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Opinion

Emerging Challenges and Opportunities in Pharmaceutical Manufacturing and Distribution

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Abstract: The rise of personalised and highly complex drug product profiles necessitates significant advancements in pharmaceutical manufacturing and distribution. Efforts to develop more agile, responsive, and reproducible manufacturing processes are being combined with the application of digital tools for seamless communication between process units, plants, and distribution nodes. In this paper, we discuss how novel therapeutics of high-specificity and sensitive nature are reshaping well-established paradigms in the pharmaceutical industry. We present an overview of recent research directions in pharmaceutical manufacturing and supply chain design and operations. We discuss topical challenges and opportunities related to small molecules and biologics, dividing the latter into patient- and non-specific. Lastly, we present the role of process systems engineering in generating decision-making tools to assist manufacturing and distribution strategies in the pharmaceutical sector and ultimately embrace the benefits of digitalised operations.

Keywords: pharmaceutical manufacturing; process systems engineering; Industry 4.0; digitalisation

Citation: Sarkis, M.; Bernardi, A.; Shah, N.; Papathanasiou, M.M. Emerging Challenges and Opportunities in Pharmaceutical Manufacturing and Distribution. *Processes* **2021**, *9*, 457. https://doi.org/10.3390/pr9030457

Academic Editors: Luis Puigjaner and Bhavik Bakshi

Received: 11 January 2021
Accepted: 25 February 2021
Published: 3 March 2021

1. Introduction

Complexity in pharmaceutical manufacturing and distribution is highly dependent on the product nature. Therapeutic drugs can be classified into two broad categories: (a) small molecules, (b) biologics. The former refers to chemically synthesised drugs, while the latter refers to products that involve components extracted from or produced by a living organism [1]. Biologics include monoclonal antibodies (mAbs), vaccines, blood products, and advanced therapy medicinal products (ATMPs). Figure 1 illustrates the drug categories considered here. Each of these products is characterised by key specifications and/or formulation that dominate decisions related to its manufacturing and supply chain. Small molecules are pharmaceuticals based on chemical components and characterised by large scale manufacturing. On the other hand, manufacturing of biologics involves cell-based production systems and complex downstream separation trains, largely performed in batch/semi-batch mode [2,3]. This often presents challenges in the optimisation and scale up of unit operations.

Enhanced clinical disease understanding has led the pharmaceutical industry to move from one-size-fits-all approaches and develop targeted therapeutics such as ATMPs. Their production process differs significantly from small molecules or mAbs as it involves a series of product- and often patient-specific steps [4]. Their patient-specific nature may challenge scale up and distribution and has led to a shift in the manufacturing and supply chain status quo, highlighting the need for smaller, more agile, and often regional manufacturing units that translate into distributed networks closer to the patient. In addition, such products are coupled with stringent distribution timelines and tight storage constraints that need to be satisfied. As a result, questions related to optimal number and location of facilities arise, as well as how can one design a robust investment planning model. Furthermore, network and task coordination become of primary importance as the supply

chain becomes more complex. Once the network has been designed, manufacturers need to ensure that distribution and storage conditions are met and maintained throughout the product journey, in order to reduce losses due to product degradation that can lead to drug shortages or reduced quality.

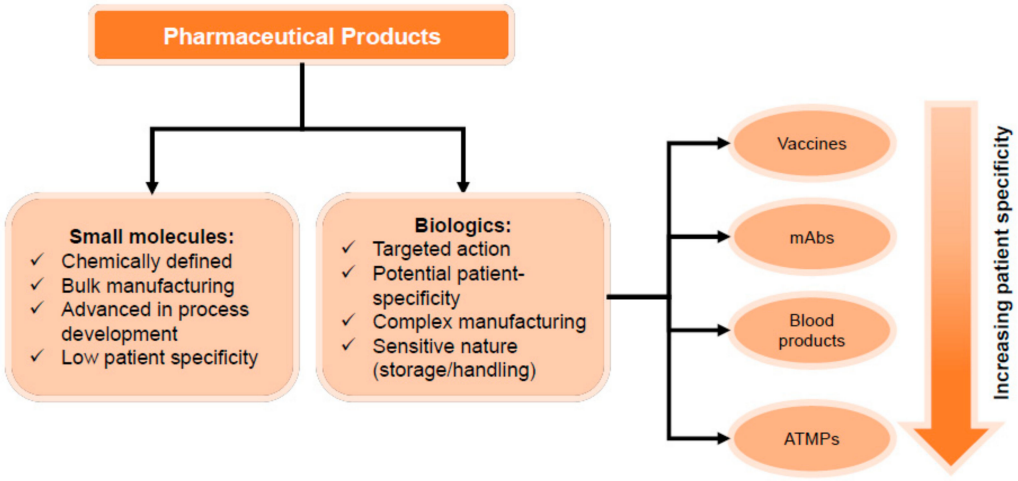

Figure 1. Schematic of simplified pharmaceutical product categories.

In this paper, we discuss how the nature of therapeutics may impact the design of suitable manufacturing processes and supply chain networks. We have performed a literature review and we summarise some of the latest initiatives taken to assist the decision-making process in the pharmaceutical industry. We also discuss how process systems engineering has been aiding innovation in this space. In the last part of this paper, we present a perspective on current and future developments in this space.

2. Engineering Challenges and Opportunities in Pharmaceutical Manufacturing and Supply Chain

Recently, the term Pharma 4.0 has been introduced, referring to the adaptation of digital strategies and tools of Industry 4.0 principles, and their application to pharmaceutical manufacturing and supply chain practices [5,6]. In this context, digital tools and orchestration platforms are being developed under Industry 4.0/5.0 principles [7]. The term refers to manufacturing digitalisation and automation of processes, introducing autonomous, computerised systems. It utilises different types of mathematical models (e.g., statistical, kinetic) and Internet of Things to facilitate and maintain internal communication within and across the factories. Application of Industry 4.0/5.0 principles aims to facilitate: (a) data collection, analysis, and interpretation, (b) man-machine co-operation, (c) online monitoring and control, and (d) intra- and inter-facility data sharing. In the last few years, we have seen the emergence of cloud-based applications coming to assist decision-making in the pharmaceutical industry. Several industrial players have embraced Pharma 4.0 either through the development of digital platforms to be used by manufacturers (e.g., Siemens) or by integrating digitalisation into their manufacturing processes (e.g., ChemeCon GmbH) [8].

2.1. Manufacturing

Pharmaceutical manufacturing is divided in two main parts: firstly, the pharmaceutical ingredient or drug (active pharmaceutical ingredient (API)/drug substance) is being produced, while the second step is focused on making this product suitable for administration to the patients (drug product). Common process steps usually involve drug formulation-specific and therefore differ across drug types. Often, small molecule primary manufacturing involves chemical synthesis and purification steps, while secondary manufacturing starts with the mixing of the API with excipients, followed by granulation,

compression, coating, and packaging. On the other hand, biologics involve the production of either the API or parts of the drug product by a living organism. For example, mAbs are produced in mammalian cell culture systems using bioreactors, a process referred to also as upstream (USP) [2]. Following USP, the product undergoes a series of separation/purification steps, including filtration and chromatography to ensure that impurities are removed from the final formulation. Different to all other categories, ATMPs, such as chimeric antigen receptor T (CAR-T) cells, often involve one or more patient-specific steps [9]. Autologous CAR-T cells are a representative example as their manufacturing is based on T cells that have been extracted from the patient's blood stream [10,11].

Pharmaceutical manufacturers are focused on delivering efficacious and safe products at quantities that meet the global demand. In addition, process and product standardisation are primary goals to ensure batch-to-batch variability is minimised. In parallel, production processes need to be economically viable, adding to the complexity of identifying the best candidate design(s). These are often conflicting objectives (Table 1) that require systematic procedures for the identification of the most suitable operating units and modes that will meet product specifications, while yielding a profitable process. In an effort towards process improvement and modernisation, the pharmaceutical industry has pioneered by creating new and/or adapting existing innovations. Here, we present some of them and discuss the challenges that remain open in each space.

Table 1. Summary of the key challenges and opportunities in pharmaceutical manufacturing and distribution. The tick sign highlights the relevance of the identified issues and solutions to each drug product category.

Decisions	Challenges and Issues	Small Molecules	Conventional Biologics	Personalised Products	Solutions and Opportunities
			Manufacturing		
Product Portfolio	Identification of product profile		✔	✔	Understand QTTP; Outsource manufacturing and development to contractors
Process Design and Operations	Long approval times	✔	✔	✔	Standardisation; Single-use technology; Multiproduct facilities
	Batch solutions are well-established	✔	✔		Incentivise investment in continuous manufacturing
	Batch-to-batch variability and shortages		✔		Continuous manufacturing; QbD
	Identification of optimal operating units and modes	✔	✔	✔	Process optimisation tools; QbD
	Measurements availability and lack of process understanding		✔	✔	Develop online PAT tools; Digital twins of process; QbD
Capacity Planning	Long lead times for scale up	✔	✔		Scale up existing suites; Scale out through new suites instalment; Single use equipment
	Patient-specific products and process			✔	Scale out and set up of parallel suites
	Uncertainty of long-term demand	✔	✔	✔	Decision-making tools for long-term investment strategies; Multiproduct facilities; Outsource production to CMOs and CDMOs

Table 1. *Cont.*

Decisions	Challenges and Issues	Small Molecules	Conventional Biologics	Personalised Products	Solutions and Opportunities
Production Planning and Scheduling	Adaptability to short-term demand fluctuations	✔	✔	✔	Real time demand forecasts; Continuous manufacturing for flexible campaigns; Single use equipment to reduce changeover times Planning and scheduling decision-making tools
	Time constraint and patient specificity			✔	COI and COC; Monitor patient schedule; Planning and scheduling decision-making tools
Quality Control	Quality assurance tasks lead times	✔	✔	✔	Continuous manufacturing; QbD
	Unavailability of measurements	✔	✔	✔	Digital twins for real-time monitoring
Distribution					
Inventory Planning	Prevention of shortages	✔	✔		Real-time sharing of stock data, inventory levels and forecasted demand
	Monitor CQAs and CPPs		✔	✔	Track & Trace tools; Outsource distribution to contract logistics providers
	Time constraint and patient specificity			✔	COI and COC; Track & Trace tools
Network Structure	Compliance and coordination of stakeholders.	✔	✔	✔	Track & Trace tools; Data sharing
	Time constraint and patient specificity			✔	Decentralised supply chain closer to the patient
Transport Modes and Connections	Monitor CQAs and CPPs		✔	✔	Track & Trace tools; Outsource distribution to contract logistics providers
	Counterfeit drugs entering supply chain	✔	✔		Track & Trace tools
	Time constraint and patient specificity		✔	✔	Track & Trace tools; Outsource distribution to contract logistics providers

2.1.1. Quality by Design

The emergence of biologically derived drugs has underlined the necessity for thorough system understanding that includes detailed mapping of how process conditions may affect product quality. Quality by design (QbD) was firstly discussed by Juran [12] in 1992 and refers to the integration of quality into the process and product. In other words, all design and operation decisions are taken aiming to meet a predefined product quality. In the pharmaceutical industry, QbD has been increasingly endorsed by regulators and adapted by manufacturers [13–16], while in recent years it has become an integral part of approval submission dossiers. QbD suggests that firstly the quality target product profile (QTTP) needs to be decided, followed by the identification of the critical quality attributes (CQAs) [16,17]. CQAs are defined as product properties and/or characteristics that need to be within certain limits. The process is then designed, aiming to meet the pre-defined QTTP, while maintaining CQAs within the allowed threshold. This is achieved by manipulating those process parameters that directly affect CQA performance, known as critical process parameters (CPPs). QbD offers a systematic procedure for the development of processes based on thorough system understanding and prior knowledge integrated to the design and operation. Efforts have been made to integrate mathematical models with QbD principles to explore CPP-CQA interplay. Such understanding enables the determination of a set of *feasible* points within the space of the operating conditions that

assure that the CQAs are within specifications, known also as "design space" (DS). This has allowed manufactures to move away from *uniquely optimal* operating profiles and adopt a more flexible strategy, whereby the manufacturing process is approved to operate within the DS and allowing greater flexibility for post-approval improvements within the DS.

Despite the wide application of QbD in mAbs and lately in vaccines, when it comes to ATMPs, QbD-driven processes remain an open challenge [18]. The often patient-/donor-specific nature of the starting material renders systematic CQA identification impossible to perform. In addition, the manufacturing performance of cell-based therapies is highly dependent on the quality of the extracted cells, leading therefore to a highly variable CPP-CQA interplay. As ATMP manufacturing matures and more understanding on the optimal portfolio of conditions is gained, QbD principles can be adapted to incorporate patient profile and incoming materials as key CPPs and map their impact on the process and product performance.

2.1.2. Continuous Manufacturing

Process performance has been the driver for many of the latest advances in the pharmaceutical industry, such as the one of continuous manufacturing (CM). CM offers the possibility for robust processes that involve smaller equipment size. In addition, by running longer and producing higher product yields, CM processes can lead to decreased batch-to-batch variability and therefore minimise the risk of drug shortages due to unmet quality specifications [19,20]. On the other hand, operating in continuous mode is translated into a must-have requirement of rapid, online measurements and a high level of process understanding to allow the operator to ensure that the product will meet specifications. This is of utmost importance in CM as its *plug-and-play* profile means that an intermediate intervention is not possible which translates into a significant financial and shortage risk if the process deviates from the optimal significantly. CM is one of the most discussed trends and innovations of the latest years in the pharmaceutical industry, endorsed by regulators [21]. Promising eco-efficient processes of higher productivity, CM has been successfully applied in many existing production processes leading to significant improvements [19]. Small molecules have seen applications of CM early on with the initiatives from Novartis-MIT on continuous crystallisation [22] and the GSK-Pfizer partnership for the development of continuous processing technology for oral solid dosage (OSD) drugs [23]. Innovation has been demonstrated in the space of biologics as well with Genzyme and Bayer as leading adapters of perfusion and other continuous manufacturing processes [24], while Novasep, GE Healthcare, Knauer, and ChromaCon are some of the equipment manufacturers offering small- and pilot-scale continuous chromatography systems. Warikoo et al. [25] demonstrated one of the first fully continuous pilot-scale bioprocesses for the production of a mAb and a recombinant human enzyme. They designed and used a system composed by a 12 L perfusion bioreactor connected to 4-column periodic counter-current chromatography and they successfully demonstrated the production and purification of the desired products. Godawat et al. [26] showcased an end-to-end continuous bioprocess using a perfusion bioreactor connected to an ATF cell retention device. The upstream mixture was then processed by two 4-column PCC systems. Additionally, Karst et al. [27] presented a lab-scale continuous mAb production process using a perfusion cell culture, a surge tank, and a continuous capture process.

Despite the success of CM in small molecules, challenges still exist that prevent biologics from reaching a fully continuous process at scale. A significant percentage of this slower adaptation can be attributed to system complexity. Relying on living organisms as production systems, biologics are coupled with complex process dynamics that challenge the identification and maintenance of the optimal operating profile. Although, CM promises more stable processes and decreased batch-to-batch variability, it requires increased certainty that the optimal operating conditions will be maintained throughout the process. This is to ensure that the desired product will meet specifications and reduce financial and supply risks associated to out-of-spec batches. To enable the design of robust processes that

are continuously monitored requires suitable analytics to be in place. Despite advances in the field of continuous online measurements [28–32], process analytical technologies (PATs) are yet to be further developed in order for uninterrupted CM to be realised. Focusing on biologics and specifically mAbs, another limiting step that hinders end-to-end continuous processing is upstream/downstream (USP/DSP) integration. Process intensification via process integration in mAbs is a challenge, firstly as DSP units are not at the scale to handle the volumes produces by the USP counterpart. A way to mitigate this would be scaling up DSP equipment, risking increasing the already high DSP cost (80% of the end-to-end process).

Aiming to tackle this, initiatives have been made towards the development of smaller scale separation units, operating in continuous mode, increasing therefore their volume processing capabilities [26,33,34]. Another alternative could be to scale out the DSP step, offering also higher operating flexibility. Some of the remaining challenges are currently being tackled through the development of computer-modelling platforms as discussed later in the manuscript. Manufacturing challenges increase as products become more specialised. For example, CAR-T cells (ATMPs) are manufactured using *closed-box* production platforms that do not allow for task parallelisation or scale up [35,36]. This translates into integrated lines of unit operations being occupied for the entire manufacturing (>10 days) duration of a single therapy before they can become available to receive the next one. As ATMPs gain momentum, manufacturers will be required to increase their capacity. Given that volumetric scale up is not possible, other possibilities can be explored, such as scale-out, referring to multiple suites running in parallel or a completely granular manufacturing procedure where every step is performed in a separate unit, allowing therefore for sequential manufacturing with decreased waiting times. The latter model could greatly benefit from process intensification initiatives as it resembles the well-known model of biologics.

2.2. Supply Chains

Supply chain design decisions, strategies, and operations are highly dependent on the product that is delivered to the patient. With increasingly complex portfolios and stringent regulations to deliver an effective and safe therapy to end-users, pharmaceutical supply chains costs are on the rise. The nature of the product type, from the chemically-derived small molecules to highly targeted biologics, such as mAbs and ATMPs, entails different distribution and storage challenges [37]. Table 1 summarises the main challenges faced in pharmaceutical supply chains and related innovations.

2.2.1. Demand Scales

The pharmaceutical industry is inherently global, and its supply chains comprise a network of manufacturers (primary and secondary), which include in-house or external contractors, packaging facilities, regional distribution centres (wholesalers), and final healthcare providers, such as hospital and pharmacies. Off-the shelf products, prescription drugs and vaccines can be produced on a large scale, with single manufactured batches delivering numerous patient non-specific doses, following a one-size-fits-all distribution approach. This strategy is preserved in the case of emerging specialty drug products as well. Demands for these products, which are often biologics, including mAbs, can be predicted to be smaller in scale as they provide treatment of rare and complex chronic diseases, which only certain patient subgroups present. However, as the complexity of the treatment increases, it becomes increasingly difficult to synthesise a product that is compatible with the entire patient cohort. In the case of ATMPs, distribution has been envisioned through two channels: allogeneic and autologous. Allogeneic therapies are manufactured in larger batches from unrelated donor tissues [38]. Off-the-shelf production offered by the allogenic route is presenting several donor-patient matching challenges which have slowed down the success of these therapies in clinical trials. By contrast, autologous ATMPs have thus far been more successful clinically [9] and have the potential to reconfigure standard supply chain structures, as they represent a turning point in the feasibility of personalised

medicines. Figure 2 illustrates the general supply chain structure for batch-produced drugs and patient-specific therapeutics. In the instance of CAR-T cell therapies, a sample of cells is extracted from the patient, shipped, modified, and administered to the patient, with a minimised cycle time (17–19 days return time for leading commercial products) [39–42]. The supply chain for these therapies is closer to the customer and the need for a *1:1 business model* emerges, where the product released by a single batch is patient-specific. Opportunities of scale up are limited and decentralisation of manufacturing is a promising approach [43]. Companies, expanding their primary and specialty drugs portfolios to personalised therapeutics, are expected to deal with a spectrum of decoupled demands simultaneously, which require extensive coordination of the stakeholders in the supply chain [44].

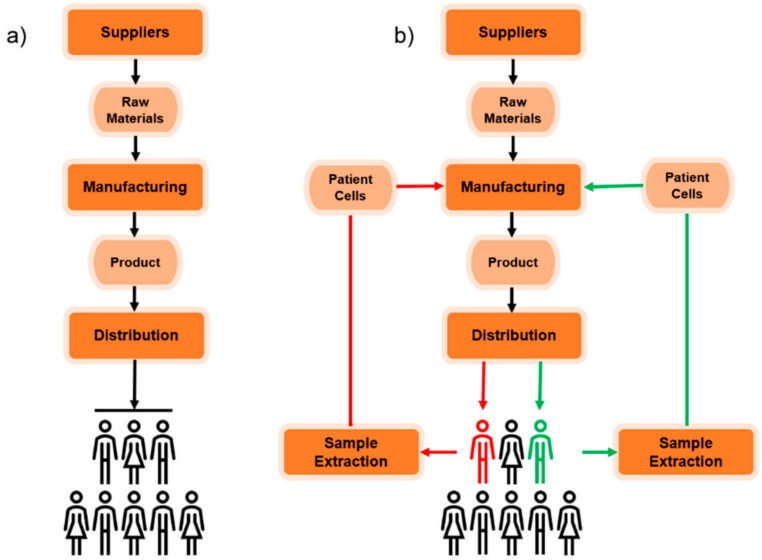

Figure 2. Pharmaceutical supply chain for (**a**) batch-produced drugs and (**b**) patient-specific therapeutics.

2.2.2. New Players

The pharmaceutical ecosystem comprises large R&D multinationals, local companies, generic manufactures, contract development, and manufacturing organizations (contract manufacturing organisations, CMOs, and contract and development manufacturing organisations, CDMOs) and biotechnology companies [45]. Large R&D multinationals are the key players in the marketplace, with presence in branded products and manufacturing sites across many locations. In recent years, their research focus has shifted to unmet needs of smaller patient populations, such as prevention and cure of rare diseases [46]. The increasing complexity of novel targeted therapeutics and lack of in-house manufacturing expertise of large multinationals in these contexts have determined an increased in mergers and acquisition (M&A) and outsourcing strategies through CMOs or CDMOs [46]. For instance, CellforCure was acquired by Novartis, expanding the company's manufacturing capabilities in CAR-T cell therapies, Hitachi acquired Aptech to increase manufacturing capabilities in Europe, Thermo Fisher acquire CMO Brammer Bio for $1.7 bn and GE Healthcare was acquired by Danaher ($21.4 bn) [43]. CMOs and CDMOs are equivalently attractive for biotechnology companies, which are often the main innovators in genetically engineered therapeutics, but lack of manufacturing resources and liquidity for in-house manufacturing. As the number of stakeholders involved in clinical and commercial supply chains increases, end-to-end monitoring of CQAs becomes increasingly difficult [47]. Outsourcing distribution and handling to specialised contract logistic providers is an appealing option to assure safe and secure delivery of complex biological drug products; however, management and coordination between the multiple agents becomes the key challenge.

2.2.3. Logistics Considerations

Manufacturers indicate on the product label the stability conditions for the product, which must be maintained throughout the whole supply chain. Small molecule drug products can typically be stored at 25 °C [43]. By contrast, the stability of bioproducts is highly compromised by temperature excursions and shocks. For instance, blood products, conventional vaccines (e.g., live-attenuated viruses) and monoclonal antibodies must be transported and stored under refrigeration conditions of 2–9 °C [48]. If cold chain logistics introduce additional costs in the supply chain, these are further exacerbated when handling ATMPs. CAR-Ts can be stored and transported either fresh (−80 °C) or cryopreserved (−180 °C), depending on the manufacturing practice, noting that they are also highly sensitive to shear stress and vibrations, because of their cell-based nature [9]. This ensures stability, maintains viability, and prevents genetic changes. Other genetically engineered products, such as mRNA vaccines, must be stored and handled under similar conditions (−70 °C) [49]. Monitoring the CQAs in relation to storage and transport environment conditions and ensuring timely delivery of therapies becomes increasingly crucial as the product structure and scope increases in complexity. Whether distribution is tackled in-house or outsourced, transparency of manufacturing and logistics operations facilitates quality assurance and effectiveness of the entire supply chain [47].

2.2.4. End-to-End Monitoring

CAR-Ts and personalised therapies offer a new perspective on the importance of track and trace capabilities for supply chain management and real-time monitoring. In these supply chains, chain of identity (COI) and tracking is crucial in order to ensure return of the therapy to the right patient by the end of the product cycle [9]. In addition, chain of custody (COC) principles must be applied with the aim of recording data related to handling, collection, and performed actions on the sample, thus monitoring the patient-specific product profile closely. It is worth noting that potential success of off-the-shelf ATMPs will equally require donor information to be tracked throughout the supply chain to ensure compatibility and aid effective donor-patient matching. Patients will also need to be monitored for several years after receipt of therapy; this information should be used to improve therapy design wherever possible. Initiatives to improve end-to-end visibility of supply chains are emerging in the fields of conventional non-specific products as well, such as Merck KGaA's commitment to utilise data analytics to predict and prevent drug shortages [50]. Companies are in fact becoming more aware of the improved supply-and-demand forecasting that traceability offers, including its potential to prevent API stock-outs and counterfeit drugs from entering the supply chain. As discussed above, drugs, including targeted biologics and small molecules, can also greatly benefit from real-time monitoring of CQAs, as the risk of failing to comply with labelled requirements can be reduced.

As highlighted by Papathanasiou [51], cloud-based platforms can facilitate communication and seamless connection between stakeholders. Maintaining and upgrading data security will though become a constant requirement for reducing vulnerabilities to the increasing sophistication of cyber-attacks. Particularly, secure safeguarded systems to protect data will become central to foster patient trust for data sharing and conduct the research needed to drive personalised medicine [52]. Alongside cloud-based solutions, blockchain-based alternatives are being developed in recent years. In a nutshell, blockchain is part of the broader category of distributed ledger technologies (DLTs) and it is based in the participation of a network of devices, called nodes, that keep a copy of the database [53]. A distinct advantage of the blockchain is that it does not require a central trusted party to verify the validity of the data but it relies on a consensus protocol which is publicly available and agreed upon by all the participants [54]. The information stored in the blockchain is public, immutable, and tamper-proof, while the security of the sensible data is assured by the utilization of strong state-of-the-art cryptographic algorithms. By adopting the blockchain a unified distributed health records database that can be accessed by every stakeholder along the supply chain, from the raw material providers to the final patient,

with different levels of access to the information. For instance, information about the QC and storage conditions of a therapy along the supply chain could be accessed by everyone at any time by scanning a QR code attached to the therapy, while patient-specific data would be cryptographically sealed for most of the stakeholders except the patient himself and the hospital. An extensive review of blockchain solutions in the healthcare sector is out of the scope of this work and can be found elsewhere [55]. Despite the great potential, scalability of blockchain application remains an issue and is yet to be demonstrated. An interesting use-case is the recent partnership between NHS England and Hedera Hashgraph, a company providing blockchain-based solutions, in an attempt to use blockchain for enabling cold chain monitoring of COVID-19 vaccines for a selected group of facilities [56]. Other examples of blockchain-based tools for real-time monitoring of storage conditions of sensitive goods and traceability solutions are being developed by Modum.io [57] and is under investigation in a leading Italian company of the ophthalmic sector [53].

2.2.5. Production Planning and Scheduling

Despite the exciting opportunities brought by digitalisation and advanced monitoring, well-established technologies still present a large margin of improvement in terms of adaptability of production levels to demand. One of the main bottlenecks of current manufacturing and distribution networks, for both small molecules and conventional biologics is the planning and scheduling of production in response to short-term demand fluctuations [45]. Primary manufacturing sites usually comprise multipurpose batch equipment setups to distribute the capital cost over a spectrum of products. In the instance of biopharmaceutical manufacturing, such as manufacturing of mAbs, perfusion and fed-batch modes are preferred modes of operation due to improved fermentation titres [58]. Significant losses in revenues can result from downtime due to changeovers and required extensive cleaning tasks to prevent contamination. This pushes manufacturers to operate the site in long product campaigns, which ensure profitable utilisation of the plant throughout the time horizon [45,59]. Small molecule drug substances exiting the primary sites are stored up to 1 year and can be further processed in secondary manufacturing sites upon demand. Simpler tasks of fill and finish and packaging taking place in this secondary stage allow more flexible scheduling of operations and supply products to distribution centres.

The intermediate storage installations between drug substance and drug product manufacturing can act as a buffer to tackle variations in market dynamics: the customer-facing end (hospitals and pharmacies) place orders on wholesalers, carry out an assessment on inventory levels and if necessary, place orders upstream. In the event of an API shortage, the lack of responsiveness of primary manufacturing long campaigns emerges, which can then lead to drug product shortages and impact patients in need of the therapy. Stockpiling has been a profitable option for well-established chemically synthesised drug products; however, it is not always the best-suited solution for more complex and expensive biologics with short shelf lives. The high value of these products constrains the size of product inventory held as this might constitute tying up working capital [60]. Off-the-shelf production has followed the above planning paradigm for years, but patient-specific therapies come to reshape this approach. Scheduling production becomes *patient scheduling*, where each batch contains solely a dose of therapy that is specific to the patient [9]. The business model changes radically and adaptation to demand dynamics becomes increasingly important as operations are now constrained by return times between collection of the sample at the start of the supply chain, manufacturing, product release, and re-infusion.

2.2.6. Capacity and Investment Planning

Investment planning into expansions, establishment, and shutdown of facilities would have to be carried out under high uncertainty of demand of pipeline products and drugs under development. In order to avoid financial losses related to poor forecasting and suboptimal utilisation of facilities, R&D companies are externalising development and manufacturing of novel entries in their portfolio to contractors. The problem of capacity

management is outsourced to the CMO, which is able to better balance utilisation by making products for multiple innovators [43]. Stainless-steel plants are well-established production facilities for conventional vaccines, mAbs, small molecule products and are suitable for large scale production. The capital investment for these facilities can extend from $500 M to $1 bn [61], highlighting the financial losses that can derive from underutilisation of the facility. The process of setting up entirely new facilities can extend up to 5–10 years, which once more hinders flexibility and responsiveness to varying therapeutic needs of the population. It is often the case that capacity within the facility is expanded by either setting up suites in parallel or scaling up existing ones with larger equipment [62].

Nevertheless, the operational burden of cleaning tasks, contamination concerns, and the ever-present need of more flexible production as biopharmaceutical products become more advanced and complex, is pushing many companies to utilise single-use production technologies. This trend in manufacturing offers multiple advantages in terms of savings in instalment, which fall in the range of $20–$100 M (2–20% of the capital investment), and operational costs. Set up times for new facilities are shorter (1.5 years) and the advantage of parallelising production with suites is preserved, in order to cope with short-term demand changes. Interestingly, COVID-19 vaccine producers choose to rely on flexible single-use systems as opposed to traditional commercial-large scale bioreactors and fermenters, valuing the potential to install manufacturing capacity at a higher speed, which is crucial during a global health crisis [63]. The advantage of single-use equipment is seen also in the space of personalised medicines, where cross-contamination risk between products can cause loss of patient specificity and have detrimental effects on the patient's health. Changeover time within each suite is decreased from 1 month to 0.5 days [61] as equipment components no longer require, cleaning, but are rather disposed, substituted, with an adaptable capacity to the incoming patient schedule. The environmental drawbacks of utilising high purity water and heat to clean and sterilise stainless steel equipment are removed. Disposal routes of single-use technologies is, however, still an issue to be considered. Used components are typically bio-hazardous, which entails that waste treatment tasks have to be carried out on-site prior to landfill disposal. Another option is to send used components to geographically separate waste-to-energy facilities for incineration and recovery of electricity. Latterly, initiatives, such as the Biopharma Recycling Program, are investigating recycling strategies to further reduce the environmental footprint of plastic single-use equipment and exploit the full benefits of flexible manufacturing [64].

3. Assisting Digitalisation in Pharmaceutical Industry via Process Systems Engineering (PSE)

Process systems engineering (PSE) has been traditionally assisting decision making in the pharmaceutical industry [46,65–68]. The adoption of digitalisation in pharmaceutical manufacturing and the supply chain will be key for seamless data exchange across manufacturing facilities and supply chain networks, as it will allow connectivity of processes, products, and people. As highlighted previously in this manuscript, there is a wide range of opportunities to improve the strategies and operations of the entire pharmaceutical supply chain in order to meet the evolving therapeutic needs of the population. In this space, the concept of enterprise-wide optimisation [69,70] is at the core of a coordination between R&D, supply of materials, manufacturing, and distribution of pharmaceutical products. The main objectives of an enterprise-wide approach are to maximise profits, responsiveness to customer needs, resource utilisation and minimisation of costs, stock levels, and environmental footprints. This is achieved while accounting for the complex interactions between the many stakeholders of the supply chain. Instant flow of information and data sharing can also be achieved via the adoption of *transactional* IT tools, such as track and trace tools, cloud-based and blockchain platforms. Such tools can improve communication and operations across the supply chain, specifically in the evolving pharmaceutical ecosystem that comprises multiple players. Nevertheless, these digital tools do not provide comprehensive frameworks to support the decision-making process. Therefore, it is of paramount importance to develop *analytical* IT tools to explore, analyse alternatives, and

predict actions for the design, planning, and operation of each of the components of the supply chain. The PSE community has largely focused on the development of sophisticated optimisation and decision-support tools so as to yield optimum performance and ensure customer satisfaction. Figure 3 presents a summary of key considerations and challenges currently faced by the pharmaceutical industry, as well as some of the most remarkable computational and other innovations that can assist the decision making.

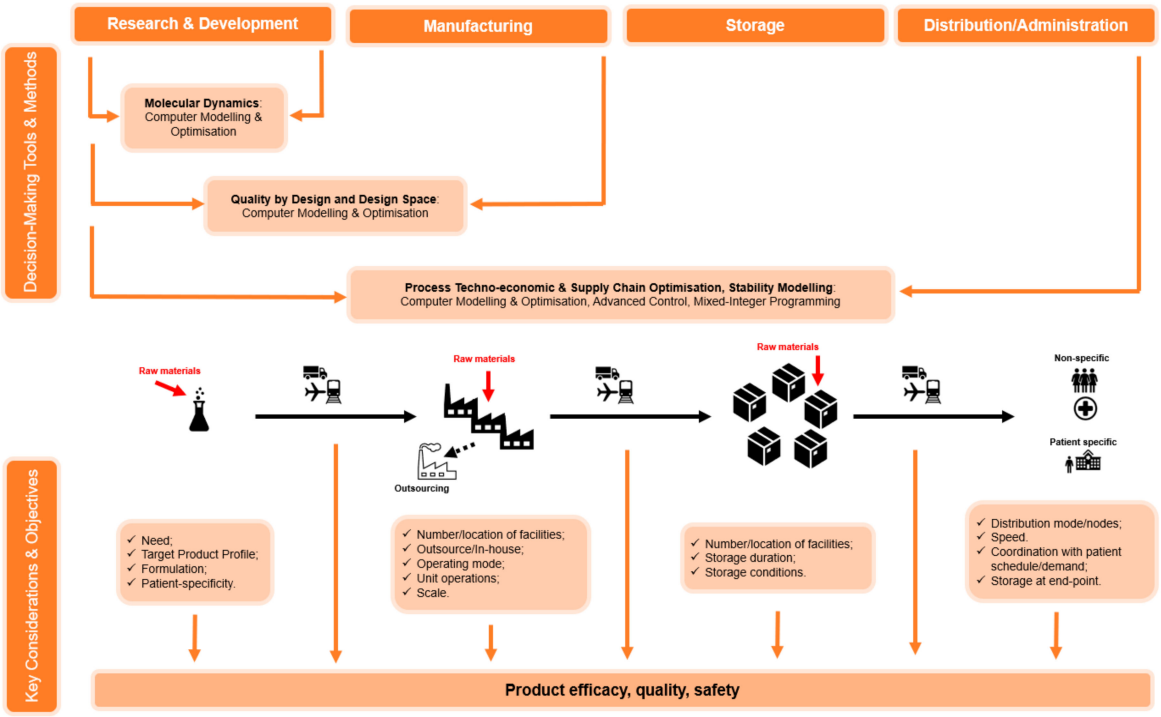

Figure 3. Pharmaceutical manufacturing and supply chain ecosystem.

In the pharmaceutical sector, changes introduced to approved processes and/or products need to be registered re-approved by regulators. This poses an additional challenge to the adaptation of new methods and technologies. Initiatives such as quality by design and design space identification that allow thorough process and product understanding can lead to more flexible processes and therefore faster approval procedures. In that respect, computer-based modelling initiatives and tools demonstrate significant potential as they offer lower-cost experimentation platforms and the ability to identify the optimal process operating profiles offline. Such models and platforms, also known as *digital twins*, find applications across a variety of activities in pharmaceutical manufacturing. Computer-based modelling in product development and manufacturing has demonstrated significant potential, offering low-cost experimentation platforms to assess CQA-CPP interplay under a vast spectrum of conditions [71–73]. In a similar fashion, PSE researchers are also looking to quantify parameter uncertainty and its impact on product and process performance [74,75]. From an operational standpoint, many groups are developing using digital twins for the design of optimal operating setups, optimisation profiles [76–79], and smart controllers [80–82] that can operate bypassing measurement unavailability.

In the field of supply chain management, optimisation-based approaches have improved strategies and operations of pharmaceutical and bio-pharmaceutical processes and distribution in multiple ways. Computational tools have been developed to seek optimal long-term strategic plans, considering the problem supply chain design and capacity planning, as well mid- and short-term decisions, addressing the problem of production planning and scheduling [69]. Supply chain design, capacity, and investment optimisation models focus on the long-term decisions regarding the strategic locations of the plants,

storage, and sourcing of raw materials, contracts with CMOs and CDMOs and logistics providers as well as future investments in new capacity over the years [58,62,83–87]. Tools to optimise production planning and scheduling offer great potential in assisting operational, day-to-day decision-making. Systematic approaches in production planning yield estimates of production targets, inventory levels, and material flows across the supply chain over a horizon of several months [59,60,88]. Scheduling tools, instead, provide detailed sequencing of tasks and operations, fulfilling orders and meeting the production targets, relying on a more granular description of the manufacturing and distribution processes and accounting for resource constraints [89,90].

Integrating the different levels of decision-making across many time scales is an issue of great interest in research [91,92], alongside coordination between multiple geographically distributed manufacturing and storage facilities comprising the supply chain. The size of the optimisation problem becomes challenging to solve by commercially available solvers and numerous approaches, including rolling horizon, spatial [88], and temporal decomposition [88,89] schemes have been proposed in literature. Solving the above problems under uncertainty remains an open challenge [93]. Uncertainty introduced by demand fluctuations, on-going global competition and pending clinical trial results, challenges the long-term strategic decision-making. Most of the frameworks proposed in literature use stochastic programming and scenario-based approaches [85,86,94], often coupled with decomposition strategies [95] to tackle computationally intractable formulations. Case studies have mainly focused on manufacturing and distribution of chemically derived drugs and conventional biologics. Therefore, the novelty of patient-specific products and ATMPs is a fertile ground for PSE tools to support investment planning exercises and establish supply chains that can cope with the predicted demand and success of these products. Similarly, planning and scheduling tools can aid the decision-making and tackle the operational challenges brought by patient specificity and time constraints of the therapy cycle [96,97].

4. Conclusions and Outlook

In the latest years, pharmaceutical products have evolved towards disease- and patient-specific therapeutics, involving meticulous manufacturing steps. In addition, cell-based therapeutics and vaccines present high sensitivity to environmental and transport conditions, complicating supply chain logistics. Increased drug specificity and demand uncertainty are adding a further level of complexity when it comes to the design and operation of robust manufacturing processes and distribution networks. As discussed in this paper, the pharmaceutical industry has taken significant steps towards the improvement of existing and/or the development of novel processes that promise agile, responsive, and reproducible manufacturing. Similarly, distribution networks in the pharmaceutical sector are undergoing a paradigm shift, exploring the capabilities of decentralised models.

Such developments are accompanied by digital innovation in the pharmaceutical industry that comes to enable seamless communication between process units, production plants, and distribution nodes. As discussed earlier, process systems engineering has been at the forefront of enabling digitalisation through the development of computer modelling tools. The latter can assist with real-time monitoring of storage conditions that are critical for sensitive pharmaceutical products with short shelf-life, thus increasing drug safety. One of the main challenges hindering fast exploitation of Industry 4.0 principles in pharmaceutical manufacturing is the change of mindset. Practitioners should embrace the benefits arising from the realisation of Pharma 4.0 towards replacing paper-based systems with cloud-based servers. This will allow significantly improved agility and productivity in the operations of the pharmaceutical sector.

Author Contributions: Conceptualization, M.S., A.B., N.S. and M.M.P.; methodology, M.S., A.B. and M.M.P.; investigation, M.S., A.B. and M.M.P.; images/tables, M.S.; writing—original draft preparation, M.S., A.B. and M.M.P.; writing—review and editing, M.S., A.B., N.S. and M.M.P.; All authors have read and agreed to the published version of the manuscript.

Funding: Funding from the UK Engineering & Physical Sciences Research Council (EPSRC) for the Future Targeted Healthcare Manufacturing Hub hosted at University College London with UK university partners is gratefully acknowledged (Grant Reference: EP/P006485/1).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors would like to acknowledge expert opinion received through multiple conversations with the User Steering Committee of the Future Targeted Healthcare Manufacturing Hub. Financial and in-kind support from the consortium of industrial users and sector organisations is also acknowledged.

Conflicts of Interest: The authors declare no conflict of interest.

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