature of the problem in European pharmacy practice; finally, in Sect. 5, the related conclusions will be presented.

2 Hospital Pharmacists: Their Role and Daily Life

The main role of hospital pharmacists is briefly remembered, as well as their typical daily life is re-visited. Hospital pharmacists provide and recommend safe and effective treatments for the benefit of patients; they safeguard the seven patient rights in relation to medication ((i) right patient; (ii) right medicine; (iii) right dose; (iv) right route; (v) right time; (vi) right information; and (vii) right documentation); and they increasingly take on clinical roles in reviewing patients' medication, and giving direct education to patients about their medicine (e.g., reconciliation, therapeutic drug monitoring), in conformity with the European Statements of Hospital Pharmacist (2014) of the EAHP.

All services provided by the hospital pharmacy are structured, organized and planned according to the needs of the inpatients and outpatients. It is imperative to have established procedures and schedules for the implementation of each task that contributes to the implementation of the drug distribution processes that allow patients to have access to the seven rights and the best quality of health care.

Although each hospital pharmacy has its specific schedules, one can have as an example, a service in which from 8 a.m. to 5 p.m. the tasks are distributed as follows:

- 08:00 a.m., team meeting, where the briefing is presented and the day is prepared; after that, at
- 09:00 a.m., the priority patients are identified, e.g., discharge and urgent supply; then, at
- 10:00 a.m., the newly prescribed medicines are responded to; at
- 10:30 a.m., the medicines of new patients are reconciled; at
- 11:00 a.m., the medication needs of long term patients are reviewed; at
- 01:00 p.m., there is a lunch time training; at
- 02:00 p.m., the dispensing process is facilitated, liaising with wards; at
- 03:00 p.m., the medicines stock in the hospital is reviewed; at
- 04:00 p.m., the medication for discharge is provided; and, finally, at
- 05:00 p.m., the handover to on call pharmacist is carried out.

However, when a medicine shortage happens, all goes out of control and the patients' rights risk being compromised. In fact, based on daily practice and in the evidence already published, we can indicate that medicines shortages are a major disruptive force to fulfilling the professional roles of hospital pharmacists and serving the patient.

3 Outcomes of Medicines Shortages

The medicines shortages occurrence is distracting pharmacists from core activities, causing extra burdens on health system staff and resource, increasing stress and workload in the pharmacy environment, and the substitution of medicines can confuse doctors, nurses, and patients. These issues related with the shortages outcomes are better described in the following lines.

Medicines shortages are a critical problem for pharmacists fulfilling their role, and to effectively use the available time. Indeed there are consequences of the health staff distraction from core activities and time spent, since patient services have to be curtailed, or even not provided. While improvement initiatives are frustrated, quality of services may suffer due to reduced available time, and individual one-to-one time with patients is being reduced.

The increased stress and burden have consequences too, namely: increased stress is linked with heightened risk of medication error, being widely recognized this issue; errors arise when actions are intended but not performed; in fact, the ramping "stress-time" can increase this likelihood; safety critical tasks, like dose calculation

or pondering drug-drug interaction, require an environment of concentration; and staff welfare, retention, and job satisfaction also are important issues for hospital pharmacists.

Concerning the consequences of medicines substitution, some pertinent issues are related with the unfamiliarity and confusion for doctors and nurses. This can also heighten the risk of medication error, while there is confusion for patients too, especially those on regular medication. In addition, potential risks on higher costs to health system from using more expensive alternatives can be realized, time delays occur in patients waiting for their medication, as well as it increases the time taken in relation to communication and other associated procedures.

All the above leads to the conclusion that a medicine shortage is an unwelcome event in the hospital pharmacy, added by the fact the workload related to drug shortages in general is underestimated, because other health care professionals such as doctors and nurses are also charged with the management of shortages. In this way, a collaborative work to mitigate the negative effects of medicines shortages is required.

All of this highlights the importance of the communication on medicine shortages. All the health staff, including patients, doctors, nurses and pharmacists, they want the answer to the same questions (Fig. 1):

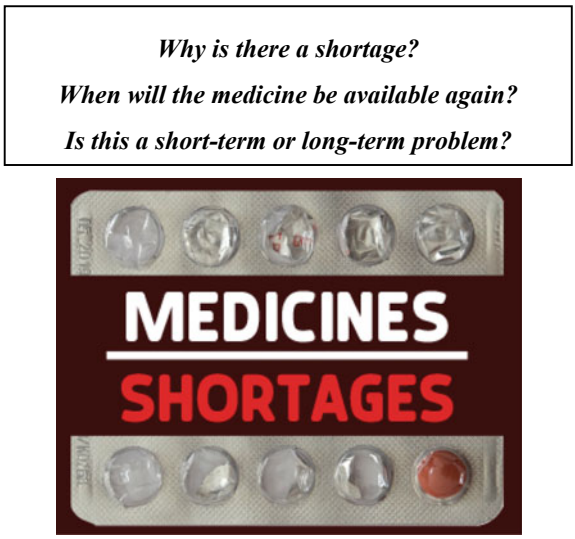

Fig. 1 Medicines shortages and some questions to be answered. Adapted from Batista (2017)

Unfortunately, too often, the answer is not available. The issue is leading to difficulties in planning, and to uncertainty either for patients, doctors, nurses or pharmacists. Beyond the potential stock-piling, also the integrity and credibility of both the medicines supply chain and the health system are being questioned. So, it must be asked too:

***Where is the information*?**

In this way, we are able to identify the communication on medicines shortages as a major challenge, which will be important both to deal and to overcome.

4 Prevalence and Nature of the Shortages Problem in European Pharmacy Practice

In this section, the prevalence of the shortages problem in hospital pharmacy, as well as the problem nature, and relevant examples are presented. In 2014, the EAHP carried out a survey about the prevalence of medicine shortages in hospital pharmacies, with over than 600 individual responses from 38 countries. The main results are summarized in below:

- **86%** of the respondents reported that medicines shortages are a current problem in the hospital they work in;
- **66%** of the respondents indicated that medicines shortages affect their hospital pharmacy on a daily or weekly basis;
- **75.4%** of the hospital pharmacists either agreed or strongly agreed with the statement "medicines shortages in my hospital are having a negative impact on patient care."; and
- **63%** of the hospital pharmacists estimated that the typical medicines shortage normally lasts for a number of weeks.

This description does not correspond to a good scenario, and measures to deal with shortages and the most critical medicines must be pondered. Usually, antimicrobial agents, oncology products, emergency medicines, cardiovascular medicines, and anesthetic agents are the most affected by medicine shortages.

In a way to better describe the shortages landscape, some examples of international shortages and related consequences follow too:

- An antibiotic led to the change of the protocols to fight infections; however that is very difficult, especially when it happens frequently. In fact, when the shortage problem with a certain antibiotic continued for a long period, the hospital had to change all the protocols, with all the administrative and logistics implications and time consumption. The hospital pharmacy also has some mechanisms to solve shortages; for instance, to substitute a certain medicine by another one. The hospital pharmacists have some flexibility in Portugal, because they do not work with drugs

of a certain brand, but with the International Nonproprietary Name (INN); so, if the drug of a certain brand is missing, they can go and seek for another drug brand with the same INN, without additional administrative requirements.

- Reported impacts for patients usually include delayed or interrupted chemotherapy treatment; the shortage has direct impact in their quality of life, since it can imply unnecessary experience by patients of side effects, that can last for long periods.
- In a hospital facing medicines shortages, the drug and therapeutic committee must face the problem; whenever a problem appears, the health professionals report it to the committee that tries to find a solution to the problem. Hospitals also deal with pharmacy shortages by lending medicines among them; that is, the network that includes all the public Portuguese hospitals is inter-connected and when one of them has a medicine shortage, it asks for the medicine to the other Portuguese hospitals. Unfortunately, when an international shortage occurs, the problem cannot be solved this way.
- The number of different medicines in the hospital pharmacy is usually high. For example, the Hospital of *Vila Nova de Gaia*, Porto, Portugal, is a medium size hospital, with 600 beds. It has many ambulatory patients, being the hospital responsible to provide medicines to patients with chronic diseases, like HIV. The hospital has a portfolio of 3000 patients that are attended concerning the chronic diseases and, considering all the described attributes, the number of INN generic names is about 2000; when considering the different brands, the number rises up into the range 3500–4000.
- There are many theoretical models for stocks replenishment, they consider either approaches based on periodic reviews or medicines levels. It must be noticed that all the hospital pharmacies in Portugal are computerized, and the all set of indications is pondered, namely, the stock levels, the consumption rates, and the lead-times that suppliers take to provide the medicines onto the hospital pharmacy. The average value for the medicines inventory is usually very important, for example, in the *Hospital Universitário Santa Maria*, Lisboa, Portugal, the trend of the last few years is to be reducing the stock level but the total yearly cost of medicines still is above 150 millions of Euros.

5 Conclusions

Based on the hospital pharmacy daily practice and in all the outcomes described, it can be stated that medicines shortages is a major disruptive force both to fully serving the patient and the professional roles of European hospital pharmacists. Namely, by distracting hospital pharmacists from their core activities, the misused time, the increasing stress, the ramping burden, and the medicines substitution; in fact, the all set of issues that are described in this chapter have heavy consequences.

The urgency of the shortages problem must be understood and the totality of causation needs investigation and response. In order to obtain information on the

problem and to advance solutions, the partners in the medication use process must work together.

Additionally, the '*responsibility gap*' between supply chain partners, government and regulators needs to be addressed, while solutions and best practice from elsewhere must be noted and adopted when practical.

All the above leads to the conclusion that medicine shortages are events to be avoided or mitigated in the hospital pharmacy, Databases on medicine shortages at national level will help the hospital pharmacy practice in all the European area, as well as collaborative work with prescribers, medical doctors, nurses, and patients will contribute for the mitigation of medicines shortages negative effects.

For all the reported here, it can be concluded that action is necessary to enhance the pharmacy practice in the European area, several groups are already working in this problem on behalf of EAHP, EMA, and HMA, and for that more information on "Medicines Shortages" is needed.

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Patients Perspectives on Medicines Shortages in Hospital Setting

Darija Kuruc Poje

Abstract Medicine shortages represent serious problem for the healthcare system leading to interference with patient care. Studies are mainly done in the USA and Canada which reported more side effects and longer hospitalization. In Europe research is mainly focused on opinions from stakeholders, community and hospital pharmacists and rarely on clinical impact or opinions from patients. Two of the biggest pan-European studies regarding medicine shortages impact on hospital pharmacists were done by European Association of Hospital Pharmacists (EAHP) in 2014 and in 2018. They have found an increase in medicine shortages from 2014 to 2018. While in 2014, 86% in 2018 92% of hospital pharmacists reported that they had current problems with medicine shortages in terms of delivering the best care to patients and/or operating the hospital pharmacy. The most affected therapeutic areas were: infectious diseases, oncology, emergency medicine, cardiovascular medicine and anesthesia. It also reported negative impacts for patients which include: delayed care, cancellations of care, medication errors, suboptimal treatment/inferior efficacy, unnecessary experience by patients of side effects, deterioration in patients' conditions and even death. Furthermore, patients' perspectives on medicines shortages in hospital setting have not been well documented in the literature. Therefore, a qualitative study is ongoing in several European countries (Croatia, Serbia, Portugal, Bosnia and Herzegovina, Germany, Greece, etc.) with the purpose of quantifying the effect of medicine shortages on patient outcomes. This study will help to be more acquainted with the patients' complaints, wishes and needs. In addition, it will fill informational gaps from previous surveys regarding patients' perspectives as well as gather contemporary data regarding these patient care issues.

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1 Introduction

During the past several years, medicine shortages have become a serious and a complex global problem posing a significant threat to healthcare (Fox et al. 2014; Hawley et al. 2016). They lead to more difficulties for clinicians in delivering the best care and compromise patient's safety on a daily basis. In addition, shortages have serious implications in terms of additional costs and staff workloads.

Furthermore, there is a higher likelihood of manufacturing problems with sterile injectables than oral medicines due to processes and equipment which are more complex and specialized to manufacture. Woodcock and Wosinska (2013) identified the fundamental problem which is the inability of the market to observe and reward quality. All these could lead to relatively few companies that produce sterile injectable drugs. Therefore, shortages of sterile injectables can last for months whereas those of oral drugs are generally resolved more rapidly. Despite the fact that most medicines do not experience shortages, this represents a significant public health problem that deserves the joint attention of government and industry. The report also illustrate that medicine shortages are increasing in frequency which lead to growing concern of the long-term supplies of key medicines worldwide.

Reports from Canada (Canadian Drug Shortage 2018), USA (International Pharmaceutical Federation 2013), and Europe (Casassus 2015; De Weerdt et al. 2017) state that the character of drug shortages is multicausal. Manufacturing problems and supply or demand issues are the most common known causes of shortages (Ventola 2011). Rationalization and consolidation of the industry increased manufacturing and the supply chain frailty. There are fewer manufacturing sites as well as active pharmaceutical ingredients which are sourced outside Europe and USA. These shortages are especially problematic when a primary or sole-source supplier of a raw material delays or discontinues production, affecting multiple manufacturers. Moreover, production capacity may be limited due to manufacturers' utilization of the same production line for multiple products. Consequently, a specific problem encountered within one production site may well lead to a global crisis.

In addition, the economic aspects are related to distribution and supply issues. In order to optimize and reduce costs, stakeholders increase efficiency and decrease waste by "just in time" inventory management, thereby reducing inventory costs (Fox et al. 2014; Ventola 2011). In that way overall susceptibility to shortages is increased, especially when a change in demand or supply unexpectedly occurs.

As has been pointed out, many parties along the entire supply chain, especially patients are affected. In spite of the fact that economic impact of medicine shortages is growing, clinical effects are much more troublesome (Becker et al. 2013; De Weerdt et al. 2017; Gatesman and Smith 2011). Lack of national reporting systems is causing difficulties in determining the quantity of patients harmed and effects of medicine shortages on patients (McLaughlin et al. 2013; World Health Organization-WHO 2015).

In this brief review, it will be shown the effect of medicine shortages through a healthcare practitioners and patients' point of view. In Europe, to today's knowledge, there is no consensus definition of medicine shortages, therefore, in this article, although imprecise, the definition from International Pharmaceutical Federation (FIP) is used: "*(Medicine shortage is) a drug supply issue requiring a change. It impacts patient care and requires the use of an alternative agent*".

2 Medicine Shortages' Clinical Impacts

Healthcare practitioners are focused on successfully minimizing the effect of shortages on patient care which make them regularly operating in crisis mode. Medication shortages lead to increased risk of medication errors and adverse drug events (WHO 2015). All these compromise patient's safety due to negative consequences such as less effective alternative medications, delays in surgical procedures, delays in clinical trials, and lack of familiarity with alternative drugs (WHO 2015; Smid et al. 2011).

A recent USA study from Mazer-Amirshahi and colleagues, reported majority or 51% (overall number of respondents was 1004) of medicine shortages occurred in critical care in the period from 2001 until 2016. Alternatives were available for majority (88.3%) drugs, although quarters (24.9%) of alternatives were impacted by shortages. Infectious disease drugs were the most common drugs on shortage, with 19.9% shortages and a median duration of 7.7 months. This is similar with the findings from 701 infectious diseases physicians which presented the response rate of 44% (Gundlapalli et al. 2018). The study was undertaken in 2016 and showed that 70% respondents needed to modify their antimicrobial choice because of a shortage in the prior 2 years. A majority (73%) reported the shortages affected patient care or outcomes by the use of broader-spectrum, more costly, less effective second-line or more toxic agents. Similar findings are associated with oncology medicine shortages which must be administered within days or weeks in order to provide maximum benefit (Becker et al. 2013).

Special problem are "crash cart" medicines such as norepinephrine which is used as the first-line vasopressor for treatment of hypotension due to septic shock. Study from Vail et al. (2017) showed that the norepinephrine shortage was associated with increased mortality in patients with septic shock despite the alternative available (the most common used alternative was phenylephrine). Patients admitted to these hospitals during times of shortage had higher in-hospital mortality.

Although rare there are situations when the entire supply of a given drug is completely unavailable which further complicates the problem. Example is natural disaster in the home of the key USA saline manufacturer, thus hospitals have to ration the remaining product for specific clinical situations or defined patient populations (Mazer-Amirshahi and Fox 2018). This current saline shortage crisis led to development of a hospital based oral rehydration strategy by emergency physicians (Patiño et al. 2018). Candidates for such strategy are adults with mild

dehydration from pharyngitis, gastroenteritis, pregnancy-related vomiting, and upper respiratory tract infection. The patients with severe dehydration or those who are unable to take liquids by mouth for other reasons (e.g. small bowel obstruction) are excluded. This protocol decreased intravenous fluid use by 30% in first week and by 15% in next three weeks of implementation.

In 2014 and 2018, the EAHP published results from the study from more than 600 responses from 36 European countries and 1666 responses in 38 European countries. While in 2014, 86% of hospital pharmacists had current problems with medicine shortages in terms of delivering the best care to patients and/or operating the hospital pharmacy, in 2018 the number raised to 92%. One fifth of respondents were experiencing a shortage of medicines every day in 2014, and 35% in 2018. A further 45% experience it every week in 2014 and 38% in 2018. The most affected therapeutic areas were: infectious diseases, oncology, emergency medicine, cardiovascular medicine and anesthesia. It also reported negative impacts for patients which include: delayed care, cancellations of care, medication errors, suboptimal treatment/inferior efficacy, unnecessary experience by patients of side effects, deterioration in patients' conditions and even death (shown in the Fig. 1). These findings are similar with those from the USA and Canada (Bible et al. 2014; Dranitsaris et al. 2017; Gupta and Huang 2013; Hsia et al. 2015; Lukmanji et al. 2017; McBride et al. 2013; Reed et al. 2016; Rinaldi et al. 2017; Schweitzer 2013; Vail et al. 2017)

In order to mitigate medicines shortages, healthcare professionals have to cancel their clinical duties and spend their time on tasks such as investigating alternative agents, developing action plans, managing inventory, education of colleagues (Institute for Safe Medication Practices-ISMP 2017). A survey from 2011 found that labor costs associated with managing shortages in US hospitals totaled approximately $216 million annually (Kaakeh et al. 2011). Conclusion of the survey was that labor costs and the time required to manage drug shortages are significant and that current information available to manage drug shortages is considered suboptimal.

3 Patients' Perspective on Medicine Shortages

Studies about medicine shortages' clinical impacts are mainly done in the USA (Bible et al. 2014; Gupta and Huang 2013; Hsia et al. 2015; McBride et al. 2013; Reed et al. 2016; Schweitzer 2013; Vail et al. 2017) and Canada (Dranitsaris et al. 2017; Lukmanji et al. 2017; Rinaldi et al. 2017). They reported more side effects and longer hospitalization. Some studies reported patients' opinions.

Patient complaints, inadequate patient care and high institutional costs have been found in one study, based on pharmacy director members' answers, which investigated effects of drug shortages on clinical outcomes (McLaughlin et al. 2013). The other study found the interdisciplinary tension among patients, medical staff, hospital leadership, nurses, and/or staff from other clinical departments which frequently or

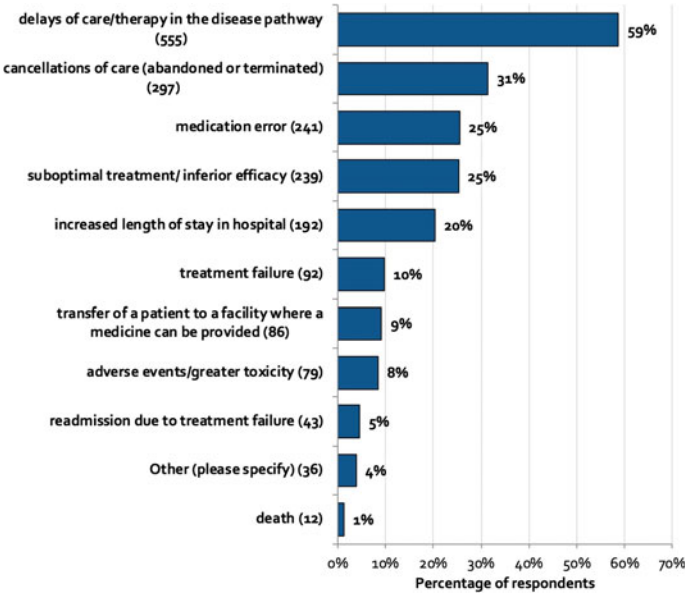

Fig. 1 Negative impact of medicine shortages on patient care (with the permission taken from: EAHP's 2018 Survey on Medicines Shortages to improve patient outcomes, MEDICINES SHORTAGES IN EUROPEAN HOSPITALS, Results of the largest pan-European survey on medicines shortages in the hospital sector, an overview of the situation and the key challenges that need to be tackled, November 2018. Available at: http://www.eahp.eu/practice-and-policy/medicines-shortages/2018-medicines-shortage-survey. Accessed 21st November 2018)

always expressed frustration with pharmacists or pharmacy staff members because of drug shortages (ISMP 2017). Few differences were seen among respondents from different settings. Canadian Pharmacists Association found that medicine shortages led to more stressed, confused, frustrated patients which led to experience a loss of trust in medication and the pharmacist. An inconvenience was also reported. It included: more waiting, calling, and physician visits required; more travelling to the pharmacy required; frequent changes to medication, causing confusion; added stress and loss of trust; increased cost to the patient, especially when alternatives are not covered by drug plans and patients who have switched pharmacies.

In Europe research is mainly focused on opinions from stakeholders, community and hospital pharmacists and rarely on clinical impact or opinions from patients in hospital setting (Bogaert et al. 2015; De Weerdt et al. 2015; Pauwels et al. 2015). Therefore, to gain information about the impact on patients, observational studies questioning patients or comparing health progression status in hospitals where shortages are experienced are needed (De Weerdt et al. 2017).

4 Conclusions

Current problems of medicine shortages represent a challenge for all parties included in the process. Although, a lot has been done in mitigating the effects of medicine shortages on clinical outcomes, the problem has never been more substantial (US Department of Health and Human Services, Food and Drug Administration 2011; WHO 2015). Patient safety is the most important thing that has to been taken into account. Patients' perspectives have to also be considered.

Patients' perspectives on medicine shortages in hospital setting have not been well documented in the literature. Further studies are needed in order to get insights into patients' perspectives, quantify the effect of medicine shortages on patient outcomes and be more acquainted with the patients' complaints, wishes and needs in hospital setting. Therefore, a qualitative study is ongoing in several European countries (Croatia, Serbia, Portugal, Bosnia and Herzegovina, Germany, Greece, etc.). These results will help to fill informational gaps from previous surveys regarding patients' perspectives as well as to gather contemporary data regarding these patient care issues.

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Rationing of Nursing Care: An International and Multidimensional Problem

António Casa Nova, Raul Cordeiro and Olga Riklikiene

Abstract Rationing of nursing care occurs when resources are insufficient to provide necessary care to all patients. This may be a result of reduced staff numbers, skill mix variation, increased demands for care or a changing patient profile. It is a result of a policy decision making by nurse managers who are faced with reduced resources while striving to provide care, rather than by policy makers, and often involves choices, which impact on care delivery and patient safety. Under the auspices of Working Group #4 in COST Action 15208—Rationing Nursing Care: an international and multidimensional problem, is developing a consensus work on the construction of a Guide for Nursing Managers called *Promoting patient safety through minimizing missed nursing care.* This work has been conducted in several stages. It was started with the development of a proposal and at this time has been discussed in several scientific nursing events throughout Europe. The task will be complete for publication by the end of 2020.

Keywords Health care rationing · Nursing care · Cost containment · Quality

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1 Introduction

The concepts of missed nursing care, unfinished care, nursing care left undone or omitted, along with the rationing of nursing care continue to be discussed in the health literature with increasing frequency since first noted through the work of the International Hospital Outcomes Research Consortium (IHORC) in 2001 (Aiken et al. 2001).

Missed nursing care can be categorized as an error of omission and some nursing care are delayed, only partially completed, or not completed at all (Uchmanowicz 2017).

Kalisch et al. (2009) have developed a conceptualization model to understand missed nursing care including structural factors contributing to missed nursing care like: labor resources, material resources, teamwork and communication.

2 The Missed Care Issue

Missed care is a well-established concept in the nursing literature. Evidence of missed care exists—the problem has been studied in several countries (Kalisch et al. 2009; Ausserhofer et al. 2014; Ball et al. 2016; Bragadottir et al. 2017).

All proposed conceptualizations look to examine the relationships between organizational factors such as staffing levels, and client and staffing outcomes (Uchmanowicz 2017).

These missed, rationed or unfinished cares seem to be, clearly, the result of insufficient resources (mainly time or staffing levels) which force nurses to make decisions about which patient care is urgently needed and which can be left undone if there is no time or not enough staff.

3 Measures to Evaluate

Instruments to measure the prevalence of the phenomena have been developed with the focus on either care left undone, missed care and implicit rationing.

The instruments include the Tasks Undone scale (TU-7 or the extended version TU-13 as used in the RN4CAST study) (Aiken et al. 2001; Ball et al. 2014), the Basel Extent of Rationing of Nursing Care (BERNCA) (Schubert et al. 2007), the Perceived Implicit Rationing of Nursing Care (PIRNCA) (Jones 2014), and the MISSCARE instrument (Kalisch and Williams 2009).

As a result of studies using the above instruments it is estimated that in the acute care sector between 55 and 98% of nurses report episodes of missed or rationed care (Jones et al. 2015), with empirical evidence of resulting adverse outcomes for

patients (Ausserhofer et al. 2013; Lucero et al. 2010; Schubert et al. 2008, 2009, 2012; Kalisch et al. 2012; Ball et al. 2018).

These outcomes include, for example, increases in patient falls, infections, higher mortality levels, lower reported levels of quality of care, and lower patient satisfaction. Conversely lower levels of rationing are associated with better outcomes for patients (Papastavrou et al. 2014; Schubert et al. 2008).

Patient safety and the implications of quality care of patient care, as well as left undone or rationed care are widely discussed, along with the impact on the well-being of the nurse. Higher extent of care left undone are associated with higher levels of nurse burnout, intention to leave, and dissatisfaction with the job and the profession (Kalisch et al. 2011; Ausserhofer et al. 2013; Ball et al. 2016). In addition, nurses report feelings of guilt and moral distress associated with taking decisions that ultimately compromise patient care (Scott et al. 2018; Papastavrou et al. 2014). At an organizational level nursing staff turnover rates also increase and patient satisfaction levels fall. Patient satisfaction, an acknowledged measure of quality of care, is known to be impacted by even low levels of care omissions (Kalisch et al. 2012).

The factors that have been shown to impact on levels of missed, unfinished or rationed nursing care include not simply workforce or staffing issues but also factors related to the work environment (Ausserhofer et al. 2014; Schubert et al. 2013). Measures of the quality of the work environment of nurses include characteristics related to nurse leadership (both at unit level and hospital level), teamwork, perceived staffing adequacy and nurses impact on quality of care. Where nurse leadership is seen to be high and staffing levels adequate, patients report higher satisfaction levels and there are reduced levels of adverse events (Kane et al. 2007; Wong et al. 2013). Supportive leadership is linked to higher nurse motivation and to better patient outcomes (Kutney-Lee et al. 2009; Aiken et al. 2012; Bruyneel et al. 2015).

Under the auspices of a working group (WG4) in COST Action 15208—Rationing—Missed Nursing care: an international and multidimensional problem, the group is developing a consensus work on the construction of a Guide for Nurse Managers called *Promoting patient safety through minimizing missed nursing care.*

Nurse managers are ideally placed to monitor and influence levels of missed or rationed care within their units. The nurse leaders in clinical settings are also faced with insufficient resources and can lead the way in decision-making processes that protect the quality and safety of patient care provision. In order to do this, nurse managers must understand the levels of missed or rationed care within their units, the patient, nurse and organizational outcomes associated with missed care, and the resources required to enable the delivery of high quality, safe patient care.

The referred *Guide for Nurse Managers* is intended to provide nurse managers with an outline of relevant research which examines and contextualizes the impact of missed care. Critically it contains a number of suggestions for data gathering and interventions which may help them to support and guide nurses to make effective decisions when faced with shortages. It is not prescriptive, but should be seen as a practical aid designed to support managers and nurses in all care settings to address the issue of missed or rationed patient care.

The primary goal of the guide is to assist nurse managers in selecting the best management and leadership strategies to reduce levels of missed or rationed nursing care through supportive workplace environments. Such environments will support the provision of safe, high quality nursing care to patients and reduce adverse outcomes for patients, nurses and organizations.

The guide has the following objectives:

– To stimulate awareness among nurse managers about patient safety, missed care, and its impacts;
– To provide a framework for reducing episodes of missed care, which includes a set of indicators;
– To stimulate ideas and priorities for quality improvement and research.

The guide aims to be a challenging and inspiring document, but ultimately to be a realistic and practical instrument for nurse managers in all settings and across all health services. The guide should be an effective and effective decision making by nurse managers around resource allocation, wellbeing staff, care provision and patient safety which in turn would result in reduced levels of missed or rationed care across health services.

The target audience for the *Guide for Nurse Managers* is wide with some users listed below. This list is not exhaustive, but is intended as a guide:

- National Nursing Associations;
- Regulatory bodies on nursing and health;
- Nurse managers at all levels;
- Health professionals;
- Hospital managers, health care institutions;
- Quality departments;
- Nurse educators;
- Nursing students.

In this guide (work in progress), several indicators related to the organizational structure (e.g., nurse staffing), the care process, the nursing resources (e.g., job satisfaction) and the patient—centered outcomes (e.g., adverse incidents occurrence) are inventoried.

4 Conclusions

The evidence suggests that in healthcare, missed nursing care is commonplace, but the phenomenon often goes unacknowledged by nurses.

If nurses do not highlight the issue within their workplaces there is a real danger that frequently missed care could become the norm, with some nursing work disappearing entirely.

The *Guide for Nurse Managers* is not easy to develop due to the various contexts that exist in Europe regarding the organization of nursing care. This is a task that

requires broad discussion and consensus involving the organizations of managers, patients and nursing professionals, and the guide should be complete for publication by the end of 2020.

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Linear Programming and Cloud Computing for Pharmaceutical Supply Chains

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Abstract Linear Programming (LP) is a well-known, powerful method to solve many problems in industrial and scientific applications. The objective of the present study is to propose the resolution of user LP problems by cloud computing, i.e., without the usual installation of computer programs for the purpose. We also compare our resolution with other peers' approaches and on-line solvers, typical problems being addressed (transportation, transshipment, assignment, scheduling) applicable in numerous activities, including the pharmaceutical Supply Chains (SC). Thus, instead of providing software for the user to download and install, we offer a website where the user can insert his problems' data and obtain their solutions. Some websites propose comparable solutions, but in little practical ways. The proposed style of action provides a practical and quick access to the advantages of cloud computing, which will encourage users and practitioners from pharmaceutical SC and many other related areas to delve further into the subject.

We use 'website' and 'web page', according to the Oxford Dictionaries (2018).

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1 Introduction

Linear Programming (LP) problems are very important in industry in general and benefit mainly from a well-known method of resolution, the "simplex method". Mentioning LP does not exclude its variants, mainly the Mixed Integer Linear Programming (MILP), not specifically addressed here but also available in our website. The simplex method was created by G. B. Dantzig in 1947 (Stanford 2018), and is one of the "top 10 algorithms of the 20th century" (Cipra 2001). It continues to be the best choice in practice, although a few other methods have been proposed, e.g., Karmarkar's algorithm (1984). Those other methods have proved to be more efficient; nevertheless, the simplex method shows better performance for a wide range of industry applications.

The LP connection to the Supply Chain is well-known, and the presence of the latter is constant in the pharmaceutical context, due to the inherent time and cost constraints, as reported as mere examples by Agwunobi and London (2009), Aronsson et al. (2011) or Pinna et al. (2015).

In order to solve LP (and MILP) problems, we selected IBM CPLEX (2018), because of its highest quality and its availability to the academic environment, in which we have used it for several research tasks. The name (CPLEX) comes from "C", the language in which it is written, plus "simplex", the cited algorithm created by Dantzig (Informs 2018). This software can be used in three different ways: as a standalone product, as an add-in to other products, and as a callable library.

i. The standalone version can be used in several operating systems, such as Microsoft (MS) Windows and Linux, and has a programming language of its own (OPL, "Optimization Programming Language").
ii. The add-in is installed together with MS Excel, with a performance that is superior to the usual Excel Solver.
iii. Finally, the callable library is a tool that works with any programming language able to call the C language.

This third mode is the one we have used to create the web pages shown below. The code programs in Fortran 90 were able to use the callable library, this kind of library sometimes equivalently called an API (application programming interface).

This innovative approach to solve LP problems (and many others in other scientific domains) consists of using the Internet, or cloud computing, to make CPLEX available, in controlled sized problems to respect the legal conditions. The computing speed depends on the nature of the computing infrastructure and the implemented system, but it could be a similar solution for any company or organization that intends to avoid any repetitive installation. Noting that software installations are time-consuming, sometimes cumbersome or dangerous (e.g., virus sensitive), the running times are not easy to compare while the communication times (for data input and results output) can be pondered too for large sets.

The availability of our website will hopefully encourage users and practitioners from Pharmaceutical SC and many other related areas to delve further into the subject,

namely integrating multiple criteria decision making (Miranda et al. 2017). In plus, we have consistently used this approach to cloud computing and presented it in many scientific gatherings (Casquilho 2013; Ferreira and Casquilho 2013; Casquilho and Miranda 2017; Barros and Casquilho 2018).

2 Approaches to Cloud Computing

Mentioning this innovative approach implies the existence of other researchers' options. In a similar way, the approaches presented in Ponce's Vlab (Ponce 2018) and Arsham's site (Arsham 2018) are both remarkable. Namely:

- Ponce's initiative (since the year 2000) is the closest to ours (which we began in 1998). It is dedicated to Hydraulics, solving many problems in this field, and including an extraordinary collection of texts, images and videos, mostly related to his domain of research.
- Arsham's initiative includes extensive and thorough explanations of subjects in Operational Research, Statistics, and Management Science, and provides computing, though with difficult data entry.

In different approaches to make scientific tools available, other peers present excellent applications too, but without providing the computing facility. For example:

- Beasley (2018) offers extensive information on Operational Research topics, but no computing.
- Vanderbei (2018) offers many live problems in OR and other areas, but which depend on Java (with its security issues) or javascript (running, if enabled, on the user's computer), some of which having awkward data entry. Some problems were not found in the website, and some depend on the browser's nature.
- Trick (2018) makes numerous texts and presentations available, but no computations.
- Chinneck (2018) offers several programs, but they have to be downloaded and installed, or they need add-ins such as Adobe Flash.

We do not include SAS or even its section SAS OR (2018), with both excellent software and website, because no real-time resolution is provided. Data management topics are, however, easily missing in most of the cloud applications, and the documentation notes provided from the commercial utilization of cloud computing is often addressing data property and data privacy. For instance, the utilization of online platforms for surveys and questionnaires is commonly embedded with statistics basics, graphics tools, and reporting attributes, the property and privacy of data being referred explicitly. The confidentiality attributes required for many companies, however, especially when pondering strategic or financial data, is still a key point to develop when discussing calculations through cloud computing.

In solving LP problems, each variable can be continuous or integer. With continuous variables only, we have LP proper, whereas with one or more integer variables we

have MILP, not explored here but also resoluble in our web pages. The CPLEX API is in the background, being, without the user's awareness, called by the implemented program. The presence of integer variables makes the resolution much harder, and the use of dedicated software (such as CPLEX) is, of course, mandatory. Anyway, the user must be aware of the difficulty, because a large-scale problem can end up unsolved due to unpredictable time, memory or storage limitations.

Other LP solvers of recognized quality are available, such as Gurobi (2018), Mosek (2018), Lindo (2018). All of these and others can be freely used at the NEOS site (2018), but not as the cloud developments described in this text.

In plus, MILP examples are made available in the cloud too; since the Transportation problem presents integer solutions when input-data is integer, following the well-known integrality property, then illustrative examples related with the typical transportation cases (Casquilho and Miranda 2016) follow in the next section.

3 Illustrative Examples: Transportation Cases

The Pharmaceutical SC includes many problems related to LP itself and many others, such as the Transportation Problem. We address these topics in the following sections in a innovative perspective, at least from our experience in searching a similar approach. We mean to make available these typical problems in the cloud, permitting the user to solve these problems just with a browser, having to install no programs.

All our problems shown below are solved with the CPLEX solver (2018), as mentioned, a high quality software. Although we also have solved LP problems with our own codes and programs, the utilization of commercial packages is supposing high numerical robustness and computational reliability.

In the following, the problems are presented in a simple formulation, because our objective is not to bring new facts about them, but to show this innovative pathway to resolution, i.e., computing over the web,[1] the cloud computing environment. Thus, the references about the problems are indicating mostly well-known sources, such as web references and fundamental handbooks, namely, in Operational Research.

3.1 Transportation Problem

The Transportation Problem (TP) aims, in its typical form, to provide the optimum solution, i.e., the cheapest solution, to transport goods from a certain number of sources to a certain number of destinations. This is a classical problem, first stated by Frank Lauren Hitchcock in 1941, (AMS 2018), even before the simplex algorithm had been found, with the creation of the stepping-stone method to solve it. The mathematical model of the TP is (Eq. (1)).

[1]Meaning 'world wide web' or Internet.

$$[\min] z = \sum_{i,j} c_{ij} x_{ij}$$

subject to

$$\begin{cases} \sum_{j} x_{ij} = s_i \quad j = 1 \ldots n \\ \sum_{i} x_{ij} = d_j \; i = 1 \ldots m \end{cases} \tag{1}$$

where z is the total cost, to be minimized, c_{ij} is the unit cost of transporting from source i to destination j, s_i is the capacity (goods supplied) from source i, d_j is the capacity (goods received) of destination j, and m is the number of sources, and n, the number of destinations. Thus, the number of variables is $m \times n$, considering the x_{ij} fluxes from all sources to all destinations, and the number of restrictions is $m + n$ (indeed, $m + n - 1$ due to equilibrium), considering one restriction per each source i and per each destination j.

This model is easily entered and solved in MS Excel, for example, through its own solver, but besides the need to use this proprietary software there is a limitation in such approach: the total number of variables cannot surpass 200 (so, a modest problem with 15 sources and 15 destinations, giving 225 variables, cannot be solved). The writing of a TP in matrix-like presentation can, anyway, be useful for the submission to our respective web page, where it can be inserted by simple copy-paste of the cells or of a "comma separated values" ('csv') file.

In the context of this chapter, we follow the general rule that all the web pages refer to a typical Transportation case, with data and related results, in order to make the subject clearer and immediately accessible to the user.

The data for the TP example is given in the web page below, together with a brief explanation and the result to be obtained.

A default example problem is given at the web page ***Transportation Problem***. From the default problem, the data (input) and result (output: solution, graphic) are given in Figs. 1 and 2.

3.2 Production Scheduling

The Production Scheduling problem is related to the TP, and is a "transportation" in the time domain, instead of in space. The minimum global production cost is sought. A typical example can be described by Table 1, where, in consecutive columns, we have: 4 production months (January to April); the customers' orders; the maximum production per month; the (variable) unit production cost; and the (variable) cost of storing. The equivalent TP problem will acknowledge the fact that you cannot manufacture in February, say, to sell in January (producing in January to sell in January, February, etc., is assumed normal).

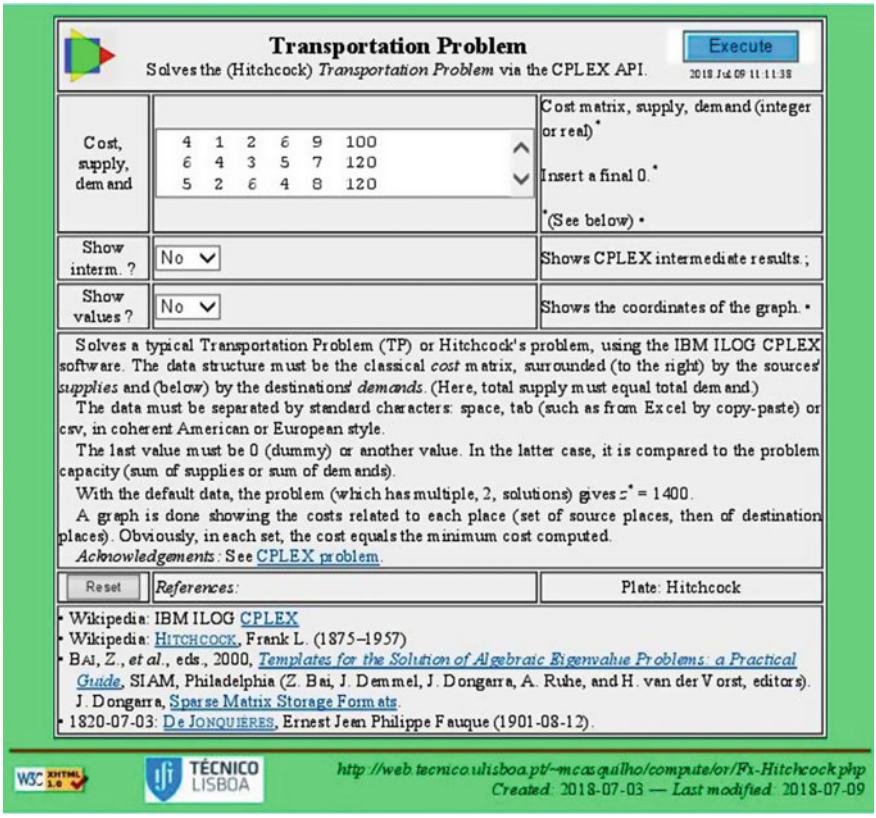

Fig. 1 Data (input) for an illustrative transportation problem

This problem is converted into an equivalent TP as follows (Table 2), where a fictitious destination (with capacity 30, excess production) is introduced to put the problem in equilibrium.

For computation, M, which would mean "infinity", to forbid the corresponding transitions, must be given as a "sufficiently large" number. This might be a very large number, but, indeed (to avoid possible computer overflow), it must only be great by comparison with the remaining values in the matrix, possibly 100 in this example. If, notwithstanding its magnitude, the algorithm assigns some positive number to the quantity "transported" from a month to a previous month, M will be made greater and the problem is repeated. If, finally, the (mathematical) problem keeps giving these absurd solutions, the conclusion is that the original (physical) problem is impossible. This is, otherwise, the general rule to be observed in solving LP, i.e., the artificial variable technique.

The data for the example are given in the TP web page, file "prodsched.txt". From the default problem, the result is given in Fig. 3.

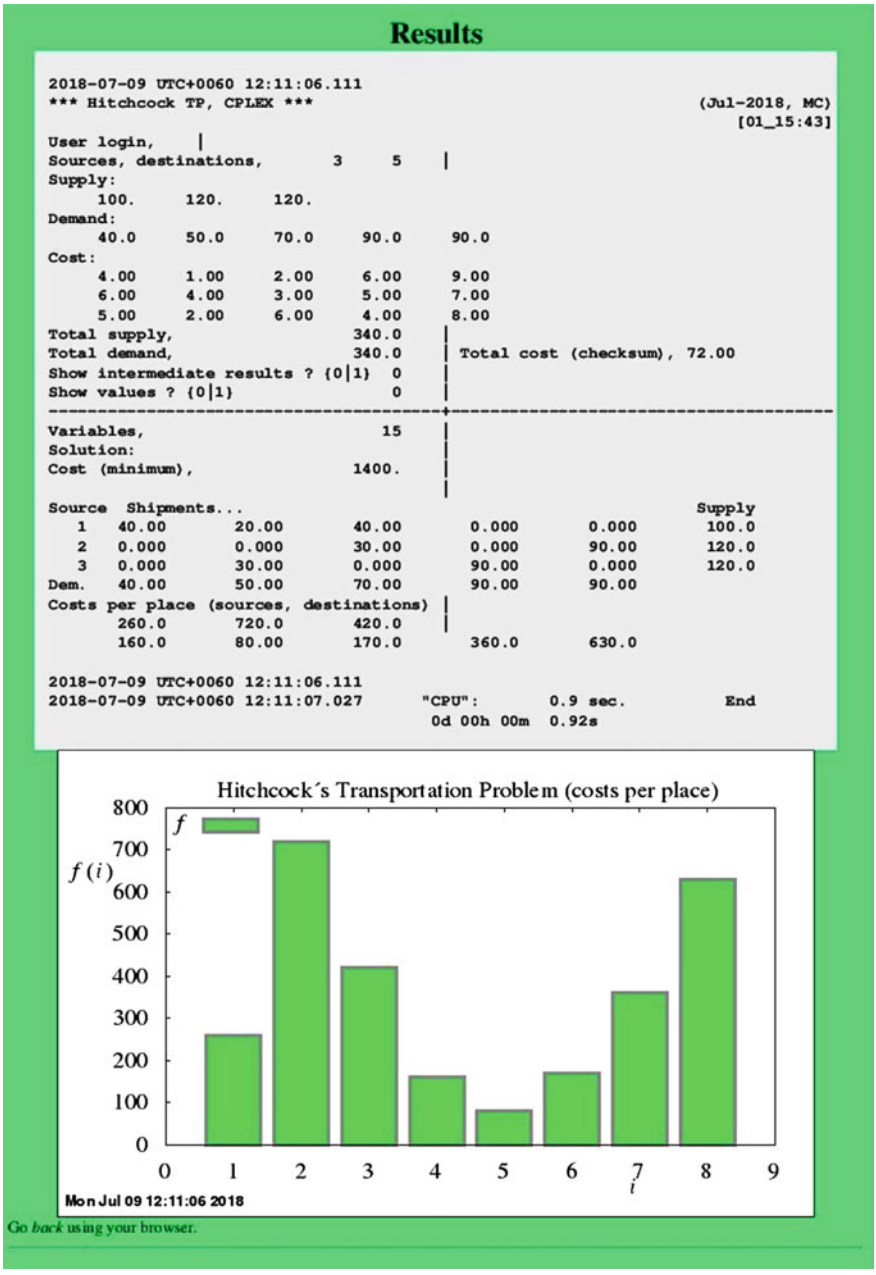

Fig. 2 Results (solution and graphic) for the illustrative transportation problem

Table 1 Data for a production scheduling problem

Month	Orders	Maximum production	Unit production cost	Unit storage cost
1 (January)	10	25	1.08	0.01
2 (February)	15	35	1.11	0.01
3 (March)	25	30	1.10	0.01
4 (April)	20	10	1.13	–

Table 2 TP equivalent to the production scheduling

Month	1	2	3	4	Fictitious	Supply
1 (January)	1.080	1.09	1.10	1.11	0	25
2 (February)	*M*	1.10	1.11	1.12	0	35
3 (March)	*M*	*M*	1.12	1.13	0	30
4 (April)	*M*	*M*	*M*	1.13	0	10
Demand	10	15	25	20	30	(100)

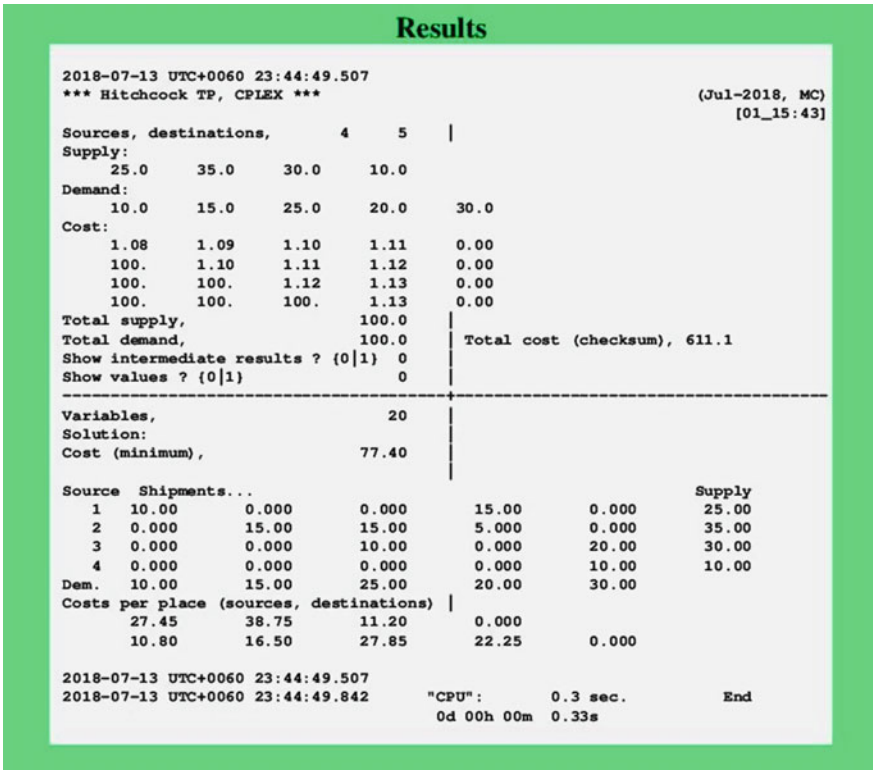

Fig. 3 Result for the production scheduling problem

3.3 *Transshipment Problem*

The Transshipment Problem is a more complex case of transportation, but a simple routine can be used to transform it into a TP. Starting with the problem in Fig. 4, three types of entities can be identified: (pure) sources, Points 1 and 2; (pure) destinations, Points 5 and 6; and "transshipments", Points 3 and 4. The sources and destinations (Points 1, 2, 5 and 6) have the usual function, their capacities being assigned *positive* values for sources (+95 and +70 units, respectively, for Points 1 and 2), and *negative* values for destinations (–30 and –45 units, respectively, for Points 5 and 6). The transshipments can have also the character of sources, as Point 3 (+15 units), or destinations, as Point 4 (–30 units).

To transform the Transshipment Problem into an equivalent Transportation Problem (TP), the general capacity, Q, is added to the transshipment points, which are simultaneously sources and destinations, so the TP will be in equilibrium. In the example, $Q = +95 + 70 + 15 = 180$, from the "sources". As the destinations have a different (smaller) capacity ($30 + 30 + 45 = 105$), one (always one) fictitious destination is introduced, to bring the problem into equilibrium, one (always one) fictitious source in the opposite case.

With the transformations mentioned, the final, equivalent TP tableau for this Transshipment Problem is the one given in Table 3, where the matrix values are unit costs, $, and supplies and demands are quantities. The symbol M indicates a large value, meaning an impossible transportation. For instance, the segment from Point 1 to Point 4 (or Point 1 to Point 6, etc.) does not exist, so its cost is made prohibitive. The costs from a certain Point to itself (Point 3 to Point 3 or 4 to 4) are made zero because they correspond to virtual and non-real flows.

The solution to this problem is given in Table 4, where, as is frequently used, the zeros are not shown and the value in italics are interpreted as quantities not passing. The total cost, obtained from the resolution as a TP is 590 monetary units.

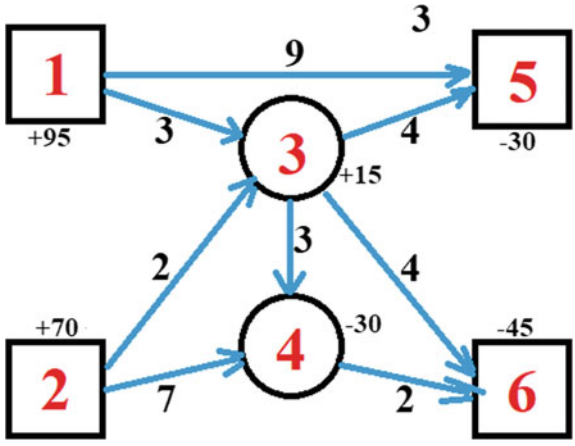

Fig. 4 Transshipment problem, with unit costs ($) on the arrows and capacities near the Points (1–6)

Table 3 TP equivalent to the transshipment problem

	3	4	5	6	Fictitious	Supply
1	3	*M*	9	*M*	0	95
2	2	8	*M*	*M*	0	70
3	0	3	4	4	0	15 + 180
4	*M*	0	*M*	2	0	0 + 180
Demand	0 + 180	30 + 180	30	45	75	(540)

Table 4 Solution to the transshipment problem

	3	4	5	6	Fictitious	Supply
1	20				75	95
2	70					70
3	*90*	30	30	45		195
4		*180*				180
Demand	180	210	30	45	75	(540)

3.4 Assignment Problem

The Assignment Problem (AP) is the case of assigning a certain number of tasks to the same number of persons in the most economical way. This problem can be solved through the so-called Hungarian algorithm, created by the American mathematician Kuhn (1955), who named it in recognition of the related work by two Hungarian predecessors (Kőnig and Egerváry). The Hungarian algorithm is a very interesting algorithm on its own, but the AP can be immediately recognized as a TP where each source "sends" one unit and each destination "receives" also one unit.

The data for the AP example is given in the web page ***Assignment Problem***, together with a brief explanation and the result to be obtained.

From the default problem, the data (input) and result (graphic) are given in Figs. 5 and 6.

4 Conclusions

We have presented a set of problems closely related to LP, in continuous variables, that can be solved via cloud computing in our innovative web pages. In addition, MILP problems can also be solved there. These MILP problems are typical cases of LP, and they are solved through IBM CPLEX as an API to our own programs.

We made available several other scientific subjects in the same style in Engineering, Computing, Operational Research, and Statistics. As true cloud computing examples, the user does not have to install any programs, just needing a browser,

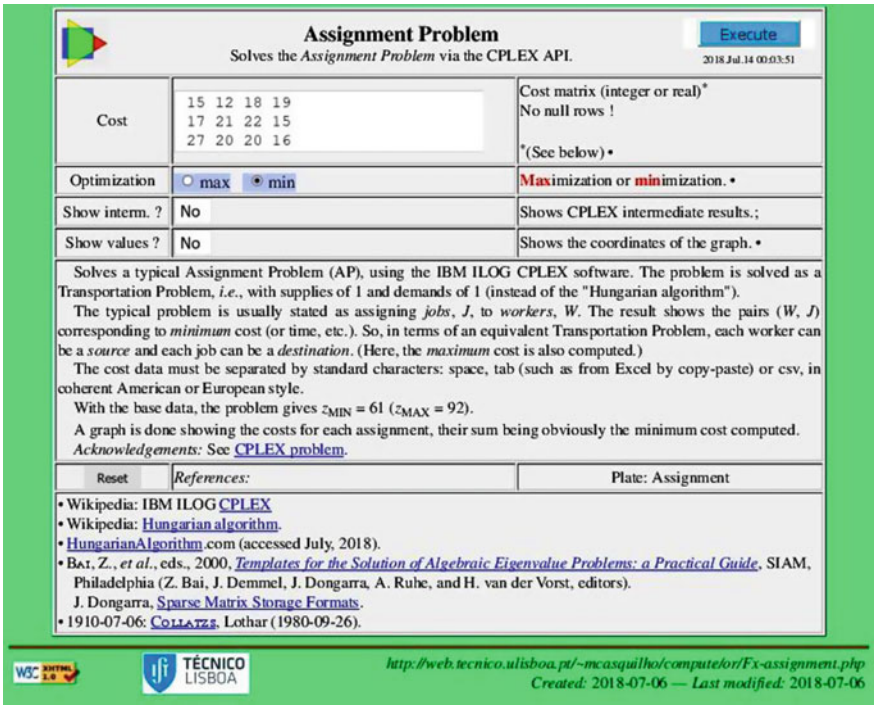

Fig. 5 Data (input) for an illustrative assignment problem

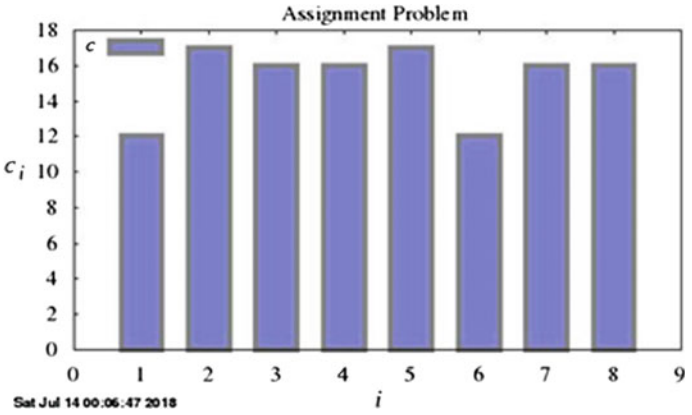

Fig. 6 Results (graphic) for the illustrative assignment problem

avoiding operating system incompatibilities, own computing insufficient power and installations. We have not found other significant similar web pages, and think that ours are a convenient way to offer an important tool to the general user, attracting attention to this very important subject and to its study. This may also be an efficient route for the cooperation between University and Industry, data privacy and intellectual property rights ("IPR") issues being addressed whether they may arise.

Our illustrative examples are yet to be combined with the current IBM Watson question-answer computer system. Indeed, IBM Watson is based on the use of natural language, and the emphasis is in the problems nature and the availability of web-based tools. The applications are wide both in industry and in academia, so their resolution on the cloud is useful and attractive, and it may induce users to study these subjects further.

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IBM Watson Studio: A Platform to Transform Data to Intelligence

Roy R. Cecil and Jorge Soares

Data Science (Tukey 1993; Naur 1966; Hayashi et al. 1998) is fast emerging as the inter-disciplinary field that converges in specialist professionals, domain expertise, data modelling expertise, statistical expertise and computer science. Data scientists transform raw data to intelligence through a systematic process of data understanding and model building based on their understanding of the data. However, to become effective in achieving their objective of transforming raw data to intelligence, they are challenged with a disjointed collection of tools, processes and unsatisfactory data acquisition and curation techniques. Recently there is an emergent concept of Insights Platform-As-A-Service (Hopkins 2017) that attempts to solve some of the problems in this space. In this paper, we want to survey the steps involved in intelligence creation, challenges facing data scientists and the solutions using Insights Platform-As-A-Service approach with the help of IBM Watson Studio (IBM United States Software Announcement, 218-095 2018) as an example.

1 Introduction

In this age of Information, we are surrounded by an enormous deluge of data. Every aspect of human interaction produces data. The data however needs to be identified (data discovery), collected (data ingestion), sifted (data refining) and transformed (data modeling) into intelligence to be useful in shaping our future. Information technologists and researchers need tools and techniques to enable this transformation. However, they are faced with an enormous cacophony of disjointed tools and approaches that increases the entropy and thereby reducing the efficiency of the pro-

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cess by which this transformation of data-to-intelligence takes place. In this paper we will survey some of the problems the industry faces in this space and some approaches towards solving some of these problems. The chapter is organized into the following sections: in Sect. 2, Stages in Data Processing describes the logical flow of transformations that happen to data as they are acquired up until the data is transformed into intelligence; in Sect. 3, Problems in Data Analytic Processing surveys some of the common problems that slows down and, in some cases, inhibits the application of analytics to data: in Sect. 4, Next we look at Insights Platform-As-A-Service using Watson Studio and related technologies as an example; and finally in Sect. 5, the conclusions.

2 Stages in Data Processing

Data Discovery and Ingestion: The first step in any analytics project is to obtain data. Data have origin in a wide variety of sources. The sources can be broadly categorized into Human Generated Data (Ghotkar and Rokde 2016) and Machine Generated data (Ghotkar and Rokde 2016). Human Generated data can include data that are generated by humans at various intersections of human-to-human and human-to-machine interactions. They also include non-structured and semi-structured content like digital forms, images, texts and videos. In contrast stands Machine generated data that are generated by machines from various sensors, machinery, software applications and service endpoints and from device-to-device interactions. In the age of information explosion (Hilbert 2017, 2018), we often have more data and the issue becomes one of finding relevant data to the problem we are trying to solve as opposed to simply acquiring the right data and the problem suddenly transforms itself from one of simple data acquisition to one of information discovery. Often in the context of the myriads of data sources we have available to us, one needs tools to quickly classify, organize and tag data assets including auto-tagging and auto-classification techniques, so that the assets are easily discoverable. Besides one need to enforce policies to this knowledge discovery phase to ensure that the data assets thus discovered can be trusted to generate valuable insights and not lead to erroneous conclusions (Fig. 1).

Data Storage: Once data is acquired, data needs to be stored in a form that is easier for the analytic processes that are applied to them. This is an important step because the ease with which data can be analyzed often depends on the manner in which the data is represented and stored. Besides there might be temporal requirements placed on the data storage rate to ensure no data loss owing to the Data Processing Systems not being able to keep pace with the speed with which data is generated. An example of such a problem would be many sensors trying to insert data into a database where the rate of generation far exceeds the rate at which the system can ingest data (Meehan et al. 2017). Data thus stored can be placed in a large variety of systems such as Relational, NoSQL, Message Queues, Hadoop, Object Stores, Flat Files etc.

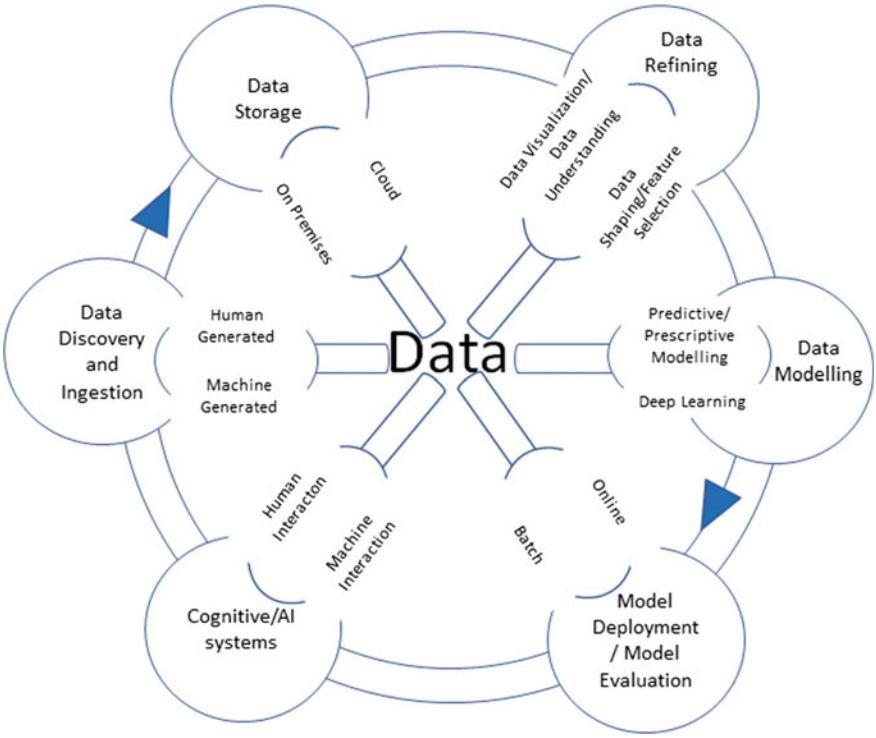

Fig. 1 Stages in data processing

Data Refining: Data Refining or Data Purification can be imagined as a similar process to transforming crude oil to graded fuels. This step often involves the following two sub-steps that often are repeated in an intertwined manner until the desired quality and shape of data results for use in data modelling.

Data Visualization/Data Understanding: A first step towards obtaining "intelligence" from data is to be able to visualize and understand data. This step often involves, data profiling, building statistical summaries of the data, univariate, bivariate and multivariate analysis on the data that allows users to understand the data, the predictors and the relationship between various dimensions of the data. Often this kind of analytics allow users to describe and summarize data for various users and allows for building preliminary hypotheses based on our understanding of the data (Tukey 1993).

Data Shaping/Feature Selection: The data at this stage needs to be shaped into a form that can then be easy for various analytical models to be applied to it. This stage ensures that the raw data is cleansed, the trust in the data can be enhanced and data normalized before being fed to downstream systems. For example, when faced with the goal of building a Boolean search engine for key words on a corpus of free form textual data, it might be advantageous to store the data in the text as a large matrix

with the name of the text and the keyword as dimensions. Such a representation facilitates the intended processing and quite often this step is guided by the manner in which the Data scientists intends to use the data. Data also needs to be validated for null or missing values, omitting erroneous values etc. enhancing the fidelity of the data (Tukey 1993). Feature engineering (Khalid and Nasreen 2014; Heaton 2016) is another important aspect in preparing our data for analysis. Of the many dimensions the dataset provides the data scientist often needs to extract a subset that is relevant to the hypothesis they are modeling for and sometimes they need to construct new dimensions that are based on the original dimensions in the data. The data needs to be also treated for bias so that the model we build can make an accurate prediction (Glauner et al. 2018).

Data Modelling: Based on our understanding of data, mathematical models can be built that allow us to build predictive models (Mishra and Silarkari 2012) that predict the future based on our experience. Some of these models often need their parameters fixed by training such models with data from observation. These are often termed as "Machine Learning" (Samuel 1959) algorithms that allow a computer to use data from a specific domain to train generic data models. Often care should be taken to not over-fit the models. Overfitting is the phenomenon of training the model with all data we have available so that the model accurately predicts the outcome of any random point in the problem space it has seen already but fails for some set of points in the problem space it has not yet seen (Hawkins 2004). Models can be evaluated based on various criteria such as the accuracy of the prediction and computational complexity in terms of space and time.

Machine learning algorithms can also be termed supervised, semi-supervised or unsupervised algorithm (Russell and Norvig 2010) depending on whether and how much the algorithm requires a training step before being ready to be used as a predictive model. Supervised learning is also necessary to correct model bias. Model building is an iterative step that involves making a series of hypothesis, building various mathematical models, training the models using training data sets, evaluating the model accuracy using test data sets and incorporating feedback from various stakeholders such as domain experts. Various techniques for evaluating model accuracy can be used to select the best suited models from a set of candidates to be selected for application in a given context. Models should also be robust enough to handle data drifts so that as either the distribution or range of input data changes the model continues to produce robust results. Model ensembles can be used to combine various models that predict subsets of the problem space well together in an ensemble that overall has much better accuracy (Russell and Norvig 2010).

There are some modelling techniques that has gained ground in recent times owing to the availability of large compute power at the dawn of the third millennium. They are prescriptive modelling (Wright et al. 2006), Deep Learning (Alom et al. 2018) techniques and Genetic Algorithms (Mitchell 1996). These mathematical techniques were well known since the latter half of the twentieth century but huge strides in the practical applications could not be achieved since we did not have sufficient compute power to light up these models. Prescriptive models have enormous application where goal-oriented models can be built that optimize certain outcomes and help choose the

best input variables to be selected to achieve the desired outcome and, in that sense, can shape our future. Deep Learning Models often tend to apply principles we learned from how human brain works and implementing them in software or hardware levels. They have huge applicability in pattern recognition especially feature recognition in images, as well as text and speech recognition. Most of these models work on Tensor mathematics and GPU's are especially suitable for this kind of computational models (Schlegel 2015). However, there are also efforts to build native neural processors as opposed to our current approach which is aimed at simulating Neural Networks in a Von Neuman machine. A good example of this is IBM's TrueNorth chips (Akopyan et al. 2015). Compute environments well suited to implementing these mathematical models is a key ingredient of a successful and effective analytic platform.

Model Deployment/Model Evaluation: Once the modelling phase is complete, by which is meant that the error between the model prediction and the actual outcome is below a tolerance value, the models we have built can be deployed and we can build applications that encode the intelligence, encoded in the model, to be used in computer systems that can behave intelligently depending on the data they see, vastly improving our world (Caruana and Niculescu-Mizil 2004) complementing and/or supporting us. This step often involves deploying the models in a model runtime, and continuously monitoring the performance of the model and retraining the model if data and/or model drifts are detected for e.g. when the model performance goes down owing to changes in the real-world process that is abstracted by the mathematical model. Model deployment often needs flexibility to handle different deployment requirements placed on it. A practitioner, needs to be able to quickly deploy a model he has designed, developed and tested online or when a model needs to be deployed conditionally based on upstream logic based on data refresh. Consequently, model deployments can either be online or batch mode or induced by stream processing logic.

Cognitive/AI systems (Langley 2012): Cognition refers to the capability of a system to sense its operating environment and take actions based on the input data and its experience by a process of continuous sensing and learning. Advances in Computer Vision, Speech Recognition and Natural Language Processing allows building software systems that can manifest cognitive capabilities. This allows the building of applications that composes the model with predictions from AI models that are pre-trained with domain specific knowledge base. With the advent of the maturation of tools and techniques we can develop systems that can perceive and reason the way a human being can and use such systems to adjust our models, discover patterns hidden in data that are often difficult, and influence just about every facet of model life-cycle.

Horizontal Processes: Besides the above-mentioned activities there are several cross-cutting concerns around Data Quality (Olson 2003), Data Governance (Ladley 2012), Data Security, Data Privacy and Streaming Analytics (Schales et al. 2014). that needs to be addressed at each stage of data processing as data moves up the value chain. These take the shape of both tools and processes that need to ensure that many legal requirements are satisfied, and data trust and security is maintained.

3 Problems in Data Processing

Machine Learning data pipelines are mostly error prone to silent errors. The techniques used in machine learning and statistics in general are like the ones used in noise reduction in network traffic. It is therefore important that proper understanding of data flows and Data Quality (Olson 2003) are met. So, care must be taken in validating the data source, versioning the data source (Roddick 1996) and enforcing data governance policies such that throughout the lifecycle of the data, the data quality can be maintained. Not all data quality problems can be solved with the application of technology because human beings defy technology. So robust data handling processes must be used as supplemental steps in addition to technological advances to ensure that the data quality can be maintained throughout the life-cycle of the analytic projects.

Second problem we encounter often is that of data silos (Kim et al. 2016). Data assets we want to use often are the result of organic growth over a period. They have traditionally been acquired and stored using a diverse collection of tools both proprietary and open source and it is difficult to bring them together to be analyzed together. This is further complicated by such factors as data security problems; for e.g. who has proper access to the data. Techniques such as Data Anonymization (Zhou et al. 2008) provides answers to some of these challenges.

Data handling is further complicated by the fact that the entity analyzing the data is subject to legal and regulatory constraints. This further prevents data from being freely combined leading to less effective intelligence being mined from it. Data security and data availability often places contradictory pressures on Analytics projects leading to costly negotiation between stewards of data and Data Scientists.

"Tower of Babel" (Genesis 11.1–8, 2004) problem which alludes to a mythological time from when human civilizations broke into tribes speaking different languages thereby preventing them from achieving a larger purpose that could be achieved if they shared a common language, also plagues Advanced Analytics projects. There exists an enormous variety of tools, statistical packages, data processing languages, database flavors and skills across these tools and it is a big challenge to bring diverse skills and provide a single space for all these contributors to interact. Often this gives rise to delays and failure due to communication channel proliferation.

Besides these one needs the ability to "fail fast and cheap" (Khanna et al. 2015). Traditional analytic systems are built with a forward projection of resources needed to do an experiment which do not have a decidedly predictable outcome. Consequently, investments need to be made that might or might not result in a better outcome. But to be successful, practitioners need a way to fail fast and with as less an investment as possible overall bringing down the cost of extracting intelligence from the data.

Finally, we need to be able to introduce feedback loops that continuously improve our understanding, models and predictions (Wiering et al. 2011). Such feedback loops can be enhanced by connecting various bits of intelligence to connect the dots and

have cognitive capabilities. Intelligence is the outcome of several expert systems working in tandem, that provides connects entity relations across different datasets and across different applications (Minsky 1986).

4 Insights Platform

Most of the problems recounted in the previous sections are well known and there have been several attempts to solve them in the industry. However, there is very little attempt in the industry and academia to converge known solutions into a single platform that introduces a production line approach to transform data to insights. In this paper we will look at one of the solution to such an approach to solving the problem, IBM's Watson Studio. The design philosophy behind Watson Studio is to not attempt to build a monolithic solution but rather use the well known micro-services paradigm. The platform is built on cloud and is agnostic if the platform resides on public, private or hybrid cloud (Coyne et al. 2018). This allows end users with conflicting requirements to enjoy the benefits offered by the platform regardless of the deployment choice they must make. Oftentimes, these decisions are driven by business or non-technical reasons and hence very important for the end user.

The micro-services (Chen 2018) approach allows each building block to be integrated into the platform thereby imparting the platform the ability to be easily extended to solve problems in data analytics. Data can easily be ingested into the Platform by the Data Refinery service. A data engineer defines and establishes connections to external data repositories including data that are behind firewalls using a secure gateway, defines data services within the IBM Cloud that act as data source or target systems. Heavy duty data movements can be optimized using IBM Aspera High Speed File Transfer that uses patented Fast, Adaptive and Secure Protocol (FASP) that cuts down network protocol overhead over WAN. Data from the source systems can be profiled, and quick visualization capability allow the Data Engineer to understand relationships between variables in the data set. Data Refinery also provides sophisticated data transformation capability that allows him to cleanse the data and improve the data quality. The shaped data can be stored in Watson Knowledge Catalog where Data Stewards can implement required Data Governance Policies, thereby ensuring trust in the data. Data engineers can also define streaming data endpoints in the platform that makes streaming data available to Data Scientists. Multiple organization wide Data Catalogs can also be added to a Watson Studio Project allowing Data Scientists to discover data, models and other assets that are relevant to the problem they are working on.

Once the data required for the project is enhanced with trust and shaped into forms required by the Data Scientists, the team of Data Scientists can study the data and experiment with it. The platform enables them to use various tools to understand, explore and visualize the data. The platform makes available to the Data Scientist most of the popular Data Analysis framework and remains language and tool agnostic. This includes the ability to integrate Python, R, Scala, SPSS environments to the

analysts. Both Visual Modelers that allow analysts to use drag and drop components into a modelling canvas to build Machine Learning, Deep Learning and Streaming Analytics models and applications. Jupyter notebooks that allow data scientists to write code in python, Scala and R provide teams of diverse skills to collaborate. The platform is permissive rather than restrictive which allows the end user to extend their development environment with other popular frameworks such as TensorFlow™, H2O.ai™ etc.

The notebook environment integrates visual menus to add data into their environment from the catalog by providing boiler plate code that takes away the tedium of integrating data from the sources. The notebook also integrates multiple elastic runtimes to run the models. They include spark clusters, Hadoop clusters, IBM stream runtimes, Watson Machine Learning runtimes and DOCPLEX runtimes. Taken together they allow the Data Scientists, to build, evaluate and deploy models. Model building is an iterative step and involves multiple stakeholders and the platform allow the team to collaborate effectively. Multiple stake-holders can work on different aspects of Machine Learning pipelines that can be each individually developed and tested. Deployed models can be scheduled to be retrained by constantly measuring its performance and when new data is available. The platform also generates boiler plate code in python, java, R, Scala and REST API's that allows Application developers easy access to embed the models in their applications.

Artificial Intelligence is the subject that deals with the topic of imbuing human capabilities of intelligence to machines. Our current state of the art is that Intelligence is the outcome of a combination of Machine Learning models working co-operatively. Specific faculties that mimic intelligence that can be separated and implemented as microservices is a good way to provide cognitive capabilities in a program. This is how they are implemented on IBM Cloud. Watson API's provide these faculties as a set of pretrained services that allows us to build specific faculties such as conversations, visual recognition, knowledge discovery, natural language understanding etc. Watson Studio integrates these API into the platform allowing the data scientist to include the Watson API's to imbue data models and applications with cognitive abilities, for e.g. the ability to recognize objects and texts in picture, ability to understand concepts in texts, understand the tone, sentiment and emotions in text etc. These services are scalable and platform and language agnostic making it easy to integrate them into an advanced analytic application.

The platform also integrates the ability for Data Scientist to build optimization models based on knowledge about domain. They allow the practitioner to build Linear Programming, Network flow, Quadratic and Discrete optimization models among others.

The platform goal is to reduce the time between data is acquired to when intelligence is derived from the data. This is done by enabling all the actors that collaborate to produce this intelligence. Additionally, the platform can also integrate with devops tool chains that short circuits the time to develop insights from raw data. They allow organizations to define rapid application development processes and provide support for functions such as issue trackers, code repositories, application delivery

and deployment pipelines. The platform also allows Information Designers to put together interactive dashboards so that key findings can be shared as information visuals that can be embedded into other applications.

5 Conclusions

Data Science has emerged as the leading transformative opportunity we have that is redefining how intelligent software systems are built. They are changing every aspect of our lives from predicting traffic congestion to assisting doctors to diagnose more accurately to predicting drug shortages in pharmaceutical supply chain. At the same time, there are huge challenges that need to be solved so that Data Scientists spend more time on actual analysis than how they are able to do today. There are studies that indicate that the time spent on actual analysis could be as little as 20% (Wilder-James 2016). This is the challenge we are faced with and the Insights Platform-As-A-Service approach exemplified by IBM Watson Studio goes a long way to making the Data Science teams spend far more time in productive research and development. Much more needs to be done to ease the job of Data Scientists in their pursuit to transmute data to intelligence.

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The Integration of a Flow Model into a Stakeholder-Based Framework for Vaccine Supply Chain Design

Stef Lemmens, Catherine Decouttere, Nico Vandaele, Mauro Bernuzzi, Kim De Boeck, Sherif Hassane and Stany Banzimana

Abstract Many rigorous flow models have been developed to support the design of manufacturing supply chains. However, supply chains supportive of Access to Medicines (ATM), like vaccine supply chains, impose considerable additional challenges on this design process. The incorporation of a broader base of stakeholders delivers a balanced set of Key Performance Indicators (KPIs) and substantially enhances the societal and human impact of the ATM supply chain service delivery. To evaluate such a set of KPIs, we emphasize the need of three distinct models: a flow model which relates the operational issues, a financial model which supports the financial side and finally a value model which considers the value-based or humanitarian aspects. These models are interconnected, dependent and together lead to a combination of KPIs against which the new design options or scenarios are

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evaluated. In this chapter we describe the flow model that covers the manufacturing part of a rotavirus vaccine supply chain and elaborate on how it is embedded in a stakeholder-based framework. We demonstrate the relevance of a vaccine manufacturer's capacity utilization, total lead time and total supply chain stock as proposed technological or operational KPIs.

1 Introduction

In general, vaccines are the most effective way to protect the world's population against infectious diseases. However, the design and operation of a vaccine supply chain are extremely challenging as they need to support the humanitarian operations. Like in many other supply chains, there is a permanent strive for balancing supply and demand. However, in case of vaccine supply chains, some additional challenges are present which make the supply/demand balancing act more complex. Such challenges include the heavy reliance on quality issues and the presence of a complex stakeholders' structure (Decouttere et al. 2016; Lemmens et al. 2016a). Today, like in many other health care systems, medical technology pushes ahead to keep up with global health concerns. Furthermore, the cost of health care is growing rapidly. Finally, a balancing act from a societal and humanitarian point of view is also mandatory. This results in a complex set of trade-offs, which is particularly outspoken in a vaccine supply chain. In order to cope with this humanitarian dimension we developed a framework to analyze and support the decision making for the rotavirus vaccine supply chain (Decouttere et al. 2016).

Vaccine supply chains need to excel on technological, economic, and a vast amount of social aspects such as Access to Medicines (ATM). Due to the multitude of stakeholders involved, it is a challenge to identify improvements for an existing vaccine supply chain or to design radically new health care systems leading to an overall better societal, economic and technical performance. There are important stakeholder alliances and strategic initiatives in the global vaccine system that surround the vaccine supply chain. As significant budgets are involved, radical changes to the vaccine supply chain cannot be realized by a sole stakeholder on its own. Ideally, a strategic group decision precedes the adoption of a new system, where multiple stakeholders' perspectives are taken into account.

In this chapter we mainly focus on the derivation of the Key Performance Indicators (KPIs) as this is a part of the basis for balancing the different performance measures. The objective is to not only perform well on the technological and economic dimensions but on the ATM dimension as well. The goal of this chapter is to show that a reconciliation of technological, economic and humanitarian aspects is important and we demonstrate a methodology to calculate the relevant technological performance measures to support this reconciliation effort. The key element throughout this approach is the adoption of a stakeholder perspective.

2 Literature Review on Supply Chain Design Models for Vaccines

To a large extent, the literature on traditional model-based supply chain design falls short on the reconciliation of the technological, economic and ATM performance dimensions of a vaccine supply chain design model (Lemmens et al. 2016a). Despite the existence of a wide range of different extensively elaborated economic performance measures in the supply chain design literature, the presence of technological performance measures is still subordinate while the ATM dimension is even more scarce (Lemmens et al. 2016a).

For our purposes, the performance of a vaccine supply chain must be measured according to multiple criteria. The vaccine supply chain is considered as slow and unresponsive (Shah 2004, 2005), motivating us to study the integration of technological performance metrics such as lead times and supply chain responsiveness, into supply chain design. Ideally, a value criterion can be proposed to obtain, for example, an equitable vaccine distribution or to measure the humanitarian impact of a vaccine supply chain. Such performance measures are absent in the current literature on supply chain design (Lemmens et al. 2016a).

The results of Lemmens et al. (2016a) illustrate a dominance of the number of single criterion optimization techniques for supply chain design. Imposing multiple performance criteria requires an appropriate multicriteria decision making method. Furthermore, their results reveal multi-objective optimization and the epsilon constraint method as the most frequently used mathematical programming and heuristic method respectively to deal with multiple criteria supply chain design models. These methods avoid weighting multiple criteria, but lack the practical relevance to satisfy a stakeholder group's preferences (Lemmens et al. 2016a).

3 A Stakeholder-Based Framework for Vaccine Supply Chain Design

It is clear that any health care system, from its intrinsic purpose, has a fundamental humanitarian goal of creating sustainable well-being for people (Musgrove et al. 2000). For vaccine supply chains in particular, this is a mandatory issue. Our experience led us to conclude that several important stakeholders must be involved. However, this is clearly situated beyond the scope of the mathematical modeling, so a broader perspective is necessary. In order to enable system designers and modelers to take into account these important aspects, we have proposed a five-step integrated design and modeling process, starting from the stakeholders (Decouttere et al. 2016).

For the purpose of vaccine supply chain design, we make the distinction between two groups of stakeholders: internal and external stakeholders. Internal stakeholders are the people, roles, activities and organizations directly or indirectly impacting and impacted by the vaccine supply chain. These stakeholders are actively involved in

the design and the decision process of the new supply chain. External stakeholders belong to the close environment of the global immunization system. They have an impact on the performance of the supply chain, but are not impacted by the supply chain themselves. These stakeholders often play a major role in the determination of the available design options for the new supply chain but are typically beyond the control zone of the supply chain decision makers. They can however be influenced by other stakeholders or by the supply chain once it is operational and should therefore be taken into account during the design and decision process. Examples of external stakeholders are advisory and regulatory bodies such as the Food and Drug Administration (FDA) and World Health Organization (WHO) as well as funding organizations such as the Global Alliance for Vaccine Immunization (GAVI) and the national governments. Also opinion spreading entities such as universities and religious groups are relevant external stakeholders. An adaptation of a stakeholder map for a (rotavirus) vaccine supply chain for developing countries considering ATM as a priority is shown in Fig. 1 (based on Decouttere et al. 2016).

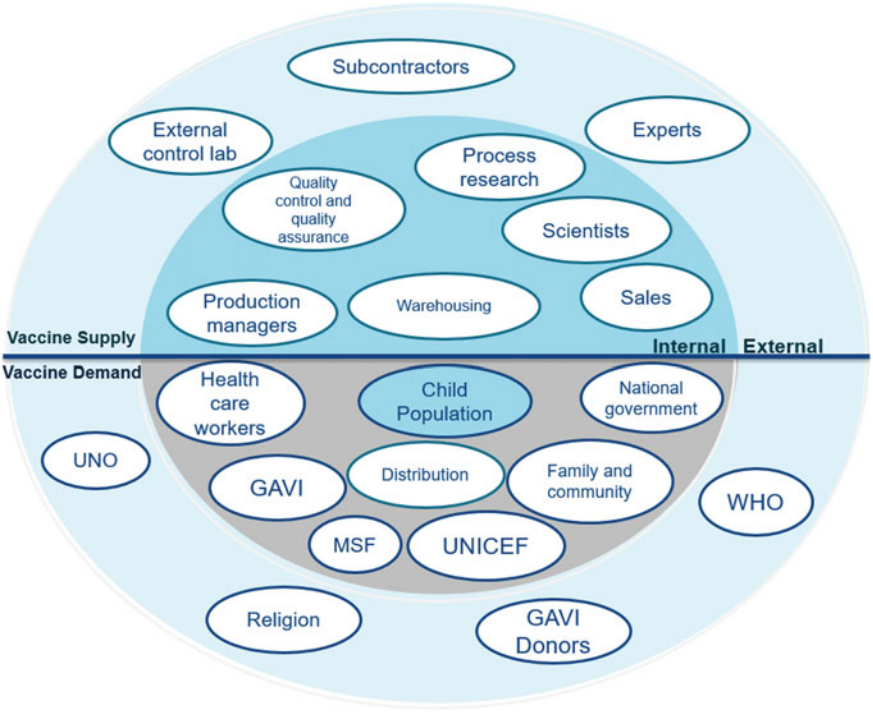

Fig. 1 Example of a stakeholder map (Acronyms: Global Alliance for Vaccine Immunization (GAVI), Médecins Sans Frontières (MSF), United Nations International Children's Emergency Fund (UNICEF), United Nations Organization (UNO), World Health Organization (WHO)) for a rotavirus vaccine supply chain for developing countries (based on Decouttere et al. 2016)

4 Derivation of the Vaccine Manufacturer's Key Performance Indicators

A vaccine supply chain is not only characterized by the typical issues all supply chains are concerned with, but on top of that it also contains some specificities which heavily aggravate the three-dimensional balancing act mentioned above (Decouttere et al. 2016). Firstly, technology-wise, we have to take the rigorous quality and regulatory requirements, long and highly variable manufacturing lead times and cold chain operations into account. Also belonging to this category is a complex market structure, characterized by tenders, variable demand and repeat orders. All three sources of demand prominently compete for the same shared, limited production capacity. Secondly, from the economic point of view, both the inherent high cost of production and complex pricing are not without compromise on a global scale. Profit is not easily brought in line with the delivery and world-wide availability of vaccines. This leads to important considerations like decisions related to the (dis)continuation of the production of vaccines with a decreasing market potential (due to eradication, government policies, competition, donors' policies, etc.), the prioritization on the use of scarce and shared resources and the impact of the vaccine product portfolio decisions on governmental and institutional budgets. Thirdly, the ATM dimension, embedded in the mission and vision of both private, public and non-governmental stakeholders together with their alliances comes into the picture. This is expressed, among others, in terms of saving lives, religious issues, public safety, and military and anti-terrorist interest.

Figure 2 shows the manufacturer's vaccine supply chain design as a subsystem of a global vaccine network. When we go down the road to the modeling effort behind the (re)design of the manufacturing part of the supply chain, we end up with rigorous flow modeling embedded in a multi-dimensional design approach as depicted in Fig. 3. The flow model is used as a basis to model the input and output characteristics of different supply chain scenarios.

The (rotavirus) vaccine supply chain is confronted with keeping large inventory volumes which represent a substantial amount of the manufacturer's working capital. These inventories accumulate partly due to the long and variable lead times of the manufacturer. Figure 4 emphasizes the rotavirus vaccine supply chain's long lead times and their variability from formulation until shipment based on real data of 2013 and 2014. Such a lead time driven performance indicator is important for vaccine supply chains, but the presence of such performance measures is often dominated by economic ones (Lemmens et al. 2016a).

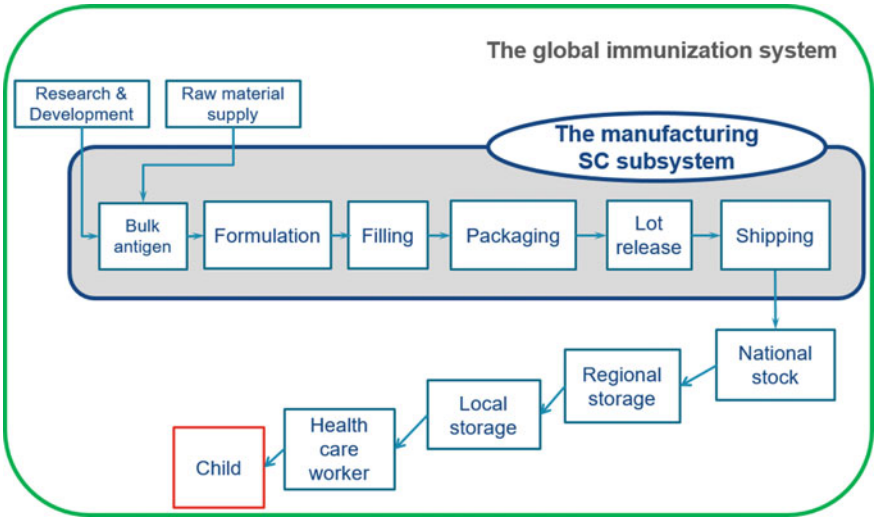

Fig. 2 The vaccine manufacturer's supply chain as a subsystem of the global vaccine network (based on Decouttere et al. 2016)

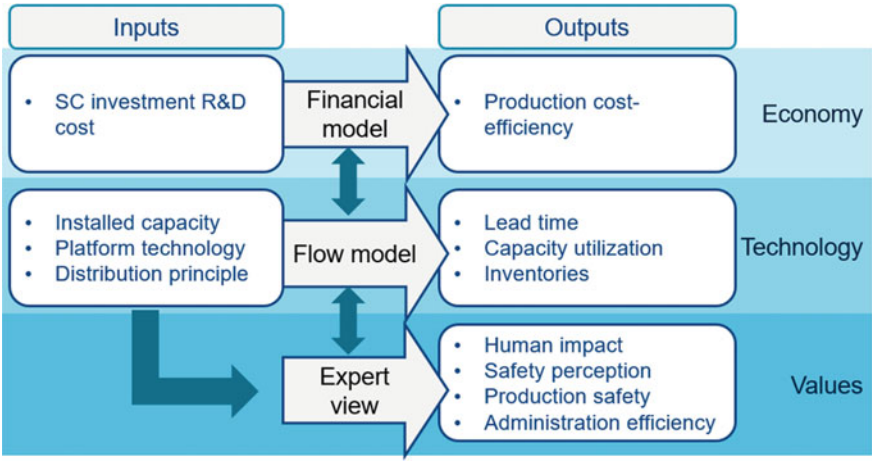

Fig. 3 An integrated design approach and assessment (based on Decouttere et al. 2016)

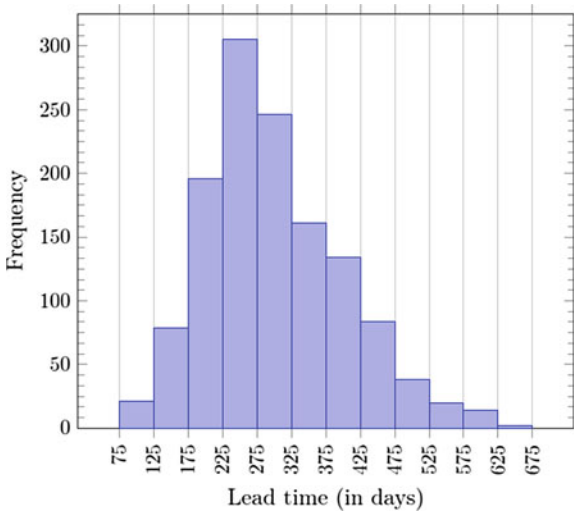

Fig. 4 Histogram of the rotavirus vaccine supply chain's lead time durations (from formulation until shipment)

5 Methodology to Evaluate the Vaccine Manufacturer's Key Performance Measures

We propose a modeling methodology which includes the vaccine manufacturer's lead time, inventory and capacity aspects, but which is also extendible and appropriate to use in our broader view on vaccine supply chain design. We aim to maintain a general modeling methodology such that it can be modified and is able to evaluate the impact of externalities on the supply chain's performance. To compute the vaccine manufacturer's capacity utilization, lead time and supply chain inventories, we propose a methodology which consists of three phases (Lemmens et al. 2016b; Lemmens 2018):

1. The first phase calculates the capacity utilization and the average and the variance of the lead time for the filling and packaging lines by the use of approximate G/G/m queuing networks (Whitt 1983).
2. The second phase postulates the lead time distribution for these manufacturing steps.
3. The third phase uses the calculated lead time information and the postulated lead time distributions of the previous phases to minimize the supply chain's inventories. The methodology to minimize the supply chain's inventories is based on the Guaranteed Service Approach (Graves and Willems 2000; Humair et al. 2013).

Table 1 shows the output of a base case scenario for the rotavirus vaccine supply chain (based on Lemmens et al. (2016b), Lemmens (2018)). For a vaccine manufacturer, it is interesting to compare these results with other scenarios stemming from internal or external stakeholders, such as:

Table 1 Results for the three phases (based on Lemmens et al. 2016b)

	Capacity utilization	Average lead time	Inventories
Phase 1	• Filling: 37.62% • Packaging: 34.38%	• Filling: 1.3748 days • Packaging: 1.1021 days	
Phase 2		Lognormal	
Phase 3			37.75 mio doses

- The increase of the number of countries which introduce rotavirus vaccines. This leads to a radical increase in demand;
- The implementation of lead time reduction programmes;
- The development of new manufacturing technologies (e.g. Blow-Fill-Seal);
- The development of thermostable vaccines;
- The installment of additional capacity units.

Using our suggested approach, a vaccine manufacturer can compare the impact of multiple scenarios on a set of technological KPIs. This can support and guide the decisions related to the (re)design of the (rotavirus) vaccine supply chain.

6 Conclusions

In this chapter we discuss the (re)design of a vaccine supply chain. We propose the reconciliation of an analytical modeling approach with a more descriptive approach. In this way, our goal is to fulfill the ATM aspirations together with the financial and technological ambitions. Therefore, we put forward a stakeholder-based approach such that the willingness to implement a new vaccine supply chain design is maximized.

We emphasize the importance of three technological criteria for a vaccine manufacturer: capacity utilization, lead time and supply chain inventories. We outline a methodology which can evaluate these three criteria for various scenarios. Our proposed modeling methodology matches the vaccine supply chain's characteristics as we observe long and variable lead times. Our approach takes the (nonlinear) relationship between capacity and lead time into account and models the supply chain's total stock as a function of the lead distribution of the different processes.

Undoubtedly, the stakeholder approach can be deployed to other vaccine supply chains and even to supply chain design in general. Finally, we point out that our combination of supply chain stock calculations and G/G/m queueing networks is a generic approach and can be extended to other complex vaccine supply chains as well as to other supply chains.

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The Concept of Medicines Shortage: Identifying and Resolving Shortage

Aurelija Burinskiene

Abstract It is not easy to find out when scientific researches concerning shortage (scarcity) were started. In the field of first studies, authors revised time delays and variable demand, when they moved to item stock and disequilibrium analysis. Later, more sophisticated studies emerged. These involved understanding that drug shortage is affected by supply uncertainty. In the pick of popularity of the topic, the shortage was analyzed in line with logistics costs. Extra studies have become focused on lost sales, batch inspection errors and imperfect quality of products, i.e. medicine. The author of the article investigated shortage cases and the development of shortage concept. In the theoretical part, the author describes the shortage cases and historical concept changes. In the empirical part, author presents simulation results, which are provided to highlight the negative influence of handling errors on logistics costs. Finally, the study covers the aspects of medicines shortage which are undertaken to the production order quantity (EPQ) and to the contribution of inventory models and their application. The scientific literature analysis and synthesis methods are used for the study.

1 Introduction

The concept of shortage emerged as a research object in 1974, when it was offered by Van der Meiden (1974). Since then, related to the topic studies have been shifting towards medicine, e.g. the study made by Seppala and Pulkkinen (1982). However, the topic of shortage remains open to debates among economists that are endlessly searching for the best practices of avoiding shortage. All techniques, methods that improve forecasting, distribution, and handling; may prolong products' durability and lead-time-demand bring the reduction of shortage in many industries (i.e. Lacko 1989).

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The object of this study is to examine the models of inventory management. The article covers the literature regarding inventory planning and avoiding shortage; investigates the causes of operational shortage and formulats the suggestions of possible imprvements. The study provides valuable insights on the topic.

The study has its limitation as the focus area is narrowed to the shortage concept and its reflection on the inventory management models. Nevertheless, the results are very valuable for the experts occupied with the topics of shortage and costs reduction improvement. The originality of the research comes from the author's analysis of the inventory management models and the shortage concept, while a historical approach to the analysis reveals the development of the concepts, methods, and models that are concerned herein.

2 The Shortage Concept

The shortage might be a result emerging from many activities: stock planning, its distribution, handling, and stock keeping. The author distinguishes the four main shortage causes: (1) Inaccurate demand forecasting; (2) Too long distribution time; (3) Insufficient handling accuracy; and (4) Loses emerging after product's expiration term comes to affect. The shortage is usually associated with demand forecasting and supply uncertainty. Among all the four shortage reasons only the first one is dedicated to demand forecasting uncertainty, while the other three are oriented to supply uncertainty. In details all these shortage causes are showed in the Fig. 1.

Each shortage reason is described in detail in the picture. Let's start from demand forecasting.

1. Forecasting depends heavily on information gathered about previous demand and applicable lead times to meet future needs. Therefore, logistics system should

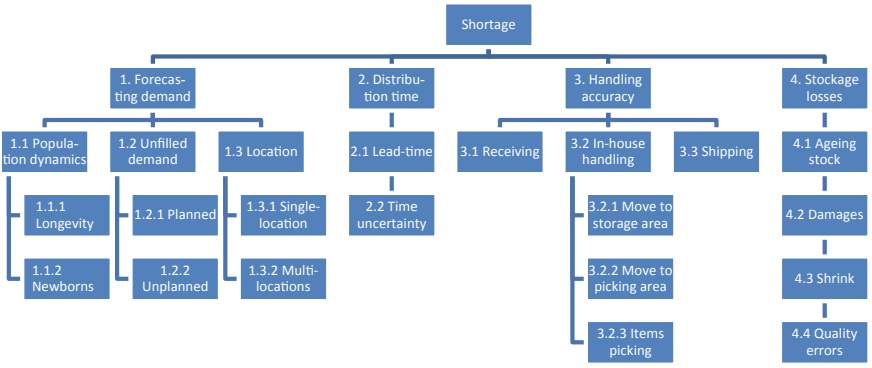

Fig. 1 Identifying shortage causes (constructed by the author)

have inventory buffer to cover demand shocks, i.e. "safe" inventory for periods of unexpectedly high demand.

1.1 Population forecasting is not an easy issue. Demographics dynamics are analyzed by Keyfitz (1981); ageing population is emphasized by Zabawa et al. (2017). These authors pointed out to the reasons of supply shortage that forecasting is due to deal with the forecasting of demand of medicine products concerns population dynamics in the first place.

1.2 Unfulfilled demand could be classified as planned and unplanned. Planned shortage is managed by advanced orders referred to as backorders. A company uses the backorders for new (not yet produced) products as a rule of thumb. In cases of planned shortage, production process starts as customer's order is received (the concept is referred to as "Make-to-order"). The production process takes additional time that means some wait time for a consumer to receive an item. The unplanned shortage is related with operations management (stock distribution and handling issues; damages that occur in storage, etc.). For example, statistically 95% of products arrive on time, 99.5% of products are picked to customers in full and 98% is a stock accuracy level.

1.3 As the number of locations grows in storage, higher inventory level is required. This means that during forecasting the company must consider the number of locations at internal and external facilities. Usually demand is forecasted based on historical data. The demand forecasting may employ two approaches: top-down approach and bottom-up approach. The first one is developed for the market and then it is broken down by region, district, territory, etc. The second one is used to estimate purchases or forecast demand for the specified future time in selling spots. The number of stocking locations is important for demand planning.

2. Lead-time is used as constrain in many inventory models: stochastic and deterministic ones. The lead-time is treated as delivery requisition to order in days.

2.1 In studies, the lead-time is presented as having different characteristics: as fixed—by Hoque and Goyal (2004) and as variable—by Moon et al. (2014) and Ouyang et al. (1996); as fuzzy—by Rong et al. (2008) and as stochastic—by Das and Hanaoka (2014).

2.2 In addition, time is classified as controllable by Pan and Yang (2006) or having time uncertainty, such is emphasised by Lee et al. (2017), or Cheng (1986).

Most of the inventory models address only one type of uncertainty that results to shortage in the production process. However, there are much more types of uncertainty.

3. In the literature, there are distinguished several issues of process accuracies related to the material handling: receiving, in-house handling and shipping. During the material handling inaccurate stock (inventory) measurement appears. The results of accuracy are seen at inventory audit, from client's claims, from lost

sales, from costs associated with errors corrections, and from products availability. When a picker indicates a shortage situation or products are out-of-stock, the system should do three things:

(1) to move product to picking;
(2) to order a new pick task to be picked (usually with next picking route);
(3) to direct product's stock count to discover, why the discrepancy occurred.

In this circumstance, a buyer wants to purchase extra quantity of, for example, medical products, then available quantity, and material allocation mechanism (such as "first come, first served") determines which buyer is served. The shortage of inventory is time-dependent and place-dependent. In addition, there are stockage losses, which effect shortage. Several stock losses types are presented below:

4.1 Ageing stock—the stock, which fails to move on to the next point beyond its shelf-life, because of expiring term of the products. The actual sales, resulting in unsold stocks and ultimately expired stocks. A company must compensate directly or indirectly the affected parties in the distribution system and ultimately incur the loss itself (Sengupta 2017).
4.2 Damages—a term that includes stocks damaged in transit or stocking. The transit requires controlling reverse flow of damaged products. Because the factor of damage occurrence is identified after the shift to next location.
4.3 Shrink is the difference between recorded inventory on a company's balance sheet and its actual inventory. The term "shrinkage" is also used by production in general; it refers to the loss of products or their sub-parts during transactions.
4.4 Quality—another emphasis on improving the production process to guarantee products quality reducing number of rework-able items and scrap items.

3 The Inventory Model Encountering Shortage

Since 1915, authors developed different types of inventory models. One type of these models minimizes total costs and optimizes a shortage period. Shortage costs (lost sales costs) are both made up of fixed costs and variable costs which depend on the length of the shortage time. The shortage costs are lost sales because of unserved present customers, which also do not return in future.

The most of inventory models involve only planned shortage (backorders) leaving other shortage causes not considered. Shortage appears when replenishment order does not arrive at or before the inventory position drops to zero. Therein annual shortage costs are equal to penalty for incurring the shortage of a unit, which is multiplied to times shorted throughout a year. Usually average shortage level is used during modelling. Nevertheless, unplanned shortage can still occur if the demand rate and deliveries do not stay on schedule. In addition, defective items could affect shortage and handling errors. Sulak et al. (2015) suggested that inventory model

should be oriented to defective items and shortage. The detailed overview of shortage concept in inventory models is presented in Table 1.

The studies presented in Table 1 in the period of 1970–1996 focus on time delays and variable demand. In the second part of presented period, i.e. in 1991, studies involve the understanding that shortage is affected by supply uncertainty. In the pick of popularity of the topic, in studies linked with the period 1997–2010, shortage is analyzed in the line with logistics costs. Extra studies arise in 2010, involving into inventory models batch inspection errors and imperfect quality of products.

The most of inventory models do not involve shortage planning. Inventory model, in fuzzy sense, is developed for inventory planning without backordering by Lee and Yao (1999). The model is used for calculating the appropriate reorder point and the optimal reorder quantity to ensure the instantaneous replenishment of inventory encountering no shortage.

The purpose of inventory model encountering shortage is to reduce fixed costs, minimize inventory holding (carrying) costs, and improve overestimating/underestimating demand costs. The model minimizes the total costs of inventory—such as holding (carrying) costs, ordering and production set-up costs, shortage costs and excess costs. During stock out period, customers are ready to wait for some certain time until their orders are carried out. However, if delay time is too long, some customers will be lost, and a company lose sales and profit, while other customers will ask to provide salvage (discount or time-weighted penalty costs).

Each of inventory models is based on assumptions: Economic production order (EPQ) assumes that a producer will handle its own production quantity, and products will be available after production process. Economic order quantity (EOQ) assumes that quantity will arrive when the order is placed. Following these assumptions author is working with EPQ inventory model formula.

The following nomenclature for inventory model encountering shortage is assumed:

Q^* Optimal order quantity for single item;
C_o Costs for ordering and set-up production per order/batch;
C_h Holding costs per unit per year;
C_s Shortage costs (lost sales including lost profit costs);
C_e Excess costs;
D Annual demand;
p Production rate (Production a day);
u Consumption rate (Demand a day);
k Service level factor.

Inventory Model Encountering Shortage

$$Q^* = \sqrt{\left(\frac{2C_0D + C_s}{C_h}\right)\left(\frac{p}{p-u}\right)k} \tag{1}$$

Table 1 The employment of historical shortage concept in inventory management models

Year	Topic	Author	Title
1970	Random demand	Philippakis (1970)	The cost of using EOQ with variable demand items
1984	Demand uncertainty	Mykytka and Ramberg (1984)	On the sensitivity of the EOQ to errors in the forecast of demand
1984–1986	Time delays	Aucamp and Fogarty (1984) and Cheng (1986)	EOQ with limited backorder delays
1991	Supply uncertainty	Parlar and Berkin (1991)	Future supply uncertainty in EOQ models
1996	Time-dependent demand	Hariga (1996)	Optimal EOQ models for deteriorating items with time-varying demand
1997	EOQ model with shortage	Ray and Chaudhuri (1997)	An economic order quantity (EOQ) model with stock-dependent demand, shortage, inflation and time discounting
2001	EPQ with shortage	Cardenas-Barron (2001)	The economic production quantity (EPQ) with shortage derived algebraically. The EPQ differs from EOQ by component presenting production rate and consumption rate
2010	Stock and demand	Jain and Kumar (2010)	An EOQ inventory model for items with ramp type demand, three-parameter Weibull distribution deterioration and starting with shortage
2012	Production uncertainty	Krishnamoorthi and Panayappan (2012)	An EPQ model with imperfect production systems with rework of regular production and sales return
2013	EOQ model with quality	Hsu and Hsu (2013)	An EOQ model with imperfect quality items, inspection errors, shortage backordering, and sales returns

The equation is helping to calculate optimal order quantity. The last part of equation is dedicated to stock service level factor k, which is calculated using two components shortage costs divided from the sum of shortage costs and excess costs.; k is subject to

$$k = NORMSINV\left(\frac{C_s}{C_s + C_e}\right) \tag{2}$$

The Costs Mentioned in Inventory Model Encountering Shortage

During the production run, there are two activities: demand reduces the inventory and production adds more units to the inventory. Ordering/producing costs C_o are average costs for specified activities. The primary driver to hold inventories is the presence of a fixed production costs A and ordering costs O that are incurred every time a positive number of units are produced and ordered. To determine the number of units to produce and order every time the fixed production and ordering costs are incurred. Producing or ordering in large quantities reduces the average fixed production/ordering costs.

$$C_0 = O + A \tag{3}$$

The production set-up costs A are presented below. Herein production costs per unit C_p are multiplied from batch size y.

$$A = C_p y \tag{4}$$

Holding costs C_h represent annual unit holding costs, i.e. holding costs of product in warehouse(s) in period, where product inventory is subject to the average number of units in inventory throughout a year. Holding costs are derived as percentage of item price. Since the item is being storage as inventory, it losses some value by the rate of inflation. So, the holding costs of each item are calculated by multiplying inflation rate i with unit price, which below is represented by unit costs U and sales profit P.

$$C_h = i(U + P) \tag{5}$$

The order is lost if stock shortage appears. C_s are shortage costs per unit per time i.e. loss of profit. For the equation of shortage (stock-out) costs sales price per unit S and unit costs (or unit purchase price) U are taken.

$$C_s = S - U \tag{6}$$

Planned shortage is permitted, i.e. backordered demand units are withdrawn from a replenishment order when backorder is delivered. Backordering is as well positively affecting holding costs per unit, per unit time and the variable part of these costs could be taken into the equation of shortage costs.

Excess costs C_e are the losses given from overestimated demand D, i.e. is difference between sales price per unit and salvage price per unit W. These costs are related with ageing stock losses (represented in shortage concept Fig. 1 point 4.1); they are negatively affecting holding costs per unit, per time C_{hT}

$$C_e = S - W + ChT \tag{7}$$

The Shortage Concept in Inventory Management Model

Author try to find the best way to introduce shortage concept into inventory model. Demand planning is quite complex task. Some ideas on forecasting drug demand are proposed by Clark (2013), where demand is forecasted using probability analysis. Below is quite universal equation for demand forecasting. Population changes could be estimated by trend. The equation is linked with shortage concept (Fig. 1) point 1.1.

$$D = (underlying\ value + trend) * seasonal\ index \tag{8}$$

The shortage is planned and unplanned. Probability to have shortage is opposite to probability *Prob* to arrive to Demand. The next equation is linked with shortage concept (Fig. 1) point 1.2.

$$1 - Prob(C_s) = Prob(D) \tag{9}$$

To serve demand in different regions stock is present in multiple facilities. All locations carry the same amount of inventory, but in multi-locations case, total holding costs can be stated as holding costs in single-location C_{h0} plus additional costs C_E for each unit (pallet) of the item multiplied from the amount of space E occupied by one unit (pallet) of the same item. The equation is linked with shortage concept (Fig. 1) point 1.3.

$$C_h = C_{h0} + C_E * E \tag{10}$$

In case of Lead-time uncertainty reorder level *ROL* is calculated as lead-time *LT* which is multiplied from consumption rate u plus extra inventory I_s which is held

more than expected demand. The equation is linked with shortage concept (Fig. 1) point 2.

$$ROL = LT * u + I_s \tag{11}$$

The increase of excess inventory increases holding costs but reduces shortage costs. If excess inventory reduces the opposite actions are taken.

There joint calculation of order quantity with shortage where holding costs are replaced to C_h^* due to many conditions influencing these costs.

$$Q^* = k \sqrt{\left(\frac{2D}{C_h^*}\right)\left(\frac{p}{p-u}\right)\left[C_0 + C_s \sum_{D=ROL}^{\infty} (D - ROL) * Prob(D)\right]} \tag{12}$$

Production activities are always linked with screening and reworking. The Author is going to present equations, which are linked with shortage concept (Fig. 1) point 4.4. Screening and reworking costs fall under C_o, which includes production set-up costs A. Total screening costs C are calculated accordingly: screening costs per unit C_q are multiplied from batch size y and present the costs of inspection.

$$C = C_q y \tag{13}$$

In addition, rework costs R are equal to rework costs per unit for defective items C_r multiplied from rate r of rework-able defective items and the size of batch y:

$$R = C_r r y \tag{14}$$

After the products screening and reworking activities are finished products are moved to storage. The Holding costs, which integrate the the level of non-rework-able imperfect items t and scrap items k, are stated below. Holding costs per unit, per unit time is marked as C_{hT} and screening rate x

$$C_h = C_{hT}\left[(t+k)\frac{y^2}{x} + \frac{y^2(1-(t+k))^2}{2D} - \frac{y^2}{2p}\right] \tag{15}$$

Handling Accuracy and Holding Costs

Nevertheless, handling costs fall under holding (carrying) costs, the handling accuracy, which relates to handling activity, are not covered in inventory models. The most critical factors in the process are human mistakes, which must be solved seeking to

Table 2 Effect of handling accuracy on holding (carrying) costs

Handling accuracy (%)	Increase of holding (carrying) costs (%)
99	0.35
97	1.12
90	4.15
84	6.84
70	12.49
50	19.86
33	30.49
25	37.36
20	42.51

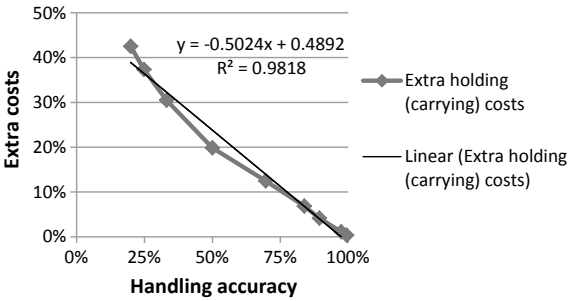

Fig. 2 Handling accuracy generates extra holding (carrying) costs (author's simulation case, study results)

avoid unplanned shortage. Author delivers simulation model and tests the impact of handling accuracy to holding (carrying) costs. Results are presented in Table 2 and Fig. 2.

The impact of handling accuracy y to the revised holding (carrying) costs C_h^* could be calculated according the next equation. This equation is linked with shortage concept (Fig. 1) point 3.

$$C_h^* = C_h * y \tag{16}$$

The inventory model encountering shortage is developed with the assumption that all products are delivered to the customers prior to their expiry date, although the practice is different. The final equation of order quantity encountering shortage covers also damages and shrink rate h (represented in shortage concept Fig. 1 points 4.2 and 4.3).

$$Q_f^* = Q^*(1 + h) \tag{17}$$

The suggested equation summarizes all components the author has involved into inventory model encountering shortage.

4 Conclusions

The classical inventory models are meant for cases when 100% of environment and products are perfect. However, this assumption may not be valid for the most cases evident in real environments. The analysis of historical shortage concept shows that shortage is quite popular in inventory management models. But more often authors provide single studies in the area, i.e. these studies do not combine all shortage causes together.

Author is trying to map causes, which influence shortage, especially which is dependent on supply uncertainty and in most cases is not planned, to present the shortage concept. The components of shortage concept are covered by inventory models encountering shortage, considering demand and supply uncertainties. Herein, the components of costs are analyzed in separate seeking to present the links between activities.

Aiming to specify holding costs, author provides simulation model, where relationship between handling accuracy and holding (carrying) costs is presented. Finally, author delivers the inventory model encountering shortage, which widens the range of inventory models and their application. This study could be expanded to various directions, including the practical applications of suggested model.

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Logistic Operations in a Hospital: A Multi-item Inventory Distribution Problem with Heterogeneous Fleet

Agostinho Agra, Adelaide Cerveira and Cristina Requejo

Abstract A multi-item inventory distribution problem motivated by a practical case study occurring in the logistic operations of a hospital is considered. There, a single warehouse supplies several nursing wards. The distribution of medical products is done by two different teams of workers using a heterogeneous fleet, that is, the available vehicles have different capacities and different structures required to be used in specific nursing wards. The goal is to define a weekly distribution plan of medical products ensuring a balanced workload of both working teams and satisfying all the required constraints (inventory capacities, safety stock levels, vehicle capacities, etc.) that minimizes the total number of visits to locations. A mixed integer formulation is presented and several improvements are discussed. This is a NP-hard problem hardly solved to optimality within a reasonable amount of time, and more so for real size instances, with hundreds to few thousand of products. To circumvent this issue, a matheuristic is proposed to solve the problem. Finally, computational tests are reported and discussed.

Keywords Multi-item inventory · Hospital logistics · Matheuristic · Supply chain management

1 Introduction

In this work we study a Multi-Item Inventory Distribution problem with Heterogeneous fleet (MIIDH) problem which occurs in the logistics activities of a hospital. In the hospital there is a central warehouse and a set of nursing wards. The central ware-

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house receives goods from suppliers and supplies the nursing wards. The demand of each ward includes a wide variety of items such as medicines, hospital supplies and medical devices. The distribution is done by two different teams of workers using a heterogeneous fleet of available vehicles. The vehicles have different capacities and different characteristics restricting its use in specific nursing wards. Each ward is supplied at most once per day (except for extraordinary deliveries not considered here) and requires only a part of the wide variety of the items it consumes. For this variety of items, safety stocks are mandatory at each location. In order to ensure that the delivery plan can be replicated in subsequent weeks, the stock level in the first and in the last period must coincide. The inventory aspects are considered only at the supplied locations, since the supply decisions for the warehouse are taken with months in advance and the planning horizon is short. Given the proximity of locations, the routing aspects are disregarded. The capacity of the vehicle as well as the ward's storage capacity bound the amount delivered in each time period.

The main focus of this work is the planning of the weekly delivery scheme of the huge variety of items to meet the demand while keeping the stock levels between the desired values, considering the inventory and delivery capacity constraints and ensuring a balanced workload of both work teams. In relation to other practical problems combining inventory management and distribution, the one considered in this paper has two particular characteristics: it includes a huge number of items and its distribution costs are negligible.

Optimization issues in Healthcare have become noticeably important and attract keen interest from the Operations Research community. In literature, there are many research papers on healthcare subjects published both on Operations Research and Health Care journals.

Rais and Viana (2011) present several applications of Operations Research in the domain of Healthcare. This article highlights current research activities in this area, focusing on a variety of optimisation problems and the used solution techniques. More recently, Volland et al. (2017) present the state-of-the-art of the research on material logistics management in hospitals. They provide research guidance through categorizing literature into four streams: supply and procurement, inventory management, distribution and scheduling and supply chain management.

From the point of view of inventory management, complex problems combining inventory management and distribution decisions have received an increased attention in the last years. Bijvank and Vis (2012) review replenishment policies in hospital inventory systems and present two models to deal with service requirements and capacity limitations. Rosales et al. (2014) discuss inventory models in hospitals. Burdett and Kozan (2018) address an optimization problem to determine the number of logistics assistants, given predefined task requirements. Constructive algorithms and hybrid meta-heuristics are developed and applied to find solutions. Lapierre and Ruiz (2007) address hospital logistic problems by coordinating the procurement and distribution of medical products as well as staffing decisions. Pharmaceutical supply chain and inventory management issues in health care industry are considered in Kelle et al. (2012), Uthayakumar and Priyan (2013) and the same research

topic is addressed in Dacosta-Claro (2002). An overall introduction into inventory management is presented in Vries (2011).

Agra et al. (2016a) consider a multi-item inventory distribution problem motivated by a practical case occurring in the logistic operations of a hospital. A mathematical formulation to obtain the weekly distribution plan of medical products that minimizes the visits to wards, while respecting inventory capacities and safety stock levels is introduced, several improvements to the mathematical model are proposed and a hybrid heuristic is described. In this approach only one vehicle is considered and the capacity of the vehicle as well as the capacity of the nursing wards is given in terms of the number of items. In the present study some other aspects are considered in order to resemble to the real case. In particular, an heterogeneous fleet constituted by three types of vehicles is considered. The vehicles are distinguished by its capacities and one is restricted to be used to a specific set of nursing wards. Some wards use a supply system based on a double box system which requires a specific vehicle. Furthermore, in the real case there are two teams of workers to deliver, hence the two work teams are considered in the proposed mathematical model. When determining the best distribution plan that minimizes the visits to wards, in addition to respecting the demands, the inventory capacities, the vehicles capacities and the safety stock levels, we also assure a balanced distribution of the deliveries by the two work teams.

We provide a mixed integer formulation for the MIIDH problem and discuss approaches to improve that formulation, such as, tightening big-M constraints and derivation of valid inequalities. The MIIDH problem is NP-hard, since it generalizes well-known NP-hard problems. Such complex problems combining inventory management with other aspects are in general difficult to solve to optimality using exact methods, therefore other approaches such as heuristics and decompositions have been used, see Agra et al. (2016a, b). Here we propose a three-steps heuristic. In each step a set of decisions (corresponding to integer variables) is determined and fixed. In the first step the number of trips per day of each vehicle type is defined, then in the second step, the assignment of each vehicle trip to a work team and to the wards is determined and, finally, in the last step the amount of items delivered to each ward is fixed.

The outline of the paper is as follows. In Sect. 2 we introduce a mixed integer formulation to the MIIDH problem. In Sect. 3 we discuss the model improvements and in Sect. 4 we introduce the heuristic scheme. The details of benchmark instances generation and computational results to test the model and also the heuristic scheme are presented in Sect. 5. Finally, the conclusions are stated in Sect. 6.

2 Mathematical Model

In this section we introduce a mixed integer formulation to the MIIDH problem.

The following notation is used for the mathematical formulation.
Parameters:

n number of items
nL number of locations (wards) to visit
nT number of time periods
nW number of work teams
nK number of vehicles
d_{ijt} demand for item i in location j at time period t
S_{ij} initial stock level of product i at location j
$\underline{S}_{ijt}$ minimum stock level (safety stock) of product i at location j at time period t
C_k capacity of vehicle k
c_i space occupied by item j
V_j stock capacity of location j
Δ maximum difference on the number of deliveries done by the work teams
nM maximum number of trips that can be done by each vehicle during each time period.

Sets:

$N = \{1, \ldots, n\}$ set of items
$L = \{1, \ldots, nL\}$ set of locations to visit
$T = \{1, \ldots, nT\}$ set of time periods
$W = \{1, \ldots, nW\}$ set of working teams
$K = \{1, \ldots, nK\}$ set of vehicles
$N_j \subset N$ set of items consumed in location j
$L_i \subset L$ set of locations that consume item i
$D \subset L$ set of locations that can be served only by a specific vehicle $k' \in K$
$M = \{1, \ldots, nM\}$ set of the trips that can be done by each vehicle during each time period.

Variables:

x_{ijt}^{wkm} integer variable equals to the amount of item i delivered at location j at time period t by the work team w using vehicle k in its mth trip at time period t
z_t^{km} binary variable equals to 1 if vehicle k makes its mth trip at period t and equals to 0 otherwise
s_{ijt} integer variable equals to the stock level of item i at location j at time period t
y_{jt}^{wkm} binary variable which takes value 1 if there is a delivery at location j by work team w using vehicle k in its mth trip at time period t.

It is assumed that each location can only be visited once per time period.
The MIIDH model is as follows:

$$\min \quad \sum_{t\in T}\sum_{w\in W}\sum_{k\in K}\sum_{m\in M}\sum_{j\in L} y_{jt}^{wkm} \tag{1}$$

$$s.t.\ s_{ij,t-1} + \sum_{w\in W}\sum_{k\in K}\sum_{m\in M} x_{ijt}^{wkm} = d_{ijt} + s_{ijt}, \qquad i \in N,\ j \in L, t \in T, \tag{2}$$

$$\sum_{i \in N_j} x_{ijt}^{wkm} \leq B\, y_{jt}^{wkm}, \qquad j \in L, w \in W, k \in K, m \in M, t \in T, \tag{3}$$

$$\sum_{i \in N} \sum_{j \in L_i} \sum_{w \in W} c_i x_{ijt}^{wkm} \leq C_k\, z_t^{km}, \qquad k \in K, m \in M, t \in T, \tag{4}$$

$$\sum_{i \in N_j} c_i s_{ijt} \leq V_j, \qquad j \in L, t \in T, \tag{5}$$

$$\sum_{w \in W} \sum_{k \in K} \sum_{m \in M} y_{jt}^{wkm} \leq 1, \qquad j \in L, t \in T, \tag{6}$$

$$z_t^{k,m+1} \leq z_t^{km}, \qquad k \in K, m \in M : m < nM, t \in T, \tag{7}$$

$$\sum_{w \in W} y_{jt}^{wkm} \leq z_t^{km}, \qquad j \in L, k \in K, m \in M, t \in T, \tag{8}$$

$$y_{jt}^{wkm} + y_{j'}^{w'km} \leq 1, \qquad j \in L, j' \in L \setminus \{j\}, w \in W, w' \in W \setminus \{w\}, k \in K, m \in M, t \in T, \tag{9}$$

$$d_{max} \geq \sum_{t \in T} \sum_{k \in K} \sum_{m \in M} \sum_{j \in L} y_{jt}^{wkm}, \qquad w \in W, \tag{10}$$

$$d_{min} \leq \sum_{t \in T} \sum_{k \in K} \sum_{m \in M} \sum_{j \in L} y_{jt}^{wkm}, \qquad w \in W, \tag{11}$$

$$d_{max} - d_{min} \leq \Delta, \tag{12}$$

$$s_{ijt} \geq \underline{S}_{ijt}, \qquad i \in N, j \in L_i, t \in T, \tag{13}$$

$$s_{ij0} = S_{ij}, \qquad i \in N, j \in L_i, \tag{14}$$

$$z_t^{km} \in \{0, 1\}, \qquad k \in K, m \in M, t \in T, \tag{15}$$

$$x_{ijt} \in \mathbb{Z}_+, \qquad i \in N, j \in L_i, t \in T, \tag{16}$$

$$y_{jt}^{wkm} \in \{0, 1\}, \qquad j \in L, w \in W, k \in K, m \in M, t \in T, \tag{17}$$

$$y_{jt}^{wkm} = 0, \qquad j \in D, k \in K \setminus \{k'\}, m \in M, t \in T, \tag{18}$$

$$y_{jt}^{wk'm} = 0, \qquad j \in L \setminus D, m \in M, t \in T. \tag{19}$$

The objective function (1) is to minimize the total number of visits to locations. Constraints (2) are the inventory flow balance of each item in each location at each time period. Constraints (3) ensure that if any item is delivered to location j at period t by the work team w using vehicle k in its mth trip at time period t, then variable y_{jt}^{wkm} must be one. Constant B is a big-M constant. Constraints (4) guarantee the vehicle capacity and constraints (5) impose a storage capacity limit at each location. Constraints (6) assure that there is at most one delivery in each location per time period. Constraints (7) impose that the vehicle k can make the $(m + 1)$th trip at time period t if it already made its mth trip in that period. Constraints (8) ensure that a delivery is made to location j at time period t by using vehicle k in its mth trip

if the vehicle makes this trip. Constraints (9) assure that the mth trip of vehicle k is done at most by a work team. Constraints (10), (11) and (12) assure balanced distribution of the deliveries by the two work teams imposing that the difference between the number of trips can be at most Δ. Constraints (13) impose safety stocks and constraints (14) define the initial stock. Constraints (16)–(19) are the variables domain constraints.

To assure that the obtained weekly distribution plan will be repeated in further weeks, it is necessary to ensure that stock at the end of the time horizon be equal to the initial stock, that is, $\underline{S}_{ij,nT} = S_{ij}$.

3 Model Tightening

In this section we discuss the tightening of formulation, that is, the derivation of a formulation whose linear relaxation is closer to the convex hull of the feasible set. Such tighten formulations are solved, in general, faster than the original formulations through branch-and-cut based algorithms since they lead to smaller branching trees.

Following Agra et al. (2016a), we use the concept of net demand of item i in location j at time period t which is denoted by nd_{ijt} and represents the minimum amount of item i that must be delivered in location j at time period t taking into account the safety stock and the initial stock level. It can be computed as follows:

$$nd_{ijt} = \max\{0, \sum_{\ell=1}^{t} d_{ij\ell} + \underline{S}_{ijt} - S_{ij} - \sum_{\ell=1}^{t-1} nd_{ij\ell}\}. \tag{20}$$

The net demand is iteratively computed at each time period. At time period $t = 1$, if the initial inventory level is enough to cover the demand and the safety stock, then the net demand is zero, otherwise the net demand is the demand in period 1, d_{ij1}, plus the safety stock at the end of time period 1, $\underline{S}_{ij1}$, minus the initial inventory level. In the following periods, the net demand is computed as the accumulated net demand until period t, that is $\sum_{\ell=1}^{t} d_{ij\ell} + \underline{S}_{ijt} - S_{ij}$, minus the accumulated net demand until the previous time period, which is $\sum_{\ell=1}^{t-1} nd_{ij\ell}$.

With net demands we can compute the minimum upper bound on the delivery quantity at each location j at time period t which is given by $B_{jt} = \sum_{i \in N_j} \sum_{\ell=t}^{nT} nd_{ij\ell}$. Using B_{jt} it is possible to tighten inequalities (3) replacing constant B by B_{jt}, obtaining

$$\sum_{i \in N_j} x_{ijt}^{wkm} \leq B_{jt}\, y_{jt}^{wkm}, \qquad j \in L, w \in W, k \in K, m \in M, t \in T. \tag{21}$$

In order to further tighten the model, some valid inequalities are included being the first two adapted from Agra et al. (2016a).

A first family of valid inequalities can be derived by the disaggregation of inequalities (21), as follows:

$$x_{ijt}^{wkm} \leq \sum_{\ell=t}^{nT} nd_{ij\ell} y_{ij}^{wkm}, \qquad j \in L, i \in N_j, w \in W, k \in K, m \in M, t \in T. \quad (22)$$

As a large number of items is considered, introducing all such inequalities can make the model too large. Hence we follow the approach proposed in Agra et al. (2016a), by adding these inequalities only for a representative item for each location. For each location $j \in L$, it is considered as representative item, denoted by $ri(j)$, the one with highest total net demand, i.e. $ri(j) = \text{argmax}_{i \in N_j} \{ \sum_{t \in T} nd_{ijt} \}$.

The second family of valid inequalities states, for each $j \in L$, that if the volume of the accumulated demand during the period from t_1 to t_2 (which is $\sum_{i \in N_j} \sum_{t=t_1}^{t_2} c_i \, d_{ijt}$) is greater than the stock capacity V_j, then this demand cannot be fully met using only inventory and at least a delivery is necessary to the location j during this period, i.e.,

$$\sum_{w \in W} \sum_{k \in K} \sum_{m \in M} \sum_{t=t_1}^{t_2} y_{jt}^{wkm} \geq 1, \qquad j \in L. \quad (23)$$

These inequalities are added for all $1 \leq t_1 \leq t_2 \leq nT$ such that $\sum_{i \in N_j} \sum_{t=t_1}^{t_2} c_i \, d_{ijt} > V_j$ and $\sum_{i \in N_j} \sum_{t=t_1}^{t_2-1} c_i \, d_{ijt} \leq V_j$.

Furthermore, for each location j let $t(j)$ denote the first time period where the net demand is positive, that is, $t(j) = \min\{t \in T \mid \sum_{i \in N_j} \sum_{\ell=1}^{t-1} nd_{ij\ell} = 0 \ \wedge \ \sum_{i \in N_j} \sum_{\ell=1}^{t} nd_{ij\ell} > 0\}$. Then, until this time period at least a delivery is necessary and so the following inequalities are valid for MIIDH problem:

$$\sum_{w \in W} \sum_{k \in K} \sum_{m \in M} \sum_{\ell=1}^{t(j)} y_{j\ell}^{wkm} \geq 1, \qquad j \in L. \quad (24)$$

Notice that $t(j)$ can be computed prior to the model building as it depends only on the model data.

The last family of inequalities results from the vehicles capacity. Aggregating equalities (2) from time period 1 to t, give

$$s_{ij0} + \sum_{\ell=1}^{t} \sum_{w \in W} \sum_{k \in K} \sum_{m \in M} x_{ij\ell}^{wkm} = \sum_{\ell=1}^{t} d_{ij\ell} + s_{ijt}, \qquad i \in N, j \in L.$$

Using (13) and (14) it follows that

$$\sum_{\ell=1}^{t} \sum_{w\in W} \sum_{k\in K} \sum_{m\in M} x_{ij\ell}^{wkm} \geq \sum_{\ell=1}^{t} d_{ij\ell} + \underline{S}_{ijt} - S_{ij}, \qquad i \in N, j \in L.$$

Now, using nonnegativity on $x_{ij\ell}^{wkm}$ and the definition of net demand, we have

$$\sum_{\ell=1}^{t} \sum_{w\in W} \sum_{k\in K} \sum_{m\in M} x_{ij\ell}^{wkm} \geq \sum_{\ell=1}^{t} nd_{ij\ell}, \qquad i \in N, j \in L.$$

Finally, combining these inequalities with (4), the validity of the following inequalities holds

$$\sum_{\ell=1}^{t} \sum_{k\in K} \sum_{m\in M} C_k z_\ell^{km} \geq \sum_{j\in L} \sum_{i\in N_j} \sum_{\ell=1}^{t} c_i \, nd_{ij\ell}, \qquad t \in T. \tag{25}$$

These constraints force to choose the vehicles with enough volume capacity to transport the total net demand. These constraints can be written as $\sum_{k\in K} C_k \left(\sum_{\ell=1}^{t} \sum_{m\in M} z_\ell^{km}\right) \geq D_t$ where $D_t = \sum_{j\in L} \sum_{i\in N_j} \sum_{\ell=1}^{t} c_i \, nd_{ij\ell}$. These are knapsack constraints with nK integer variables Y_k where $Y_k = \sum_{\ell=1}^{t} \sum_{m\in M} z_\ell^{km}$. Inequalities for such sets $Y(t) = \{(Y_1, \ldots, Y_{nK}) \in \mathbb{Z}_+^{nK} : \sum_{k\in K} C_k Y_k \geq D_t\}$ were studied in Agra and Constantino (2007). Here we added all the facet defining inequalities for $Y(t)$.

4 Heuristic Scheme

As the MIIDH problem is a complex NP-hard problem since it includes as substructures several NP-hard problems (such as the multi-item capacitated lot-sizing problem; lot-sizing problems with inventory set-ups; knapsack problems; etc.), it can hardly be solved to optimality within a reasonable amount of time, when real size instances, with hundreds to few thousand of products, are considered as the ones we consider here. To circumvent this issue, we present a relax-and-fix based heuristic that uses the mathematical model. The heuristic splits the problem into three steps corresponding to three sequential sub-problems.

In the first sub-problem the goal is to define the number of vehicle trips per period and per vehicle type, that is, to define the value of variables z. To solve this sub-problem we consider model MIIDH tightened with valid inequalities (21)–(25) and with the following changes: variables y and x are relaxed and the objective function is changed to

$$\min \sum_{t\in T} \sum_{k\in K} \sum_{m\in M} z_t^{km}. \tag{26}$$

This model is denoted MIIDH-Z.

After solving this first problem a second sub-problem is solved to determine the value of the y variables. The second sub-problem, denoted by MIIDH-Y, considers the original objective function (1) and the integrality constraints (17). For this sub-problem, the solution obtained in the previous subproblem is used to fix the value of the z variables as well as the value of variables y that are null or close to one.

The third sub-problem, denoted by MIIDH-X, determines the value of the x variables. This subproblem considers the integrality constraints (16) and fixes the value of the y variables to their value in the best solution found. The heuristic scheme is given in Algorithm 1.

Algorithm 1 A hybrid heuristic scheme for the MIIDH problem.

1: Construct model MIIDH-Z: (26) s.t. (2)–(15), (18)–(25);
2: Solve model MIIDH-Z for α seconds and let $(\overline{y}, \overline{z})$ denote the vetor of the value of variables y and z in the best solution found;
3: Consider model MIIDH-Y: (1)–(15), (17)–(25);
4: Set $z_t^{km} = \overline{z}_t^{km}$ and $y_{jt}^{wkm} = 0$ if $\overline{y}_{jt}^{wkm} = 0$ and $y_{jt}^{wkm} = 1$ if $\overline{y}_{jt}^{wkm} \geq \beta$;
5: Solve MIIDH-Y for α seconds;
6: Construct model MIIDH-X: (1)–(25);
7: Fix variables z and y to their value in the best solution found in Step 5;
8: Solve model MIIDH-X to optimality.

In the computational tests we used $\alpha \in \{1800, 3600\}$ and $\beta = 0.6$.

5 Computational Results

This section reports computational results obtained with the model MIIDH described in Sect. 2, the model with the improvements described in Sect. 3, and the heuristic given in Algorithm 1.

The computational tests were performed using a processor Intel(R) Core(TM) i7-4500U CPU @ 1.8 GHz with 16GB of RAM and using the software FICO Xpress (2016) (Xpress Release May 2018 with Xpress-Optimizer 33.01.02 and Xpress-Mosel 4.8.3).

The proposed methodologies were applied to 12 generated instances with $n = 2000$, $nL = 15$, $nW = 2$, $nK = 3$ with $k' = 3$, $D = \{1, 2\}$, $nM = 8$. These values resemble the dimensions of the real problem. We consider $nT = 5$ time periods as we assume that there are no deliveries on weekends. The first four periods correspond to a single week day, from Monday to Thursday and the last period, Friday, corresponds to three consuming days, Friday, Saturday and Sunday. We assume $\Delta = 2$.

The demands in each ward were randomly generated following the real patterns: each ward requires about 18% of the items, and approximately 1.1% of them are required in all the nursing wards.

At each ward, the demand on the first four periods is randomly generated between 0 and 60 and in the fifth period can be up to 180. The safety stock $\underline{S}_{ijt}$ is obtained by rounding up the average demand by period.

For the initial stock level S_{ij} two cases are considered: in case S1 the S_{ij} is approximately 150% of the average demand by period and in case S2 the S_{ij} is approximately 200% of that value.

The space c_i occupied by each item i is a random number between 1 and 5 and the stock capacity for ward j, given by V_j, is a randomly generated number between 50 and 70% of the total demand's capacity at this nursing ward.

In respect to the vehicles capacity C_k it is considered that vehicle type 2 and type 3 has, respectively, twice and triple of the capacity of vehicle type 1. Furthermore, two cases are considered: case C1, vehicle type 1 has 50% of the highest net demand's capacity per ward and per period and in case C2 it has 75% of this value.

For each situation three random instances are generated originating 12 instances. For example, instances 1S1C1, 2S1C1, 3S1C1 correspond to the three random instances in case S1 and C1 while 1S2C1, 2S2C1, 3S2C1 correspond to the three random instances to case S2 and C1. In average, these models have 7,230,752 variables and 119,500 constraints. The reduced presolved models have in average around 805,000 variables and 45,000 constraints.

Table 1 shows the obtained weekly delivery plan for instance 1C1S1 considering time limit $\alpha = 1800$ s. In the first column, named "t", is displayed the time period and in the correspondent rows the deliveries done by each work team w_1 or w_2, displayed in the second column named "W", are characterized by the car type used k_1, k_2 or k_3, displayed in the third column named "K" and the visited wards (locations) marked in the next 15 columns, named from "L_1" to "L_{15}".

Analysing the solution, we conclude that there are 45 delivers during the week, being four delivers in location L_7, only two delivers in location L_2 and for the remaining locations there are three delivers a week. The work team $w1$ performs 23 delivers while work team w_2 does 22 delivers.

If we increment the initial stock level, case C2, keeping all the other values the same, instance 1C2S1, in the obtained solution there is a reduction of the total number of deliveries for 41. With higher initial stock level, it is possible to ensure the demand for longer periods without deliveries. There are two delivers a week in locations 2, 6, 8, 13, and for the remaining locations there are three delivers per week.

Changes in vehicles capacity, case C1 or C2, do not cause an impact on the obtained solution due to the fact that the number of trips done by each vehicle is not optimized in the model and a heuristic approach is used to solve the problem. In this example, for instance 1C2S1 the objective value increases to 48 and in case 1C2S2 the objective value remains 41.

The computational results obtained for the 12 instances of the MIIDH problem are displayed in Table 2. The first column identifies the instance. The second and third columns, named LP and LP^+, give the lower bound obtained with the linear relaxation of model MIIDH and model MIIDH tightened with (21)–(25), respectively. The fourth column, named UB^+, gives the upper bound obtained with the tightened

Table 1 A weekly supply scheme for instance 1C1S1

			Wards (L)														
t	W	K	L_1	L_2	L_3	L_4	L_5	L_6	L_7	L_8	L_9	L_{10}	L_{11}	L_{12}	L_{13}	L_{14}	L_{15}
1	w_1	k_1													✓		
		k_1			✓												
		k_2															✓
		k_3	✓	✓													
	w_2	k_1									✓						
		k_1														✓	
		k_2					✓		✓								
		k_2				✓						✓					
		k_2						✓									
		k_2											✓				
		k_2								✓				✓			
3	w_1	k_1							✓								
		k_1								✓							
		k_2									✓						✓
		k_2						✓									
		k_2				✓											
	w_2	k_2													✓		
4	w_1	k_1							✓								
		k_2			✓		✓										
		k_2											✓				
		k_2												✓			
		k_3	✓														
	w_2	k_1										✓					
		k_2														✓	
5	w_1	k_2														✓	
		k_2			✓		✓										
		k_2											✓				
		k_3		✓													
		k_3	✓														
	w_2	k_1				✓			✓								
		k_1												✓			
		k_1									✓						
		k_2													✓		
		k_2								✓		✓					
		k_2						✓									✓

Table 2 Computational results

Instance	LP	LP^+	UB^+	$UB1$	$UB2$	*Time*	*Time-Z*	*Time-Y*	*Time-X*
1S1C1	0.8	30.2	–	44	44	4417	234	3951	232
2S1C1	0.9	30.2	–	45	45	2523	196	2099	228
3S1C1	0.9	30.2	–	45	45	4099	209	3589	301
1S1C2	0.8	30.2	62	43	42	3003	201	2501	305
2S1C2	0.9	30.2	45	47	45	2955	222	2497	236
3S1C2	0.9	30.2	–	44	44	2639	215	2167	257
1S2C1	0.8	30.2	–	46	46	5697	222	5147	328
2S2C1	0.9	30.1	–	41	41	3043	249	2492	302
3S2C1	0.9	30.1	–	44	41	2549	281	1963	305
1S2C2	0.8	30.2	–	45	45	4311	265	3804	242
2S2C2	0.9	30.1	–	46	46	2571	211	2121	239
3S2C2	0.9	30.1	–	44	44	12,307	238	11,764	305

model after 2000 s. A sign "−" means no feasible solution was found within the time limit. The last five columns give the information obtained with the heuristic. Columns $UB1$ and $UB2$ are the value of the best feasible solutions found with $\alpha = 1800$ and $\alpha = 3600$, respectively. Column *Time* gives the total running time, and the last three columns give the running times of each one of the three heuristic steps solving models MIIDH-Z, MIIDH-Y and MIIDH-X, for the case $\alpha = 1800$. For the case $\alpha = 3600$, the total running time is around 1800 s higher than the total time for $\alpha = 1800$ since the running times of solving models MIIDH-Z and MIIDH-X do not change significantly. All the computational times are given in seconds.

The results show that model MIIDH is weak in the sense that the linear relaxation gives poor lower bounds and that the improvements increase the lower bound significantly. However, the solver based on the improved model was not able to obtain always feasible solutions within the time limit. Moreover, the heuristic always provided better feasible solutions than those obtained by the solver based on the improved model. For the heuristic we can observe that the second step consumes most of the heuristic overall running time.

6 Conclusion

A multi-item inventory distribution problem occurring in the logistic operations of a hospital is considered, where a warehouse supplies a set of nursing wards with a wide variety set of items. The problem is modeled as mixed integer programming and the model is then strengthened by tightening the big-M constraints and adding valid inequalities. As the strengthened model cannot be solved to optimality within reasonable amount of time, a matheuristic that uses the improved model is proposed.

This heuristic fixes the value of the integer variables in three steps. In the first step the number of trips per time period and vehicle type is defined. Then, each trip is assigned to a working team and to a set of locations to visit. Finally, the amount of items delivered to each location in each trip is determined. The heuristic provides reasonable solutions, in general, in less than one hour.

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A Multiple-Criteria Decision Sorting Model for Pharmaceutical Suppliers Classification Under Multiple Uncertainties

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Abstract Selecting and evaluating suppliers is a major supply-chain concern for any company. It is even more crucial in pharmaceutical industries since delivering the right product to the right people at the right time requires specific conditions of storage and strict rules regarding expiry dates. In this context, supplier selection seems to be a complex task that involves a variety of conflicting criteria such as quality, performance history, guarantee policies, productive capacity, price and time. Therefore, many Multiple-criteria Decision Making (MCDM) methods have been applied to solve the supplier selection problem. However, most methods address only the ranking and choice problems. Besides, evaluating suppliers with regard to each criterion involves the presence of uncertainties and heterogeneous information, i.e., qualitative and quantitative data. The objective of this work is to propose a sorting MCDM model for pharmaceutical supplier selection under multiple uncertainties and heterogeneous information. The proposed model is based on an integration of the FlowSort and SMAA methods and Fuzzy theory. It allows pharmaceutical companies to develop a rating system to classify suppliers into categories, as actual and potential suppliers, in a context with multiple uncertainties and heterogeneous data information.

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1 Introduction

As defined by Simoens et al. (2015), drug shortage is a shortcoming in the supply of a medicinal product that affects the patients ability to access the required treatment in due time. When a drug cannot be delivered at the moment of demand, every stakeholder in the health-care system may be affected (Simoens et al. 2015). Hospitals and health systems are financially affected, with estimated losses of approximately hundreds of millions of dollars annually across the United States, for example (Morrissey 2012). Clinically, patients are harmed by the lack of drugs or by the use of inferior alternative drugs, which results in ineffective treatments and even deaths (Simoens et al. 2015). DS has also received more attention recently due to an increase in the number of occurrences of the problem over the last ten years in wealthy nations such as Canada (2010), the USA (2011) and European countries (2013).

There are different causes for the occurrence of DS. For instance, a drug disruption may occur due to a transportation problem during distribution or because hospitals or physician office staff have forgotten to order a product or because buyers may have underestimated how much product was needed. Those situations may create regional supply issues. On the other hand, if some problem occurs at the manufacturer level, it will often likely result in a problem on a national level, particularly if the manufacturer is the sole source for the medication or has a large share of the market (Fox et al. 2014). Therefore, despite the risks for supply disruption during the market distribution phase, DS's have most commonly been linked to drug-manufacturing-process problems (Drug Shortages 2017; Fox et al. 2014), including the phase of raw material supply Drug Shortages (2017). In such circumstances, drug manufacturing companies have to devote a greater amount of attention and resources to the selection and evaluation process of raw-material suppliers (Drug Shortages 2017).

Supplier selection and evaluation (SSE) is a decision-making process to identify (in the case of selection) or assess (in the case of evaluation) suppliers with the highest potential for meeting the manufacturers need consistently and at an acceptable overall performance (citacao). Different decision-making techniques have been applied to support SSE. The study conducted by Weber et al. (1991) reviewed 74 articles from 1966 to 1991 and identified the most widely applied methods and the most important variables (criteria) that may be used to select suppliers. That study presented three types of approaches applied to supplier selection: linear weighting models, mathematical programming models and statistical/probabilistic approaches. By far, the most utilized approach has been linear weighting models. The study proposed by Chai et al. (2013) also presented a literature review on the application of decision-making techniques in supplier selection and identified that three different types of techniques have been applied: mathematical programming models, artificial intelligence techniques and multiple-criteria decision making (MCDM) methods. Among them, MCDM methods are the ones most applied, with emphasis on the following methods: AHP (Analytic Hierarchy Process) Saaty (1990), PROMETHEE (Preference Ranking Organization Method for Enrichment Evaluations) Brans et al. (1986); Behzadian et al. (2010), ELECTRE (ELimination Et Choix Traduisant la

REalit) Roy (1991); Govindan and Jepsen (2016), and TOPSIS (Technique for Order of Preference by Similarity to Ideal Solution) Chen and Hwang (1992). Moreover, a research trend identified in this study addresses the SSE problem by considering the involvement of different uncertain data, not only deterministic ones. For those cases, different integrated approaches such as probability-theory and fuzzy-theory integration have been proposed in the literature.

More recently, the study conducted by Govindan et al. (2015) presented an update literature review on green supplier selection based on papers published between 1997 and 2011. The authors identified that MCDM is the most frequently applied technique and also listed the most widely used evaluation criteria. Simi et al. (2017) also conducted a literature review on supplier selection and evaluation, identifying that SSE is usually an MCDM problem under uncertainty.

In all of these studies, the vast majority of the problems are related to supplier selection (and not evaluation) and the most often techniques applied to address those problems are ranking methods. Ranking methods usually make a comparison among suppliers and give as output a ranking of the suppliers from best to worst. In the case of a generic drug company, a greater number of suppliers may be available to supply basic ingredients, since these companies work with "off-patent" drugs. Thus, ranking the suppliers may make sense. However, due to lack of supplier options (since most raw materials and ingredients used by these industries are patented), this may not be the case for a brand-name pharmaceutical company. For those situations, supplier selection may not make sense, but it makes sense to conduct a constant evaluation of suppliers in order to anticipate possible drug-shortage issues and propose improvement actions. In that case, sorting methods are more suitable than ranking methods (Araz and Ozkarahan 2007). Sorting methods assign alternatives (suppliers) into categories ordered and predefined by reference values (Zopounidis and Doumpos 2002). While a ranking method says only which the best supplier is when compared with others, a sorting method characterizes each supplier based on reference values. Therefore, the supplier ranked as the best by a ranking method may be not good enough when compared to the reference values, and only sorting methods are capable of providing this information.

Although there are several MCDM sorting methods in the literature, few studies applied them to evaluate suppliers. The study developed by Araz and Ozkarahan (2007) applies the PROMSORT method to evaluate suppliers by assessing 22 suppliers based on 10 criteria and dividing them into 4 categories: strategic partner, promising supplier, competitive supplier and pruning supplier. The PROMSORT method (Araz and Ozkarahan 2007) is an extension of the PROMETHEE method for sorting problems. The study presented by Guarnieri and De Almeida (2016) also proposed a model to evaluate suppliers in which the suppliers are classified into categories of collaboration applying the ELECTRE-TRI sorting method.

However, these studies have two limitations. First, the sorting MCDM methods used in the supplier evaluation studies do not consider the presence of multiple uncertain data, although addressing SSE problems considering the involvement of uncertainty is needed. Second, none of these studies has focused on the evaluation of supplier risk for DS prevention. Therefore, we propose in this study a

supplier-risk-evaluation model for DS prevention based on a sorting MCDM method under multiple uncertain data, which includes evaluating and sorting the suppliers into categories of DS occurrence risk according to their performance over a set of 12 criteria.

The rest of this chapter is organized as follows. In Sect. 2, a brief literature review on the set of criteria used in SSE and on DS prevention; in Sect. 3 the proposed supplier risk evaluation model for DS prevention is presented; Sect. 4 presents a numerical application of the proposed method. Finally, Sect. 5 outlines some conclusions.

2 Literature Review

In this section, we present a brief literature review on sets of criteria used in SSE and best practices for DS prevention. We also presented a literature review on sorting MCDM methods. To introduce the SMAA-Fuzzy-FlowSort (SMAA-FFS) method, method used in this paper, we first introduced the FlowSort, Fuzzy-FlowSort and SMAA methods that are the bases of SMAA-FFS.

2.1 Set of Criteria in SSE

The definition of a set of criteria is an important phase in the application of a MCDM method (citacao). Some studies have been developed with the purpose of identifying criteria that should be considered in an SEE problem, such as the studies presented by Weber et al. (1991), Guarnieri and De Almeida (2016) and Ertay et al. (2011). In all these studies, the criteria are generally relating to quality, reliability, delivery, responsiveness, flexibility, productive capacity, price, technological capacity, environment, communication, guarantee policies and company financial stability. As proposed by Ertay et al. (2011), the set of criteria may also depend on the decision problem and on the particulars of the companies involved. In this study, the DMs involved selected the twenty criteria used from a list of 101 criteria, initially taken from the literature.

2.2 Preventing Drug Shortage

Several factors related to raw material supply for drug manufacturing may result in DS occurrences. Different studies have identified these factors, and most of the literature found consists of country reports. Nevertheless, the identified factors are quite similar in all studies. The main issues related to raw-material supply are quality problems in the raw materials (Schwartzberg et al. 2017; Drug Shortages 2017), manufacturing of raw materials by a sole supplier (Schwartzberg et al. 2017; Drug Shortages 2017),

unavailability of raw materials (Ventola 2011), discontinuing the manufacturing of a raw material (Schwartzberg et al. 2017; Drug Shortages 2017; Fox et al. 2014), poor communication between supplier and manufacturer (Schwartzberg et al. 2017; Drug Shortages 2017), political upheaval and natural disasters in the origin country of the raw material (Drug Shortages 2017) and suppliers who do not comply with the regulatory requirements of the country (Drug Shortages 2017).

The studies Schwartzberg et al. (2017), Drug Shortages (2017), Fox et al. (2014) also proposed some strategic actions related to the supply of raw materials that, when implemented, have the potential to target manufacturing-related risks and reduce the incidence of or prevent DS such as: (1) conduct risk analysis of suppliers; (2) have alternative suppliers; (3) perform more frequent and unannounced on-site audits and inspections at sub-contracted facilities; (4) define comprehensive quality requirements in sub-contracts; (5) improve communication between suppliers and the pharmaceutical industry; (6) employ supply chain analytic to detect issues in the system before they become a supply problems; (7) continuous evaluation of the suppliers; (8) develop analysis to detect issues before they become a supply problem; (9) develop and employ a process to monitor suppliers.

2.3 Sorting MCDM Methods

In a sorting MCDM problem, alternatives are assigned to pre-defined order categories (Zopounidis and Doumpos 2002). Different MCDM sorting methods based on different approaches such as Multiple Attribute Utility Theory (MAUT) and outranking relation have been proposed. Under the MAUT approach we have the UTADIS method (Zopounidis and Doumpos 1999). Under the outranking approach we have ELECTRE-TRI (Yu 1992), based on the ELECTRE methodology, its extensions ELECTRE TRI-C (Almeida-Dias et al. 2010) and ELECTRE TRi-nC (Almeida-Dias et al. 2012), and also methods based on the PROMETHEE methodology (Behzadian et al. 2010). Most of methods under the PROMETHEE methodology such as FlowSort (Nemery and Lamboray 2008) require less parameters than other MCDM methods, such as ELECTRE-TRI (Govindan and Jepsen 2016).

The PROMETHEE-TRI method proposed by Figueira et al. (2004) was the first developed sorting method based on the PROMETHEE methodology, providing incompletely ordered categories. Then, Araz and Ozkarahan (2007) proposed the PROMSORT method for completely ordered categories. However, in PROMSORT the attributions of the alternatives are not independent. Overcoming PROMETHEE-TRI and PROMSORT limitations at the same time, Nemery and Lamboray (2008) proposed the FlowSort method. FlowSort is a multi-criteria sorting method also based on the PROMETHEE methodology, for independent assignments and completely ordered categories.

The FlowSort method requires different input information, which can be divided into evaluation of alternatives and preference parameters (criteria weights, thresholds, and category profiles). More than that, FlowSort requires that all such input

information be defined by quantitative and crisp values, although this is difficult, if not impossible, in most of the real-life decision-making problems (Durbach and Stewart 2012; Ben Amor et al. 2015). Indeed, uncertainties and imprecision or in more general terms, information imperfections, are often present in the input data in the form of interval data, stochastic data, linguistic variables or partial information. It can also be the case when no information is available.

Two important research papers were carried out on the use of information imperfection in FlowSort. Campos et al. (2015) proposed the Fuzzy-FlowSort method integrating Fuzzy Sets theory into FlowSort. In Fuzzy-FlowSort, the input data can be defined by interval data or linguistic variables and they are represented by triangular fuzzy numbers. Janssen and Nemery (2013) integrated the Interval theory with FlowSort. The resulting method accepts interval data as input information, which are modeled by means of intervals (Janssen and Nemery 2013).

Although these extensions of FlowSort being able to model interval data and linguistic variables, they have the limitation of not allowing stochastic input data. Another limitation is their inability to deal with the criteria weights elicitation process, which is concerned to define the criteria weights from incomplete decision-makers (DMs) preferences. This is an important limitation since the weight elicitation process is one of the most difficult problems and one of the most relevant questions in the MCDM field (Vetschera 2017).

To overcome these limitation, Pelissari et al. (2018) proposed the SMAA-Fuzzy-FlowSort (SMAA-FFS). SMAA-FFS is a sorting method capable of modeling multiple uncertain data, resulting from the integration of the Fuzzy-FlowSort method (Campos et al. 2015; Nemery 2015) and the SMAA (Stochastic Multicriteria Acceptability Analysis) methodology (Lahdelma et al. 2002).

2.4 FlowSort Method

FlowSort is a sorting method based on the PROMETHEE methodology for assigning alternatives to K predefined ordered categories $C_1, C_2, \ldots, C_k$, in which C_1 is the best category and C_k the worst one. The categories are defined by a lower and upper limiting profiles. Let $R = \{r_1, \ldots, r_{k+1}\}$ be the set of reference profiles that delimited the k categories, in which r_1 and r_{k+1} are the best and the worst reference profiles, respectively. The evaluation of alternatives also are delimited by r_1 and r_{k+1}. Since the categories are completely ordered, each reference profile is preferred to the successive ones, i.e., the condition given by Eq. (1)

$$\text{Condition: } r_1 \succ r_2 \succ \cdots \succ r_k \succ r_{k+1}. \tag{1}$$

Let us define for any alternative a_i the set $R_i = R \cup a_i, i = 1, \ldots, m$. Considering $x, y \in R_i$, positive, negative, and net flows are computed by using the PROMETHEE methodology and defined, respectively by $\phi^+_{R_i}(x) = \frac{1}{|R_i|-1} \sum_{y \in R_i} \pi(x, y)$, $\phi^-_{R_i}(x) = \frac{1}{|R_i|-1} \sum_{y \in R_i} \pi(y, x)$, and $\phi_{R_i}(x) = \phi^+_{R_i}(x) - \phi^-_{R_i}(x)$. To assign an alternative to

a specific category, its positive and negative flows are compared with the positive and negative flows related with the reference profiles, based on the following rules respectively: if $\phi^+_{R_i}(r_h) \geq \phi^+_{R_i}(a_i) > \phi^+_{R_i}(r_{h+1})$, then $C_{\phi^+}(a_i) = C_h$, if $\phi^-_{R_i}(r_h) < \phi^-_{R_i}(a_i) \leq \phi^-_{R_i}(r_{h+1})$, then $C_{\phi^-}(a_i) = C_h$. In order to assign each alternative to exactly one category, the following rule based on net flow can be used: if $\phi_{R_i}(r_h) \geq \phi_{R_i}(a_i) > \phi_{R_i}(r_{h+1})$, then $C_{\phi}(a_i) = C_h$.

2.5 The Fuzzy-FlowSort Method

Fuzzy-FlowSort is a sorting method resulting from the integration of FlowSort and Fuzzy Theory (Campos et al. 2015). It allows FlowSort to be applied when evaluation of alternatives, criteria weights or FlowSort parameters are defined by interval data or linguistic variables.

The Fuzzy-FlowSort method consists representing the evaluations of the alternatives, criteria weights or other FlowSort parameters using triangular fuzzy numbers. A triangular fuzzy number is represented by $\widetilde{M} = (m; \alpha; \beta)_{LR}$, where m is the mean value of the fuzzy number $\widetilde{M}$ while α and β are its left and right boundary values, respectively.

Similarly to the set R defined in the traditional FlowSort method, let $R_i = \{R \cup \{a_i\}\}$ be the set of reference profiles union with the alternative a_i, $i = 1, \ldots, m$. Let $g_j(x)$ be defined as $g_j(x) = (m; \alpha; \beta)_{LR}$ and $g_j(y) = (n; \gamma; \delta)_{LR}$ and w a scalar number. The global fuzzy preference degree function for each pair $(x, y) \in R_i$ can thus be computed by $\widetilde{\pi}(x, y) = \sum_{j=1}^{m} w_j \ominus \widetilde{P}_j(\widetilde{g_j}(x) \ominus \widetilde{g_j}(y))$.

Each global fuzzy preference degree $\widetilde{\pi}(x, y)$ has to be then defuzzified, which reduces the fuzzy preference degree into a crisp number. For that, the authors used the Yagers operator. Therefore, given a triangular fuzzy number $\widetilde{M} = (m; \alpha; \beta)_{LR}$, its defuzzification, denoted by M^{Def}, is $M^{Def} = m + \frac{\beta+\alpha}{3}$.

Using the crisp preference degrees functions obtained from the defuzzification, positive, negative and net fuzzy flows of each element x of R_i are computed as in traditional FlowSort and already presented in Sect. 2.4. Finally, these crisp flows values may be used to assign an alternative a_i to a category following the traditional FlowSort assignment rules established in the equations also presented in Sect. 2.4.

2.6 Stochastic Multicriteria Acceptability Analysis (SMAA)

Stochastic Multicriteria Acceptability Analysis (SMAA) was initially proposed by Lahdelma et al. (1998) for MCDM problems and arose from the need to make decisions when criteria weights are not available or are not explicit. The idea of the original SMAA method is to find out the most acceptable alternative(s). Lahdelma and Salminen (2001) proposed then the SMAA-2 method, an extension of the original SMAA that gives probabilities for an alternative to obtain a certain rank.

The first important characteristic of SMAA methods is that it allows the use of random variables as input data, requiring only the definition of their probability distribution function. Consequently, interval data can also be used, since they can be modeled using uniform probability distributions. Its second important characteristic is the non-requirement of the criteria weights, and its ability to deal with the weights elicitation process. Another important point is that SMAA can be considered a flexible and extensible structure since different aggregation method can be used in combination with it. Given this characteristic, several methods based on SMAA have been proposed for different problem situations. Consequently, the concept of SMAA family of methods has arisen referring to the set of different methods based on the SMAA method.

Depending on the method integrated with SMAA and the problem configuration, SMAA calculates statistically the probability of each alternative being most preferred, or its probability of dominating another alternative, or being placed in a particular ordering position or assigned to a certain category (see, for example, Kadziński and Tervonen 2013). Thus, different descriptive statistics are provided by different SMAA methods. The computation of these statistics is performed using Monte Carlo simulation, where the values of the random variables are sampled from the probability distributions established for them.

Lahdelma and Salminen (2010) proposed the first SMAA sorting method, called SMAA-OC. The only output of SMAA-OC is the category acceptability index, which indicates the probability of an alternative being classified in each category. In SMAA-OC, K ordered categories $C_1, \ldots, C_K$ are defined, where C_1 is the best category and C_k is the worst. To separate the categories, $K + 1$ boundary profiles are defined. The values of upper and lower profiles are deterministic values and denoted by y_{hj}, $h = 1, \ldots, k$, $j = 1, \ldots, n$. The category acceptability index C_i^k indicates, for simultaneously the uncertainty in alternative evaluation and weights, the probability of alternative a_i being classified in category C_k.

2.7 SMAA-Fuzzy-FlowSort

SMAA-Fuzzy-FlowSort (SMAA-FFS) (Pelissari et al. 2018) is a sorting method resulting from the integration of the Fuzzy-FlowSort method (Campos et al. 2015; Nemery 2015) and the SMAA (Stochastic Multicriteria Acceptability Analysis) methodology (Lahdelma et al. 2002). The required SMAA-FFS input data are the evaluation of alternatives and some preference parameters, such as, thresholds (used in the preference function) and limiting profiles (used to define the categories). Criteria weights are not a requirement and they can be total or partially missing.

Different types of input data and different scales can be used in SMAA-FFS, as described below:

- Evaluations of the alternatives: can be defined by both historical data and DMs preferences. Deterministic data, interval data, stochastic data and ordinal linguistic

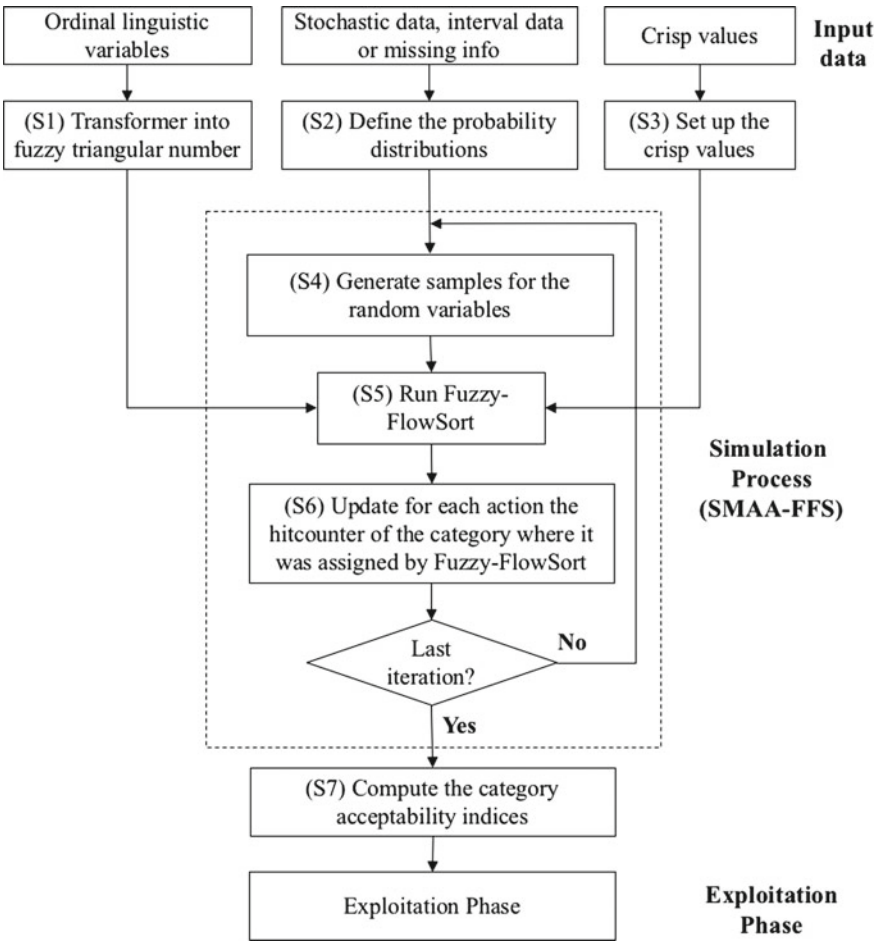

Fig. 1 The SMAA-FFS algorithm scheme

variables are allowed. The scale used in the evaluation of alternatives is directly related to the criterion scale.

- Criteria weights: shall be defined by the DM or may be missing. Deterministic data, interval data, ordinal data, stochastic data, incomplete data or wholly missing information are allowed;
- Thresholds and category limiting profiles: shall be defined by the DM. Deterministic data, interval data, stochastic data, linguistic variables are allowed. Ordinal data can not be used to define the parameters of the model, since an order of importance is already natural and required in these cases.

The SMAA-FFS method can be divided into four phases, as presented in Fig. 1: (i) definition of the input data (ii) simulation process (iii) category acceptability index calculation and (iv) exploitation phase.

Table 1 Triangular fuzzy number representation for linguistic variables of five terms

Linguistic variables		Triangular fuzzy numbers	
		With overlapping	Non overlapping
Very Low	Very Poor	(0, 0, 0.3)	0
Low	Poor	(0.3, 0.3, 0.15)	(0.3, 0.1, 0.1)
Medium	Medium	(0.45,0.15, 0.3)	(0.5, 0.1, 0.1)
High	Good	(0.75, 0.3, 0.25)	(0.7, 0.1, 0.1)
Very High	Very Good	(1, 0.25, 0)	1

In the first phase, we have to define the input data and the scales that will be used for their measurement. Input data defined as linguistic terms have to be transformed into triangular fuzzy numbers (step 1). To achieve that we can use, for instance, relationships as shown in Table 1 which relate five linguistic terms with triangular fuzzy number representations. For limiting profiles defined by linguistic terms, differently from the evaluation of the alternatives, the triangular fuzzy numbers used cannot overlap. For input data defined as random variables, we have to choose their probability distribution (step 2). If crisp/deterministic values are present, they have to be set (step 3).

The second phase is the simulation process. For the input data defined as random variables, random values are generated using their probability distribution (step 4). Then, the Fuzzy-FlowSort method is applied (step 5) using the triangular fuzzy numbers (set in step 2), the crisp values (set up in step 3), and the random values generated (in step 4). The result is the assignment of each alternative to the pre-defined categories. With this result, the hitcounter in whose category each alternative was assigned by Fuzzy-FlowSort is updated (step 6). This process should be repeated as many times as iterations are defined. The number of iterations indicated is 10,000 (ten thousand), as presented by Tervonen and Lahdelma (2007).

In the third phase, after the last iteration and once the simulation process is finished, the category acceptability index is calculated for all pairs of alternatives and categories (step 7). The calculation of the category acceptability indices through simulation is the number of times that the alternative was assigned to that category (hitcounter) divided by the number of iterations.

The last phase is the exploitation phase, in which DMs use the category acceptability indices to make their decision regarding the final assignment. The final assignment can be made in different ways as proposed by Lahdelma and Salminen (2010): (i) DMs may decide that the current information is not accurate enough to reliably assign the alternatives to categories and, therefore, new input data have to be collected and the method has to be applied again; (ii) DMs can accept the result that some alternatives are classified into multiple categories; or (iii) DMs may classify alternatives based on their category probability distributions. DMs may assign an alternative to a category whose probability exceeds some threshold, for instance 50% or another value between 50 and 100%.

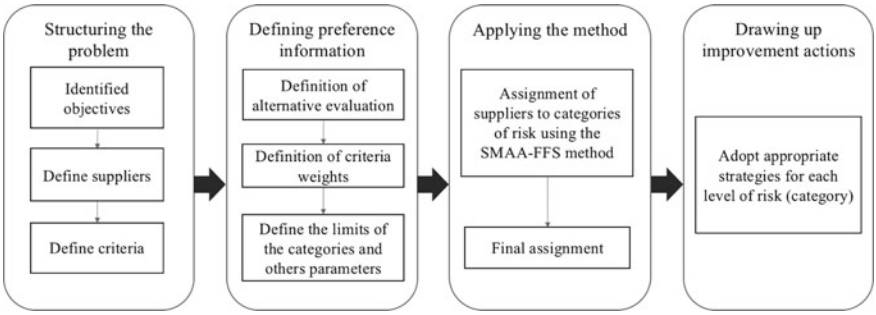

Fig. 2 Decision sorting model for pharmaceutical supplier risk evaluation

3 Supplier Risk Evaluation Model for Drug Shortage Prevention

In this section we present the suppliers risk evaluation model for DS prevention. As the modeling process here follows the MCDM approach, the proposed method is based on a generic MCDM decision-making process as the ones proposed by Ertay et al. (2011) and Guarnieri and De Almeida (2016). This model intends directly or indirectly to meet four (4) of the ten (10) best practices related to supply chain management for drug prevention. The proposed model is presented in Fig. 2, and its phases are discussed in the follows sections.

3.1 Phase 1: Structuring the Problem

First, it is necessary to identify the goals of the decision-making process. In our model, the main purpose is to prevent DS problems. Given this requirement, the pharmaceutical industry must work toward fulfilling the following key objectives in supply management:

- avoiding delays in product delivery
- improving delivery, quality and cost performances of the product
- developing strategic relationships with suppliers
- identifying alternative suppliers.

The second step is to list the suppliers to be evaluated. Then, the set of criteria has to be defined. We propose here a set of twelve (12) criteria in order to meet the vital objectives. This set is composed of the criteria most frequently used in SSE (Sect. 2.1) and some criteria related to the best practices for DS prevention (Sect. 2.2). The set of twelve (12) criteria is presented in Table 2.

Table 2 Set of criteria

Criterion related to	Criterion description	Best type of data
Delivery performance	g_1: % orders received complete	Number of orders received completed divided by the total numbers of orders received or made—(%) Binomial distribution
	g_2: % orders received on time to required date	Number of orders received on time by required date divided by the total numbers of orders received or made—(%) Binomial distribution
	g_3: Incoming material quality control	Number of approved lots/ orders in the quality control divided by the number of lots/orders inspected—(%) Binomial distribution
	g_4: % orders received defect free	Number of orders received defect free divided by the total numbers of orders received—(%) Binomial distribution
Responsiveness	g_5: Order fulfillment lead time	Normal, exponential or other distributions that fit well to lead time data
Financial	g_6: Price	Deterministic value (by unit, for instance) or normal distribution if there is a variety related to this data
Industry	g_7: Financial stability/ strength	Linguistic terms, unless the pharmaceutical company has a index to represent this information (which is not common)
	g_8: Communication	Linguistic terms, unless the pharmaceutical company has a index to represent this information (which is not common)
	g_9: Stability of source country	Linguistic terms, unless the pharmaceutical company has a index to represent this information (which is not common)
Assets/infrastructure	g_{10}: Quality performance/certifications	Linguistic terms, unless it makes sense to have a index to represent this information (such as % of certifications from a total of certifications required)
	g_{11}: Manufacturing/process capabilities	Deterministic value (process capability index)
	g_{12}: Level of technology	Linguistic terms, unless the pharmaceutical company has a index to represent this information (which is not common)

3.2 Phase 2: Defining Preference Information

After structuring the problem, the next step is carrying out the evaluation of alternatives (referred to in MCDM as intra-criterion evaluation), which consists of evaluating the performance of each supplier under each criterion. This evaluation can be defined by both historical data and DMs preferences, and using different type of uncertain data such as interval data, stochastic data (such as random variables defined by a probability distribution) or linguistic terms ("good," "medium" or "bad").

The next step is to define the criteria weights (also called inter-criterion evaluation), which consists in defining the relative importance of each criterion. The MCDM method used here, SMAA-FFS (presented in Sect. 3.3), does not require deterministic criteria weights as traditional MCDM methods. In addition to deterministic criteria weights, SMAA-FFS can be applied with ordinal weight information and even with no criteria weight information. Using multiple types of uncertain data for evaluations and criteria weighs is possible only because the sorting MCDM method here proposed (in Sect. 3.3) is suitable for these situations.

Next, we need to define the categories of risk to which suppliers are assigned. Each category represents a level of risk and gives information of how suppliers should be treated based on their risk levels. We suggested four categories of risk, similar to those proposed by Araz (2007) and Ertay et al. (2011):

- Category 1 (C_1): Very low risk—suppliers for strategic partnerships (best category)
- Category 2 (C_2): Low risk—promising supplier
- Category 3 (C_3): Medium risk—suppliers for situations of need
- Category 4 (C_4): High risk—suppliers to be pruned (worst category).

To characterize the four categories, DM has to defined limiting reference profiles which represent the minimum value an alternative need to achieve on each criterion for belonging to the category. For k categories, a set of $k + 1$ limiting profiles needs to be defined. Therefore, in this application, as we have four (4) categories, five (5) limiting profiles need to be defined for each criterion of our model. Limiting profiles may be defined in order to allow an effective targeting of the improvement of the actions required depending on the final attribution obtained. Directions for improvement actions are discussed in section The limiting profiles may be defined in order to enable an effective targeting of the actions required for improvement, depending on the final assignment obtained. Directions about the actions required for improvement are discussed in Sect. 3.4.

3.3 Phase 3: Modelling—The Sorting SMAA-Fuzzy-FlowSort Method

In this phase, a sorting MCDM method is applied in order to assign each supplier to categories of risk. Although there are some MCDM sorting methods capable of modeling uncertain data such as the Fuzzy-FlowSort method (Campos et al. 2015) to

model linguistic terms, the Interval-FlowSort (Janssen and Nemery 2013) to model interval data, and SMAA-TRI (Tervonen et al. 2009) to model stochastic data and to deal with incomplete or totally missing criteria weight information, none of them is able to model multiple types of uncertain data at the same time. Therefore, we proposed here the use of SMAA-Fuzzy-FlowSort (SMAA-FFS) following its steps presented in Sect. 2.6.

3.4 Phase 4: Drawing Up Action Plan

The final assignment of the supplier to the categories can drive DMs to define action plans, adopting appropriate strategies for each level of risk. For example, suppliers assigned to category 1 should be prioritized in relation to other suppliers, and strategic partnerships should be developed with them. Suppliers assigned to category 2 may also be used, but improvement plans w to reduce the risks associated with them should be implemented. These suppliers, before or after improvements are implemented, may be considered as alternative suppliers.

Suppliers assigned to category 3 should be used with caution and only in extreme cases of need when suppliers of category 1 or 2 are unavailable. If the pharmaceutical industry already has partnerships with these suppliers, improvements should be applied to reduce their risks in such a way that these suppliers are assigned to classes 1 or 2 in future analysis. Suppliers assigned to category 4 should be excluded as potential suppliers. If the pharmaceutical industry already has partnerships with these suppliers, these partnerships must be discontinued.

4 Case Study

In this section, the model proposed is applied to a numerical example, with the aim of showing its applicability. The numerical example is based on and adapted from the application presented by Ertay et al. (2011) and concerns an evaluation of domestic suppliers of packaging materials of a multinational pharmaceutical company.

Following the proposed model presented in Sect. 3, in the first phase (structuring the problem) we define twelve (12) suppliers that are evaluated using the set of criteria defined in Table 2, except the criterion g_9 because all of these suppliers are domestic suppliers. In the second phase we define the preference information. Table 4 shows the evaluation of the twelve (12) suppliers with regard to each criterion, and Table 5 the five limiting profiles. For the linguistic terms, we used the triangular fuzzy numbers presented in Table 1. SMAA-FFS does not require deterministic criteria weights and accepts a weights importance order that is shown in Table 3 together with the preference and indifference threshold parameters required by the SMAA-FFS method. In this example preference and indifference threshold are equal to zero (0) for all criteria for simplification. However, interval or stochastic data can also be

Table 3 Order of importance of the criteria, thresholds values, and criteria directions

Criterion	g_1	g_2	g_3	g_4	g_5	g_6	g_7	g_8	g_{10}	g_{11}	g_{12}
Importance order	3	2	6	6	1	7	5	4	6	8	9
Preference threshold	0	0	0	0	0	0	0	0	0	0	0
Indifference threshold	0	0	0	0	0	0	0	0	0	0	0
Type of data	BinD	BinD	BinD	BinD	NormD	Crisp	Qual	Qual	Qual	Crisp	Qual
Criterion direction	Max	Max	Max	Max	Min	Min	Max	Max	Max	Max	Max

BinD—Binomial probability distribution; NormD—Normal probability distribution; Qual—Qualitative

Table 4 Evaluation of alternatives

Suppliers	g_1	g_2	g_3	g_4	g_5	g_6	g_7	g_9	g_{10}	g_{11}	g_{12}
S1	95	95	95	95	N(52.6, 4)	0.20	High	High	Very good	1.2	Very good
S2	100	100	100	100	N(50, 2)	0.18	Very High	High	Medium	1.4	Good
S3	90	90	90	90	N(52, 3)	0.20	Medium	High	Very good	1	Good
S4	100	70	80	90	N(62.5, 6)	0.19	Medium	Very High	Very good	1.1	Medium
S5	80	50	80	80	N(100, 5)	0.21	Medium	Very High	Good	1.2	Medium
S6	100	100	90	90	N(50, 2)	0.20	High	Very High	Very good	1.3	Medium
S7	100	90	80	90	N(55.5, 3)	0.20	High	Very High	Very good	1.4	Medium
S8	90	90	90	90	N(55.3, 3.8)	0.22	Medium	High	Good	1.1	Good
S9	50	45	45	45	N(100, 3)	0.23	Very Low	High	Good	1	Good
S10	95	85	80	80	N(55.5, 3)	0.15	Medium	High	Very good	1.3	Good
S11	100	95	95	95	N(55.5, 3.6)	0.19	High	High	Medium	1.1	Good
S12	100	80	80	80	N(62.5, 1)	0.18	High	Very High	Medium	1.3	Medium

used as discussed in Sect. 3.3. In Table 3 we also show the type of data used for each criterion and indicate if the criterion has to be maximized or minimized.

As a third phase, we apply the SMAA-FFS model. Following the SMAA-FFS algorithm described in Sect. 3.3 and implemented in R language (2008), we obtained the category acceptability index that gives us a probabilistic assignment. The category acceptability index are presented in Table 6.

Analyzing category acceptability indices, we can see that suppliers S2 and S6 are assigned with 99% chance to category C1. Suppliers S1, S3, S7, S8, S10, S11 also

Table 5 Limiting profiles

Limiting profile	g_1	g_2	g_3	g_4	g_5	g_6	g_7	g_9	g_{10}	g_{11}	g_{12}
r_1	100	100	100	100	0	0	Very High	Very High	Very Good	2	Very Good
r_2	94	94	94	94	55	0.18	High	High	Good	1.33	Good
r_3	90	90	90	90	60	0.20	Medium	Medium	Medium	1	Medium
r_4	70	70	70	70	65	0.22	Low	Low	Bad	0.8	Bad
r_5	0	0	0	0	100	0.25	Very Low	Very Low	Very Bad	0	Very Bad

Table 6 Category acceptability index in percentage (%) and final assignments (a pessimist assignment and a optimist assignment

Categories	C_1	C_2	C_3	C_4	Final assignment (pessimist)	Final assignment (optimist)
S1	89	11	0	0	C_1	C_1
S2	99	1	0	0	C_1	C_1
S3	90	10	0	0	C_1	C_1
S4	30	67	3	0	C_2	C_2
S5	1	88	11	0	C_2	C_2
S6	99	1	0	0	C_1	C_1
S7	81	19	0	0	C_1	C_1
S8	63	37	0	0	C_2	C_1
S9	0	68	32	0	C_3	C_2
S10	74	26	0	0	C_1	C_1
S11	69	31	0	0	C_2	C_1
S12	24	76	0	0	C_2	C_2

received high chances to be assigned to category C1, but it is worth noting that these suppliers also had high chances of being assigned to category C2. In turn, suppliers S4, S5, S9, S12 received high chances of assignment to category C2. However, there is a difference between these suppliers: while S4 and S12 also receive high chances of assignment to category C1, S5 and S9 have received 12% and 32% chance of assignment to category C3, respectively.

The probabilistic information given by the category acceptability index allows different final assignments depending on several factors considered important by the decision makers. Two examples of final assignments, a pessimist assignment and an optimistic assignment, are presented in Table 6. The pessimist assignment assumes that the worst category among categories with category acceptability index greater than 30% has to be chosen. The optimistic assignment assumes that each alternative may be assigned to a category whose probability exceeds 60%. However, different assignment rules can be adopted based on the rules presented in Sect. 3.3.

Based on a final assignment, phase 4 can be conducted and DMs can draw up some improvement plans. The pessimist assignment, for instance, shows that the company does not need to cancel any agreement with any of its current suppliers, as none was

assigned to category C_4. All of the suppliers must show sufficient performance and sufficient low risk to remain as a supplier of the company; however they should be considered with different level of partnership, and therefore different action plans have to be adopted for each of them. Suppliers S2 and S6 present low risk, and therefore they are suppliers for strategic partnerships. The company should mainly provide to improve integration with these suppliers and try to increase the scope of partnership. Suppliers S4, S5, S11, S12 have a low risk and are the promising suppliers that can be considered as alternative suppliers. Supply management should carefully monitor the performances of these suppliers in order to implement improvement plans and reduce their level of risk. Supplier S_9 is assigned to category C_3 and is therefore a supplier of medium risk. It should be considered with caution only for situations of need in which the company does not have a better choice.

5 Conclusion

In this study we proposed a supplier risk evaluation model to help with the DS prevention. This model permits to assign suppliers to categories of risk and has the advantage of organizing the activities that must be performed to evaluate suppliers in order to prevent drug-shortage problems. This model also integrates twelve (12) relevant quantitative and qualitative criteria for supplier evaluation in DS prevention. The proposed supplier risk evaluation model is based on the SMAA-FFS method which provides many advantages over other sorting MCDM methods. For example, it is a sorting method able to deal with different types of uncertain data, and it does not require deterministic criteria weights, and it gives a probabilistic output (the category acceptability indices) that allows different final assignments depending on the preferences of DMs.

Adopting the proposed model, pharmaceutical companies address actions related to the management of raw material suppliers identified as important for DS problem prevention: identify alternative suppliers and conduct risk analysis of suppliers.

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Resilience Strategies and the Pharmaceutical Supply Chain: The Role of Agility in Mitigating Drug Shortages

Emilia Vann Yaroson

Abstract Supply chain resilience has been suggested to curb the impact of disruptions on supply chains. While this proposition seems coherent in theory, empirical evidence supporting this is limited, as existing literature has centred on exploring the impact of supply chain resilience on disruptions which are based on set time frames, non-supply chain specific as well as examining non-dynamic disruptive events. This study contends that resilience strategies are dynamic and as such their applications within supply chains differ. Therefore examining the impact of resilience will be appropriate on a dynamic disruption within a specific supply chain. In view of this, the paper examines through existing literature the applicability of agility within the pharmaceutical supply chain when dynamic disruptions like drug shortages occur. The study finds alertness, accessibility, connectivity and visibility as dimensions of supply chain agility that are capable of reducing the impact of drug shortages.

1 Introduction

Drug shortages as a form of dynamic disruption in the pharmaceutical supply chain has received increased attention among researchers and practitioners (De Weedrt et al. 2015). This can be attributed to the documented impact drug shortages have had on the pharmaceutical supply chain in terms of its operational as well as financial performance and to a large extent patients' safety (Kumar et al. 2015). For instance, Fox et al. (2014) explain the detrimental impact drug shortages have on patients' safety which includes medicine errors as well as adverse drug reaction as a result of wrong or inferior alternatives. Breen and Yaroson (2018) further confirm the stress related impact on community pharmacists as a result of drug shortages. Further, the survey by the European Association for Hospital Pharmacists (EAHP), provide empirical evidence of drug shortages leading to the death of patients' (EAHP 2018). These outcomes, therefore indicate the threat drug shortages pose on the various stakeholders in the supply chain and a need to proffer solutions.

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As a result of the multi-dimensional causes of drug shortages to include; access to API, quality checks failure, natural disasters, regulatory issues, managerial decisions, pharmaceutical legal framework, amongst others, it may be difficult to solve for drug shortages (Ventola 2011; Kweder and Dill 2013; Fox et al. 2014; De Weerdt et al. 2015; Bogaert et al. 2015; Heiskanen et al. 2017). This therefore, highlights the need for more dynamic strategies in the pharmaceutical supply chain capable of withstanding the impact of these shortages.

Although extant literatures have identified resilience strategies as a means in which the impact of disruptions (drug shortages in this instance) can be mitigated, some of these strategies are however limited in their applicability (Christopher and Peck 2004; Ponomarov and Holcomb 2009; Juttner and Maklan 2011; Tukamuhabwa et al. 2015). For instance, researchers propose that to cope with anticipated issues that may occur with drug production and distribution, safety stocks should be increased in anticipation for unforeseen demand (Trkman and McComark 2009; Ambulkar et al. 2015; Lucker and Seifer 2017). The underlying idea here is that if you backup supply in anticipation for a disruption, it aids in continuous drug flow which ensures that patients' therapies are not truncated half way as this may be detrimental to the patient. This approach as a resilience strategy may clog up supply process as stockpiling against disruptions by one firm may inhibit access to stock by other firms and in the long run it's the patients who suffer (Breen and Yaroson 2018). Furthermore, this strategy may not necessarily be the case in reality as drug productions are based on patients' forecast for a given period which is largely dependent on criticality, dosage as well as forms of consumption (Fox et al. 2014).

The development of agility within the supply chain has been identified as an effective tool in the mitigation of the impact of dynamic disruptions (Braunscheidel and Suresh 2009) and as such has been proposed as suitable in reducing the impact of drug shortages. Supply Chain Agility (SCA) refers to the timely manner in which the supply chain is able to bounce back to normal activities in the event of a disruptive activity. SCA differs significantly from other elements of supply chain resilience as it systematically integrates facets of supply chain resilience into a meaningful whole through its dynamic abilities. SCA possess features that are pertinent within supply chains where demand is uncertain which increases the risk associated to the disruptions. Due to the dynamic characteristics of drug shortages, it may become pertinent to ascertain if SCA may be a useful strategy in curbing drug shortages.

In view of the foregoing, the purpose of this paper is to explore through relevant literature the dimensions of supply chain agility and its applicability in curbing the impact of drug shortages within the pharmaceutical supply chain. The next section presents the concept and dimensions of agility while trying to incorporate how these dimensions present pertinent strategies that can be applied to mitigate dynamic disruptions. The paper is concluded in the third section with necessary recommendations as well as agenda for further research.

2 Dimensions of Supply Chain Agility

Supply chain agility refers to the ability of a supply chain to withstand the impact of disruptions in a business environment. Extant literature here suggest that for a supply chain to be agile, its response rate to disruptions has to be timely while seeking to satisfy all actors of the supply chain (Naylor et al. 1999). This implies that agility within the supply chain attempts to incorporate all other elements of supply chain resilience.

Several dimensions of supply chain agility have been highlighted within literature. For instance, Christopher (2000) suggests that connectivity with the end user, information sharing, integration and flexibility as ingredients of supply chain agility. Lin et al., also (2006) explain the role of collaboration, through trust and the development of core competencies as facets of agility within chains. Wieland and Wallenburg (2013) support these assertions by advocating for the need to enhance visibility through information sharing if a supply chain is to become truly agile. Based on existing literature, this study identifies; Alertness, accessibility, visibility and willingness as the dimensions of agility.

2.1 Alertness

The first dimension of supply chain agility is alertness. It is the ability of the supply chain to identify impending changes in a timely manner. This entails the capacity of the supply chain to maintain congruence in the event of turbulence. Alertness relates to the strategies supply chain actors adapt to be able to withstand changes to the supply chain. With regards to drug shortages for instance, the ability of supply chain actors to understand the impact these disruption may have on patients' treatments, financial flows (in the case of price increase) and other threats in a timely manner counts as alertness. Strategic decisions here involves questioning what other alternatives are there to continue patients' treatments, is there enough financial capital to seek substitutes and or alternatives. If there are no alternatives are supply chain members fully trained and equipped to compound medicines and as such what strategic decisions have to make prior to the impending disruption. Alertness can be strategic, episodic or operational depending on the change involved (Christopher and Peck 2004).

2.2 Accessibility

Following alertness, is accessibility for the supply chain to be truly agile. Accessibility involves the ability to obtain the resources necessary to match identified strategies. This is a vital part of supply chain agility because even if the capacity for alertness is

strong, accessibility may pose a challenge as the most strategic design may be futile if supply chain partners do not have access (Dubey et al. 2018). Accessibility can be achieved through developing the necessary infrastructure required in fostering information sharing, enhancing multi-stakeholder dialogue as well as through the use of through the use of other collaborative activities. In mitigating the impact of drug shortages in the pharmaceutical supply chain, the ability of supply chain actors to access resources is pertinent. This entails accessibility to information about impending disruptions, accessibility to alternatives at cost effective prices, accessibility to training manuals to be better equipped in the event that getting alternatives may not be feasible as well as accessibility to financial resources.

2.3 Visibility

Visibility as an element of supply chain agility is relevant as it permits supply chain actors to see through their supply chain. It provides managers the knowledge required to understand changes that may have occurred as well as detect impeding threats. Wieland and Wallenburg (2013) identify the contributions of timely and relevant information as well as investments in infrastructure in facilitating visibility. The underlying notion here is that if information is shared appropriately, disagreements relating to prices, distribution of goods as well as forecasted will be mitigated. Therefore, visibility within the pharmaceutical supply chain permits actors gain insights into what to change in preparation for a disruption and how to change it (William et al. 2013). Therefore, when faced with drug shortages, managers should be able to identify which of its supply chain actors will be affected the most, what would be the consequences for actions taken and how these actions taken will affect other supply chain partners. Extant literature suggest that visibility can be achieved through information exchange as well as internal integration (Swink and Schoenherr 2015; Williams et al. 2013). Zhao et al. (2011) states that's internal integration involves the availability of data as well as information systems between functional areas in the supply chain. The level of information shared can be classified as either market level information or partners level information types. Market-level information describes conditions in aggregate demand and supply market places, including overall requirements and availabilities at given prices. Partner-level information types are obtained directly from an organization's supply chain partners.

2.4 Connectivity and Willingness

Christopher (2000) explains that connectivity within supply chain emanates from market sensitivity. Fawcett et al. (2015) also highlights that the willingness of supply chain partners in achieving supply chain agility. Connectivity provides supply chain members with the ability to monitor changes in the supply chain as well as the

Table 1 The role of agility in mitigating the impact of drug shortages

Dimensions of supply chain agility	Definition	Applicability in mitigating drug shortages
Alertness (Williams et al. 2013)	Identifying changes in the supply chain in a timely manner	Strategic decisions to be made; How best do can this shortage be handled? What other alternatives are there? Are there resources available to cope with the shortage?
Accessibility (Zhao et al. 2011)	Access to available resources	Access to data, access to skilled manpower, access to financial resources, access to operational facilities
Visibility (Barratt 2004; Barratt and Oke 2007)	Ability to see through the supply chain at every point in time	How will information be shared? Which of the supply chain partners will be most affected? Which of the supply chain partners has the capacity to withstand the impending threats? Whom should information be divulged to, whom will this information bring benefit?
Connectivity/willingness (Brandon-Jones et al. 2014; Christopher 2000)	Market sensitivity and willingness of supply chain partners to engage in strategic decisions	Supply chain partners have to be willing to engage in supply chain activities to facilitate agility

(*Source* Researchers's Compilation 2019)

operating environment. Without the willingness of supply chain partners to engage in agile activities all other dimensions will be futile.

Table 1 presents a summary of the dimensions of supply chain agility as well as its applicability in mitigating drug shortages.

2.5 The Role of Agility in Mitigating the Impact of Drug Shortages

Studies on agility have identified alertness, accessibility, visibility, connectivity and willingness to connect as elements of agility necessary in combating the impact of disruptive activities. Therefore, for the pharmaceutical supply chain to be truly agile, in the event of a drug shortage an in-depth understanding of the nature of the supply chain is required so as to be able to identify impending threats and possible solutions in tackling the threats.

Further, questions' regarding availability of resources in the event of a drug shortage is vital for a truly agile supply chain. Thus questions like access to current and up to date data on the demand for the product, availability of human, financial and operational resources in dealing with the disruption should be asked. What are the financial implications for dealing with these disruptions? Are there alternatives readily available? If yes how are they to be used? If no what other possible solutions can be put in place so patients are not at risk? Gaining insights into current trends through data availability is also vital to supply chain agility as it aids in making appropriate decisions on how, what to do and how to change the scenario. However, these actions may not be feasible if other supply chain actors are not willing to engage in discussions, connect with partners or share information about issues within the supply chain.

Figure 1 summaries the role of agility in mitigating the impact of drug shortages in the pharmaceutical supply chain through a conceptual framework. This implies that for the supply chain to be truly agile the dimensions identified are cyclical and need to be performed on a continuous basis.

Fig. 1 Conceptual framework on the role of agility in mitigating the impact of drug shortages in the pharmaceutical supply chain (*Source* Researchers own 2019)

3 Conclusion and Recommendation

The aim of this study was to explore through existing literature, the applicability of supply chain agility in mitigating the impact of drug shortages in the pharmaceutical supply chain. Amongst the various elements of agility identified within literature four core features of SCA which include: accessibility, alertness, connectivity, and visibility—were identified as strategies which could be used in the event of a disruption.

The study therefore advocates for future studies that will critically examine the identified agility elements in relation to drug shortages in the pharmaceutical supply chain through more rigorous research methods. This study is however limited as it does not provide empirical evidence supporting the assertions highlighted in literature.

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