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Managing Uncertainty in Pharmaceutical Supply Chains: A Structured Review

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Abstract

In past decades, pharmaceutical supply chains (PSC) have become increasingly fragmented and complex making them more susceptible to supply chain (SC) risks. This has manifested in a growing number of drug shortages around the world which presents a great challenge to many national healthcare systems. PSC models provide crucial decision support and can facilitate efforts to avoid or manage such stockout situations more effectively. In this paper, we review the scientific literature on quantitative PSC models considering uncertainty in the context of drug shortages. We conduct a systematic search to obtain an overview of the current state of research in this field. The identified papers are analyzed with regards to pivotal modeling choices and their characterization of uncertainty. Our results show that many models make assumptions or abstractions which do not accurately reflect the current business environment of the pharmaceutical sector. Thus, we deduce future research avenues which might lead the way to more responsive and resilient PSCs.

1. Introduction

The COVID-19 pandemic in 2020 posed an unprecedented challenge to pharmaceutical manufacturers as economic lockdowns and demand surges impacted both ends of the SC simultaneously. This resulted in countless reports of dangerously low stockpiles and even stockout situations forcing medical institutions to ration their supplies. Unfortunately, drug shortages are not a new phenomenon as they have been a globally increasing problem long before the 2020 pandemic [1]. In the year 2018, 36% of European hospital pharmacists experienced shortage situations on a daily basis [2] and more than 250 active drug shortages were recorded in the US [3]. Hence, the COVID-19 outbreak only exposed pre-existing SC issues and, for the very first time, put them in the center of public attention.

The drug classes most commonly in short supply are antibiotics, oncology medicines, cardiovascular medicines, and anaesthetics [4]. The root causes for their susceptibility to supply failures are multifactorial and range from scarcities of raw materials to quality/manufacturing issues and demand variations among others [1]. PSCs are evidently not able to manage these influencing factors consistently. Long and complex production processes across fragmented, global SCs make it difficult to respond to unexpected developments.

Quantitative PSC models address such issues by providing decision support on the operational, tactical, and/or strategical level. These optimization approaches can incorporate uncertainties which resemble different market situations like the aforementioned root causes for drug shortages. Operating with uncertainties forces the model to prepare the PSC for multiple scenarios and thus allows for a more effective management under varying circumstances. This may result in precautionary measures like safety stocks, buffer capacities, or the establishment of backup facilities. Despite the existence and usage of such models, the number of drug shortages across the globe is increasing, raising the question whether the proposed models address this issue appropriately. This highlights the need for a thorough examination of the research in this field.

There are several literature reviews addressing PSC management from different angles. Narayana et al. [5] applied a holistic approach to identify general research trends across different themes and methodologies. Papageorgiou [6] and Lemmens et al. [7], on the other hand, specifically survey strategical and tactical optimization models. Both, however, broaden their

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scope by including models on other industry sectors or without specific industry focus in their works. Lainez et al. [8] and Settanni et al. [9] review PSC models with regards to product life cycle management and from a systems view on operations research, respectively. The described systematic reviews mostly examine the state of research at their time and derive future research opportunities from there. None of them analyzes PSC models from the angle of an ongoing issue, such as drug shortages.

Against this backdrop, we review the scientific literature concerned with the management of uncertainty in PSC planning models to obtain an overview of the current state of research in this field. We identify key issues in extant approaches and deduce future research avenues, which might lead the way to more responsive and resilient PSCs. The remainder of the paper is structured as follows: in section 2, the conceptual foundations of PSCs are outlined and the framework used for the literature analysis is developed. The methodology of the systematic search is discussed in section 3 and the results are presented in section 4. Section 5 provides a discussion of the findings. The paper concludes with summary and directions for future research in section 6.

2. Conceptual Foundation

2.1. PSC Management

According to the Council of Supply Chain Management Professionals, the definition of supply chain management (SCM) encompasses two aspects [10]: (i) SCM comprises all planning and management activities concerned with procurement, manufacturing, and logistics processes. (ii) It also includes coordination and collaboration efforts regarding business partners along the value chain and up to the final customer.

However, current SCM paradigms are mostly derived from other industrial contexts than the pharmaceutical industry and thus do not account for the specific characteristics of this sector. Pharmaceutical products are highly sensitive and their oftentimes months-long manufacturing processes are heavily regulated to ensure consumer safety. Furthermore, global and complex SCs involving numerous actors and operations in many different regulatory landscapes impede the straightforward transfer of common SCM practices [8]. In order to understand the particular role of SCM in the pharmaceutical industry, we have to examine the typical PSC structure.

A PSC commonly comprises several stages [11]. At the upstream end, suppliers provide raw materials to production sites of pharmaceutical manufacturers. The production networks itself can be divided in two major stages: primary and secondary manufacturing. The primary manufacturing stage is responsible for production of the active pharmaceutical ingredient (API) which is the core of the medication. The subsequent secondary manufacturing stage is concerned with the formulation, i.e., the transformation of the API into a consumable form (e.g. pills, capsules), and the final packaging. Then, the finished product is typically transported to a wholesaler. The downstream end of the SC constitutes hospitals and pharmacies where the medication is applied for patient care.

Primary manufacturing is generally conducted at very few but large facilities oftentimes located in China or India. Secondary manufacturing encompasses more facilities closer to the customers which is mainly due to higher transportation costs at this stage [12]. The level of market proximity further increases downstream the PSC reaching the highest point at the hospital and pharmacy level. Therefore, the typical topological structure of PSCs is strongly divergent towards the final customer.

The level of fragmentation and complexity in PSCs has increased over the last decades. In an effort to save costs, manufacturers moved production steps overseas [1] and employed more contract manufacturers [13]. According to a report by the FDA [1], about 88% of primary and 63% of secondary manufacturing sites serving the US market are located abroad. These trends elevated the prevalent SC risk as the lead time for a coordinated response (e.g. emergency production) to an immanent shortage has greatly increased [14].

Managing such complex SC structures requires extensive planning of the involved activities. SC optimization models facilitate these planning efforts by providing specific decision support for a multitude of SC tasks. Fleischmann et al. [15] categorize SC planning tasks along two dimension: *supply chain process* and *planning horizon*. The first dimension refers to the four basic SC processes *procurement*, *production*, *distribution*, and *sales*. The planning horizon dimension describes the time frame of the respective planning task which can be either *strategic* (long-term), *tactical* (mid-term), or *operational* (short-term). Optimization models typically focus on one or more elements within the resulting SC planning matrix.

2.2. PSC Model Characteristics

The developed framework addresses two key dimensions of quantitative PSC models which may affect their capability to effectively manage uncertainty.

The first one is related to *pivotal modeling choices* and includes the (1) model scope and the chosen (2) performance criteria. The second dimension covers the *characterization of uncertainty* in the model which comprises the (3) type of uncertainty, the origin of uncertainty (4), and the (5) measures taken in preparation for or in response to uncertainties.

1. *Model Scope*: The model scope refers to the central planning tasks that are addressed in a given model. We classify these tasks according to the two dimensions (SC process and planning horizon) of the SC planning matrix by Fleischmann et al. [15] described earlier. Given the oftentimes very long planning horizons in the pharmaceutical industry, it is sufficient for our purposes to only distinguish strategic and tactical/operational time frames.

2. *Performance criteria*: The performance of a PSC may be evaluated according to different criteria. Based on the work of Vandaele & Decouttere [16], we derived a classification scheme which includes a financial, business operations, and corporate responsibility dimension. Models applying financial criteria typically measure performance in terms of cost efficiency or profit generation. The business operations dimension, on the other hand, refers to PSC activities such as resource utilization or flexibility metrics. Lastly, model performance can also be judged by the amount of corporate responsibility generated which may include environmental and social efforts. Considering the detrimental effects of drug shortages, we consider drug availability under the umbrella of corporate responsibility in this study.

3. *Type of uncertainty*: Considering uncertainty in an optimization model results in planning decisions which allow the SC to function efficiently under various scenario outcomes. In accordance with Tang [17], we distinguish two types of uncertainty: operational uncertainty and disruptions. Operational uncertainty relates to model parameters which are inherently uncertain like demands or prices. Disruptions, on the other hand, are high impact events which create major disturbances in SC operations. This includes disasters like earthquakes and epidemics/pandemics, but also man-made events like economic crises and union strikes. While the likelihood of occurrence is much lower for disruptions compared to operational uncertainty, their business impact is typically a lot higher.

4. *Origin of uncertainty*: From a PSC actor's perspective, uncertainties may arise at different places of the value chain which requires responses tailored accordingly. Based on the approaches for managing SC risks proposed by Tang [17], we derived four categories describing where uncertainties can originate, i.e. the supply, operations, demand, and regulatory side. While the first three categories arise within the PSC, regulatory uncertainties affect business processes from the outside. The uncertainty's place of origin leads to distinct planning decisions and thus affects the solution provided by optimization models.

5. *Measure against uncertainty*: Measures taken against uncertainties typically aim to facilitate risk avoidance, mitigation, and/or subsequent recovery. Drawing from Klibi et al. [18], we distinguish two different measures available to decision makers. Resilience relates to long-term planning decisions made in preparation for uncertain events. These decisions are made ex-ante, meaning before the uncertainty has unfolded (e.g. backup capacities, dual-sourcing). Responsiveness, on the other hand, refers to ex-post planning decisions which are made after uncertainties have materialized. These are typically short-term, reactive measures such as the use of safety stocks or product substitution.

3. Systematic Literature Review

3.1. Approach

To ensure methodological rigor, we conduct a systematic literature review according to the principles laid out by Webster and Watson [19]. Their recommended approach comprises two main steps: the *identification of relevant literature* and the *concept-centric analysis* of it. To identify literature of interest, we performed a database search using relevant key words and critically evaluated the obtained articles for their topical fit. The resulting body of literature was supplemented with relevant papers gathered by manual search. For the concept-centric analysis, the final set of papers was classified and assessed according to the framework developed in section 2.

3.2. Database Search and Paper Selection

This literature review is concerned with the management of uncertainty in quantitative SC models for the pharmaceutical industry. To focus the database search on this subject area, we developed a search string consisting of three sets of relevant key words (including truncations and variations of these terms). The first set includes terms related to quantitative SC models such as ‘supply chain‘, ‘optimization‘, ‘model‘, and ‘planning‘. The second set entails the terms ‘uncertain‘ and ‘stochastic‘ while the third one contains the word ‘pharmaceutical‘, ‘medicine‘, and ‘drug‘. For a paper to be selected, at least one term of each set is required to be present in either title or abstract.

Using this search string, the EBSCOhost and ScienceDirect databases were extensively surveyed. The focus was narrowed to full-papers in English published in peer-reviewed academic journals. A restriction regarding the date of publication was not imposed. After excluding duplicates, the systematic search yielded a total of 368 papers as of September 23^{rd}, 2020.

This set of articles was further analyzed with regards to several exclusion criteria. Papers not concerned with quantitative PSC modeling under uncertainty were not considered for further assessments. Also, to ensure high quality standards, the journal rankings by the ‘Association of Business Schools‘ (ABS) and ‘Verband der Hochschullehrer für Betriebswirtschaft‘ (VHB) as presented in the Journal Quality List (JQL) [20] served as a landmark. We only included articles published in journals at least classified as ‘highly regarded journal‘ or ‘important and respected‘ which translates to rankings better or equal to 3 (ABS) or B (VHB), respectively.

However, according to Webster and Watson [19], it is vital for a comprehensive review to also look outside the typical literature when surveying an interdisciplinary field. Hence, we also considered the journals *Computers & Chemical Engineering* and *Chemical Engineering Research and Design*. These are renowned outlets outside the rankings described above which provide significant contributions to this field of research. The entire search process yielded 46 papers plus 1 relevant paper discovered during manual search resulting in a total of 47 papers for further analysis.

4. Results

4.1. Descriptive Analysis

According to our literature search, 16 journal contributed to the field of quantitative PSC modeling under uncertainty (see Table 1). By far the most publications were brought forth by *Computers & Chemical Engineering* (36 % of all publications), a journal standing outside the JQL rankings and without the otherwise typical management focus. Overall, Five journals, each of them having published at least three papers, account for 72% of all publications in this field of research. The remaining eleven outlets contributed with two or less respective articles amounting to a total of 13 publications (28%).

Journal	**Count**
Computers & Chemical Engineering	17
European Journal of Operational Research	6
Transportation Research: Part E	4
Int. Journal of Production Economics	3
Computers & Industrial Engineering	4
Int. Journal of Production Research	2
Management Science	2
Annals of Operations Research	1
Chemical Engineering Research and Design	1
Decision Sciences	1
IEEE Transactions on Engineering Mgmt.	1
Journal of Product Innovation Mgmt.	1
Manufacturing & Service Operations	1
Omega	1
Production & Operations Mgmt.	1
*Information Sciences**	*1*
Total	**47**

* added through manual search

Table 1. Number of publications per journal

The total amount of 47 papers over an unrestricted time span implies that this field has not received much attention in the past. Figure 1 provides a historical overview of all considered publications. To the best of our knowledge, the first paper in this context was published in 1996. However, the popularity of this topic remained low for a long time and did not permanently increase up until the year 2008. In the more recent history, we observed a growing number of publications in this research area.

Interestingly, spikes in publications, e.g., in 2004, 2008, and 2015, also coincide with times of multinational crisis which affected the pharmaceutical industry. In the year 2004, the world had just overcome the first pandemic of the century (which, in a tragic coincidence, was caused by the coronavirus strain SARS-CoV-1), and was now battling the global spread of the bird flu. The year 2008 famously marked the beginning of the global financial crisis. In 2015, widespread Ebola and Zika virus epidemics were surging in Western Africa and South America, respectively. The coinciding spikes in publications suggest a heightened interest in risk management research in times of crisis. The pharmaceutical sector, for that matter, is especially impacted by large scale health emergencies and sudden economic downturns. Since the 2020 Corona pandemic presents both of these challenges, we may see another increase in PSC modeling papers in the near future.

Figure 1 also shows that 18 of the 47 papers are exclusively concerned with R&D planning models.

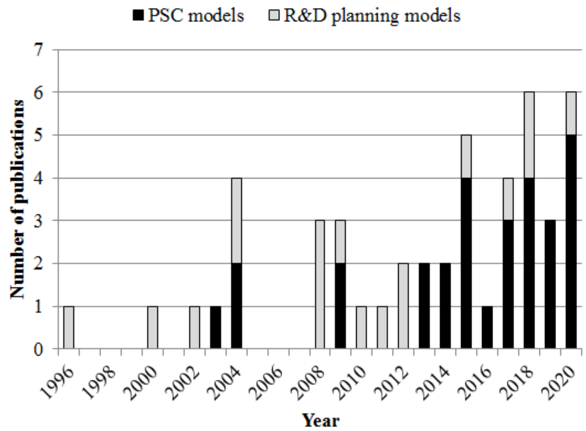

Figure 1. Historical distribution of publications

Since R&D projects in the pharmaceutical sector can take up to ten years and are extremely costly, they constitute high priority planning problems in this industry. However, the issue of drug shortages only relates to medicines in their market phase and thus is naturally out of scope for models exclusively focusing on R&D planning problems. Hence, there is no need to consider the aforementioned 18 papers for further assessments since they do not address in-market products. As a result, 29 publications remain for the further evaluation (for a list see Appendix A).

In these papers, a variety of modeling approaches were applied in order to provide decision support in PSC management (see Table 2). The most popular approach represents stochastic programming which encompasses two-stage (e.g. [13, 21]) and multi-stage models [22], both of which use discrete scenarios with known probability distributions. Fuzzy modeling approaches, on the other hand, employ fuzzy parameters, which consist of a set of possible values instead of one specific value, for the representation of uncertainty [23, 24, 25]. Four papers propose robust programming models and implement either discrete scenarios [26, 27, 28] or interval-uncertainty [29]. Some authors have combined two of the described approaches to yield robust-possibilistic [30, 31] or possibilistic-stochastic [32, 33] programs. For a more detailed description of stochastic, fuzzy, and robust modeling approaches, we refer the reader to Govindan et al. [34].

Six articles propose Markov chains in order to derive optimal decision policies (e.g. [35, 36]). In one instance, a two-step optimization framework is developed applying two-stage stochastic programming for strategic planning (first step) and, subsequently, a Markov Decision Process for tactical decision support (second step) [37]. Furthermore, two papers

Modeling Approach	**Count**
Two-stage stochastic prog.	7
Multi-stage stochastic prog.	1
Fuzzy	3
Robust	4
Robust-possibilistic	2
Possibilistic-stochastic	2
Markov Chain	6
Stochastic analysis	2
Simulation optimization	2
Total	**29**

Table 2. Applied modeling approaches

performed stochastic analyses [38, 39] and another two simulation-optimization approaches [40, 41] to obtain optimal inventory control policies.

4.2. Classification Results

In this section, we classify the identified models according to the categorization scheme introduced earlier. Two authors conducted this process independently in order to ensure inter-rater reliability. The third author resolved conflicting classifications if required.

The classification according to model scope revealed that ten models address a strategic planning horizon (see Figure 2). All of these represent forms of strategic network design (SND) problems. This comprehensive problem class may include planning tasks across all long-term SC process steps. Pariazar et al. [42] and Sabouhi et al. [32], for instance, focus on supplier selection while Zahiri et al. [31] address facility allocation decisions. Models concerned with strategic planning of distribution networks were proposed by Akbarpour et al. [26] and Zahiri et al. [33]. None of the examined articles included strategic sales planning.

On the tactical/operational level, most papers are concerned with capacity (e.g. [43]), production (e.g. [44]) and/or inventory management (e.g. [28]). Distribution planning problems were only addressed by Liu et al. [45] and Parvin et al. [37]. Other models, however, apply more comprehensive approaches which is captured in sales & operations planning. Here, planning decisions of multiple SC process steps are integrated such as procurement and inventory management [46], production and distribution planning [29], or capacity and demand planning [21]. Sing et al. [24] even combine three tasks by covering procurement, production, and distribution decisions in their model. Ordering management and demand fulfillment were not exclusively addressed by any of the reviewed models.

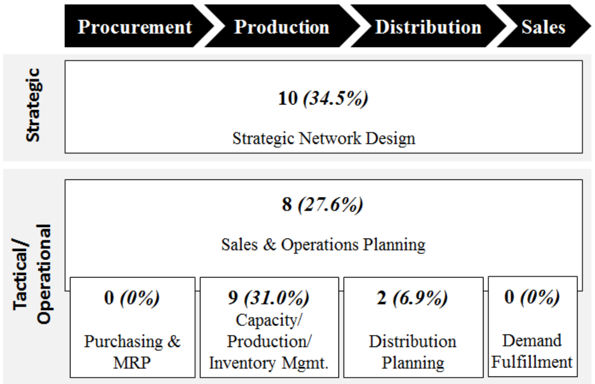

Figure 2. Paper count and relative share (in parentheses) of models with according scope

The majority of the examined papers only considered a single performance criterion (69%) as shown in Figure 3. Most of these optimization models rely on financial metrics to assess their performances as they aim for cost minimization (e.g. [13, 32, 41]) or profit maximization [27] of the portrait network. The business operations criterion was applied three times exclusively. These papers aim to optimize either the level of machine redundancy [23], operational flexibility [38], or of process flexibility [35]. Operational flexibility refers to the ability to dynamically change production volumes [47] as needed whereas process flexibility describes the ability to manufacture different product types at a facility [48]. Only once, a model's objective was to improve corporate responsibility measures [37]. The paper is concerned with the efficient distribution of a malaria medication in Malawi aiming to avoid shortage situations.

About one third of the papers employ more than one performance metric (31%) all of which include a financial performance criterion. The most prevalent combination is the one with corporate responsibility measures. These models either focus on service level optimization (e.g. [26, 40, 42]) or on the environmental impact [29]. Zahiri et al. [33] provided the only paper incorporating all three performance criteria as their model aims to improve the overall social and environmental impact (CR), the network resiliency (BO), and to minimize total system costs (F).

As shown in Figure 4, the majority of papers focuses solely on operational uncertainty (83%). By far the most popular theme among those is demand uncertainty which is included in more than half of all surveyed articles (e.g. [28, 36, 25]). Interestingly, uncertainty in cost parameters is always applied in combination with uncertain demands (e.g. [45, 31]).

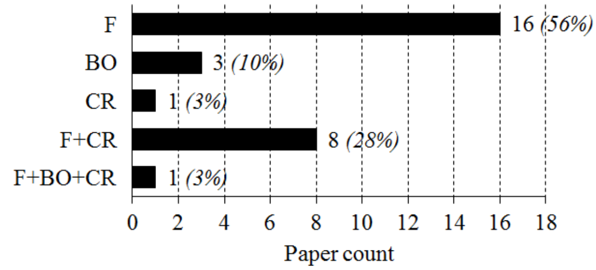

Figure 3. Models applying performance criteria (F-financial, BO-business operations, CR-corporate responsibility)

Other implemented operational uncertainties include lead times of production (e.g. [44, 41]) or regulatory processes [13] as well as machine failures (e.g. [40, 23]). Clinical trial outcomes are incorporated in 3 papers [35, 22, 49] in an effort to facilitate the introduction process of new products into the running plant operations.

Madadi et al. [50] and Pariazar et al. [42] present the only articles exclusively concerned with PSC disruptions as they focus on tainted production batches and supplier disruptions respectively. In three cases, operational uncertainty and disruptions are considered simultaneously. Lücker et al. [38], for instance, account for uncertain demands as well as for the disruption of a manufacturing site. While Saedi et al. [51] and Sabouhi et al. [32] both include supplier disruptions, the former also accounts for uncertain demands and the latter for operational uncertainty regarding disruption severity.

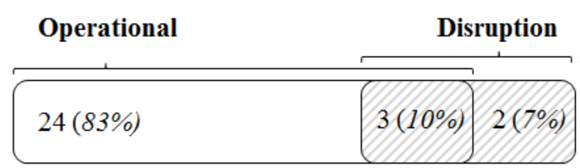

Figure 4. Number of models accounting for operational uncertainty and/or disruptions

Table 3 summarizes where uncertainties originate in the reviewed papers. Since one model can include multiple uncertainties from different sources, the total count adds up to more than 29. Uncertainty arising upstream, meaning at the supply side, are considered nine times and include delivery times [40, 41], supply failures (e.g. [42]), and ordering costs [41, 24]. Uncertainties occurring during own company operations were incorporated by eight articles. These range from machine/plant failures (e.g. [40, 23]) to production/repair times (e.g. [44]) and manufacturing/transportation costs (e.g. [31]). Most authors consider uncertainty at the downstream side of the PSC in form of demand variability (72%) which may be implemented through stochastic parameters (e.g. [13, 21]) or fuzzy numbers (e.g. [30, 33]).

Regulatory uncertainty is the only source arising outside the business processes of a PSC and, yet, can have a huge impact on those. To ensure patient safety, many approvals or authorizations by responsible authorities are required, especially concerning the introduction of new products or the implementation of new manufacturing processes. Hansen & Grunow [13] developed a model that facilitates product introduction planning and considers forced label changes and the duration of market authorization processes as uncertain parameters. The remaining three papers focus on regulatory uncertainty regarding clinical trial outcomes which determine whether a new medication is approved to be marketed at all [35, 22, 49].

Origin of uncertainty	Count	Frequency*
Supply	9	*31%*
Operations	8	*28%*
Demand	21	*72%*
Regulatory	4	*14%*

*out of 29 papers

Table 3. Origin of uncertainty considered in models

Almost half of the models meet uncertainties solely with resilience which refers to measures taken before the uncertainty materialized (Figure 5). These include risk avoidance strategies such as supplier/customer selection (e.g. [42, 21] respectively) as well as plant inspections [50]. More authors, however, relied on risk mitigation measures which often involve redundancy and/or flexibility. While redundancy is usually achieved through additional machines or components [23], flexibility is improved in various forms such as process [35], operational [43], contractual [21], and logistics flexibility [33]. Contractual flexibility, according to Reimann et al. [21], represents the degree of freedom provided in contractual agreements, for instance, regarding delivery dates. Logistics flexibility refers to the capability of transporting goods to different locations [52].

Once uncertain events have materialized, responsiveness measures can be taken in order to mitigate and recover from the situation. Govindan et al. [39] and Liu et al. [45], for instance, improved responsiveness through the use of safety stocks in their models. Others include the possibility of product substitutions [51], emergency deliveries [40], or dynamic pricing [27].

More often, however, authors implemented both resilience and responsiveness measures in their models. These include various combinations and variations of the aforementioned measures. In some articles, for instance, supplier selection is combined with emergency purchases [41] or safety stocks [24] while redundant capacities are utilized together with risk mitigation inventories [38]. Furthermore, Zahiri et al. [31] explored facility allocation decisions and product transshipments in the same model while Guerrero et al. [36] combined optimal ordering points and emergency deliveries.

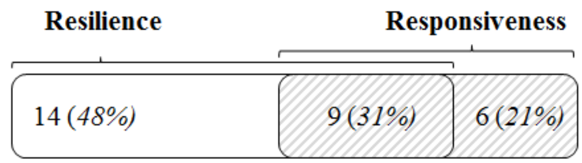

Figure 5. Number of models addressing resilience and/or responsiveness measures

5. Discussion

In this section, we discuss the current state of quantitative PSC modeling under uncertainty and identify research gaps. Generally, research in this field is still scarce despite a great need for sophisticated decision support in PSC management. Furthermore, most of the applied modeling approaches, e.g. two-stage stochastic programming, assume knowledge about the probability distribution of uncertainties. Yet, empirical data on actual operational uncertainties and disruptions is very limited. Even for industry experts it is often difficult to provide good estimates due to the length and complexity of PSCs. Given this lack of information, modeling techniques which do not require probability distributions, like robust programming, may provide more applicable solutions.

When analyzing the model scope, we find that a large portion of articles focus on the production process step while the adjacent tasks, i.e. procurement and distribution, have received less attention. Interestingly, the sales process remains largely unexplored even though the complexity and multitude of drug pricing systems in different countries presents a huge challenge for businesses. Reference pricing and pharmaceutical tenders, for instance, are suspected to induce drug shortages by driving down prices and thus causing competitors to drop out of the market [7, 53]. The reduced number of manufacturers, consequently, increases the overall SC risk.

Furthermore, our findings show that the majority of papers relies on exclusively financial performance criteria. Focusing only on cost efficiency is not congruent with expected future market requirements. Increasingly volatile markets and the trend towards individualized medicine are going to require higher degrees of flexibility within the PSC. Furthermore, global developments like the rising numbers of drug shortages and growing environmental awareness will demand for more corporate responsibility in the future.

Implementing uncertainty into quantitative PSC models improves the solution quality with regards to the specific type of uncertainty considered. The overwhelming majority of papers focuses on operational uncertainties. Yet, it is disruption risk that has greatly increased in recent decades as common business strategies have lead to more complex and fragmented PSCs. Craighead et al. [54] linked the severity of disruptions to three SC characteristics, i.e. density, complexity, and node criticality. The industry's dependence on API from China and India has increased supplier density and node criticality at that stage while global PSC structures involving a multitude of actors added to the overall complexity. Thus, there is a need for more modeling approaches that complement operational uncertainties with the risk of SC disruptions.

With regards to the origin of the considered uncertainty, we find that the majority of papers focuses on the demand side of the PSC. This is surprising given that many drug classes which are oftentimes in short supply, e.g. oncology medicines, cardiovascular medicines, and anesthetics [3, 4], are typically not subject to great demand volatility. At least on a large scale, the corresponding patient numbers can be forecasted well based on historical data. Consequently, the FDA identified scarcity of raw materials and manufacturing issues as stronger drivers for drug shortages [55]. Supply and operations have received less attention as sources of uncertainty in the examined models. Also, little work has been done regarding uncertainty arising from the complex legal frameworks that pharmaceutical companies have to operate in.

Most PSC models meet uncertainty with resilience, either exclusively or in combination with responsiveness measures. Given the very long production processes, improving responsiveness will remain difficult for any kind of PSC. Therefore, resilience through redundancy and flexibility is of great importance which is reflected in the reviewed articles. Evidently, the current levels of these measures are not sufficient to manage drug shortages effectively. Thus, more research is required to develop PSCs which reliably function in uncertain environments. Innovations like cloud computing and blockchain technology may facilitate this endeavor by providing access to detailed real-time data on PSCs [56].

6. Conclusion and Outlook

In the light of the 2020 corona pandemic, we investigated the scientific literature on quantitative PSC modeling under uncertainty against the backdrop of drug shortages. To this end, we developed a comprehensive classification scheme along two main dimensions, i.e. central modeling choices and the characterization of uncertainty, which allowed us to characterize respective models according to corresponding key features. A structured literature search was carried out yielding 29 papers for this analysis. Drawing from our results, we outlined the current state of the research and identified key issues for future research.

Our findings generally reveal a rather narrow focus of PSC models on specific topics. With regards to pivotal modeling choices, most models optimize planning tasks of the production process step whereas sales planning remains largely unexplored despite its importance for business operations. At the same time, the majority of models focuses exclusively on financial objectives which may foster rigidity and vulnerability of PSCs. When analyzing the second dimension, we find that models typically implement operational uncertainties arising at the demand side of the PSC. These assumptions may not accurately reflect the current business environment which is characterized by increasing disruption risk especially at supply and manufacturing stages. To cope with uncertainty, models primarily focus on resilience measures since responsiveness improvements are naturally limited by the rigidity of pharmaceutical production processes.

Limitations to our study pertain to the scarcity of research on quantitative PSC models. This resulted in a relatively small sample size of 29 scientific articles serving for our analysis. Furthermore, the classification of the literature is subject to a degree of interpretation by the coder. However, the extensive search of two databases and a rigorous content analysis involving multiple coders limit potential biases and provide a comprehensive picture of this research field.

Our classification results enable us to identify several research opportunities which we discussed in detail in the previous section. Generally, we find that many models fail to account for critical aspects of today's business and market situations (e.g. increasing SC risk, complex pricing systems). This may be the result of a changing industry landscape as PSCs have become increasingly fragmented and complex. However, in order to prevent and manage drug shortages more effectively in the future, it is paramount that PSC characteristics and emerging challenges are accurately reflected in optimization models.

Appendix

Model Scope	Reference
Strategic Network Design	[26][42][32][33][22] [49][50][30][31][25]
Sales & Operations Planning	[39][13][29][21][24] [41][27][46]
Capacity/Production/ Inventory Mgmt.	[40][28][35][23][36] [44][38][51][43]
Distribution Planning	[45][37]

Table 4. Paper with given model scope

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