Chapter 14
Evaluating the Business Case for Continuous Manufacturing of Pharmaceuticals: A Supply Network Perspective

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Abstract This chapter addresses the challenges of evaluating the business case for continuous manufacturing of pharmaceuticals, looking beyond traditional technical assessments made at the unit operations or individual production facility level. It provides an overview of key concepts, approaches, and tools for the early assessment of supply network configuration opportunities enabled by continuous production processing interventions. Multiple levels of analysis are considered with the aid of examples based on major UK research programs on continuous production process technologies. Particular emphasis is placed on the potential for achieving enhanced product flexibility (in terms of volume and variety) and, depending on scale, the optimum number and location of manufacturing operations to support speed to market and system-level cost benefits. In the case of multiple manufacturing operations using continuous production process technologies, where production facility replication through digital twins is becoming a key enabler, the chapter sets out a supply network design and analysis approach that evaluates the commercial and operational viability of alternative manufacturing supply network scenarios.

Keywords Pharmaceuticals · Supply chain · Supply network design · Continuous manufacturing · Business case · Volume-variety matrix

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14.1 Introduction

Conventional pharmaceutical manufacturing of so-called small molecules is generally accomplished using batch processing, an approach that has been successful in providing quality "blockbuster" pharmaceuticals to the public for decades. Growing pressure on cutting costs in healthcare systems, often achieved by favoring nonproprietary products in the procurement process, has constrained the opportunities for brand manufacturers to profit from the introduction of new products while exposing the shortcomings of traditional batch manufacturing in terms of responsiveness and excessive inventory (Shah 2004). An example of rigidities embedded in the current manufacturing footprint of international medicine supply networks is that some manufacturers' response to a possible "no-deal" Brexit was to increase finished packs stockpiling across Europe by 20% (BBC News 2018).

Some shortcomings of traditional medicine manufacturing have been addressed in terms of manufacturing practices through initiatives aimed to promote operational excellence (Friedli et al. 2013). However, most opportunities to radically improve pharmaceutical development, manufacturing, and quality assurance are driven by targeted technology interventions in product and process development, in process analysis and control, as well as in the broader healthcare ecosystem. Over the past few years, sector outlooks have particularly emphasized the role of small-scale, modular continuous processing technologies to deliver highly engineered drug products and more personalized healthcare enabled by digital technologies—see, for example, Stegemann (2015), Srai et al. (2015a), and Rantanen and Khinast (2015). This tendency reflects a more general call to effectively deploy the latest pharmaceutical science and engineering principles and knowledge to improve the efficiency of manufacturing and regulatory processes, respond to the challenges of new discoveries (e.g., novel drugs), and provide novel business opportunities, such as individualized therapy (FDA 2014).

Evidence suggests that industry is responding favorably to the adoption of continuous processing. Exemplar success stories are outlined in Table 14.1. While recognizing potential advantages in terms of agility of supply, speed of development in drug products, reduced factory footprint, and improved quality, most companies regard their continuous manufacturing strategy as exploratory and themselves as early adopters (Dell'Orco and Tix 2018). Especially in the case of pharmaceutical substances (or primary manufacturing), difficulties in producing compelling business cases are perceived by both research-driven and contract manufacturing organizations as a barrier for the uptake of continuous manufacturing in the pharmaceutical industry, despite the merits of individual technologies in enabling reaction chemistry (McWilliams et al. 2018).

To address the challenges of making the business case for emerging manufacturing technologies such as continuous processing, this chapter outlines supply network design rules for the early-on assessment of reconfiguration opportunities in medicine supply enabled by the perspective adoption of such technologies. To achieve this aim, the remainder of this chapter summarizes key insights from major UK research programs delivering demand-led intensified, continuous

Table 14.1 Summary of companies with significant investments in continuous processing

Company	Application	Location	Operations	Throughput	Scale	Investment
Eli Lilly	R&D	US	Reaction Workup Isolation	1–10 (g/h) 5–15 kg/day	Lab Pilot	
GSK	R&D	UK			Pilot	
	Comm.	Singapore				USD 50m
Lonza	Comm. (43 products)	Switzerland	Reaction (micro/mini)			EUR 1m+
Novartis/ MIT	Comm.	Switzerland	Primary and secondary		Pilot	
Pfizer	R&D	US				
		Ireland		Kilo	Lab	USD 11m
Sanofi-Genzyme		UK	Primary			
Sigma-Aldrich	Comm. (70+ products)	Switzerland	Multipurpose		Medium	

Based on Srai et al. (2015b)

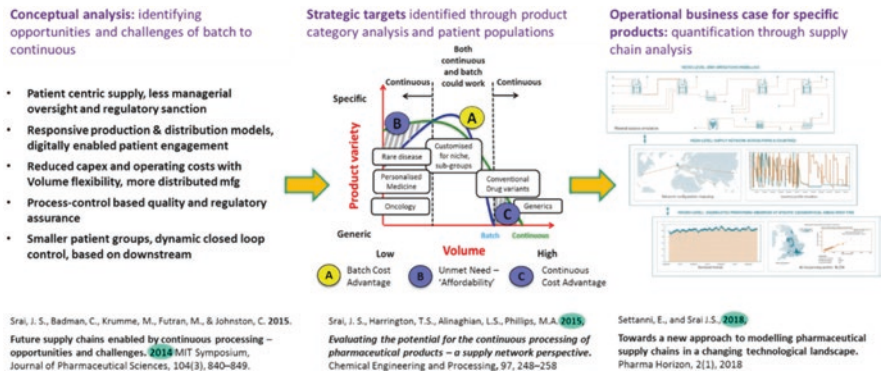


Fig. 14.1 Suggested approach to the business case for transformation problems in continuous manufacturing

technologies—from conceptual analysis through strategic target formulation to operational business case analysis, as shown in Fig. 14.1.

14.2 Overview of the Current State and Emerging Opportunities for Reconfiguring Medicine E2E Supply

As in most highly regulated activities, the structure of global pharmaceutical supply networks is fairly rigid to changes. In the 1980s, the industry shifted from owning most of its infrastructure through vertical integration to regarding activities outside

research and development (R&D) and marketing as noncore (Rees 2011); hence, starting material supply, drug substance manufacture and processing, and downstream supply chain operations are now typically outsourced through third-party commercial relationships.

This industrial setting has incentivized the contract manufacturing of pharmaceutical substances (pharmaceutical ingredients—active pharmaceutical ingredient (API)), as well as chemical intermediates in facilities compliant with good manufacturing practices (GMP): API manufacturing is estimated to account for two-thirds of the fine chemical industry's global production worth circa USD 85bn (Pollak and Vouillamoz 2012) with a progressive move of pharmaceutical manufacturing footprints toward Central/Eastern Europe and China through the 2000s (Boswell 2004, 2007). In this context, processing typically takes place in multipurpose plants consisting of batch equipment where APIs are manufactured in campaigns, the number and length of which largely depends on the need for validated cleaning and changeovers, with cycle times up to 300 days from starting materials to finished goods (Shah 2004).

The typical production-to-reactor-volume range of a commercial API in a fine chemical plant is approximately 15–30 t/m^3 per annum, with a production bay equipped with four to six vessels corresponding to 100 t/year – roughly the yearly production volume of one-third of the 500 top-selling drugs (Pollak and Vouillamoz 2012). In the presence of demanding changeovers, offering product variety can be insidious for a batch environment: for example, due to the number of languages required for blister packing, achieving an overall equipment effectiveness as low as 20% is not uncommon across European production lines (Rees 2011). However, the current industrial trends suggest an emerging need for smaller product volumes to meet more personalized, geographically dispersed demands through an increasingly fragmented product portfolio (Stegemann 2015; Srai et al. 2015a).

A market outlook with more niche volume products and fewer blockbusters will likely demand greater flexibility of unit operations, avoiding prohibitive scale-ups from laboratory to market volumes (Bieringer et al. 2013). An example of this trend is the concept of modular fine chemical plants, where continuous, intensified flow chemistry facilitates "scaling-out" the volume for a given module or "numbering up" the modules operating in parallel (Pollak and Vouillamoz 2012).

From a supply network perspective, the challenge goes beyond making a "binary" choice between batch and continuous production process technologies; rather, the ambition is to explore the potential of targeted technology interventions across the industry to transform pharmaceutical supply chains so that they are more efficient and adaptive, ultimately leading to benefits to the patients (Srai et al. 2015a).

Key opportunities and challenges arising from the pharmaceutical industry's shift toward a primarily "continuous processing"-based supply chain were articulated at the first International Symposium on Continuous Manufacturing of Pharmaceuticals, held in Cambridge, MA, on May 20–21, 2014, and are summarized in Table 14.2. In particular, system-level benefits of targeted technological

Table 14.2 Opportunities and challenges in primarily "continuous processing"-based supply chain

Challenges	Opportunities	Expected benefits
Globalized, volatile markets, increased demand for specialty products, smaller patient populations	Increasing responsiveness to specific market needs through greater product (e.g., dose) and volume flexibility Allowing for late customization in packaging through more distributed and geographically dispersed manufacturing Reducing constraints in terms of "minimum order quantities" within a supply chain design	From >200-day to <70-day inventory within primes and up to 50% reduction in the current 1–2-year inventory Halved cycle time from starting materials to packed product Achieve >5σ, right first time in manufacturing Reduce cost to market by 10%
Costly "buffers," product shelf-life shortening and country-specific regulatory nuances	Designing adaptable, "inventory-light" supply chain configurations through economical supply of smaller volumes Relying on near real-time demand signals as opposed to long-term forecast-driven campaign planning Shortening lead times in product replenishment	
Regulatory requirement for high-quality, validated, efficient, and safe production process	Improving control over process conditions and increasing consistency in chemistry "right-first-time" manufacturing Facilitating and expediting quality control and release through, e.g., in-line process analytical technologies (PAT) Increasing options in terms of synthesis routes involving short-lived unstable intermediates typically avoided in batch processing	
Reduced time windows to reach markets with branded products	Accelerating scale-up post clinical trial design through easier quality-by-design filings Supporting a more "just-in-time," exploratory approach to clinical research Reducing investigational product wastage	
Operational cost linked to increasing complexity	Cutting management burdens and overhead structural costs by minimizing human-to-human hand-offs through enhanced flow-through supply concepts Limiting inventory holding costs and working capital "held up" in multiechelon inventory Reducing footprint through reconfigurable assets with options for numbering up/scaling up	

Based on Srai et al. (2015a)

interventions, such as continuous medicine manufacturing, can be better appreciated when the analysis is carried out "end-to-end" (E2E in short), beyond the four walls of the individual factory or lab, and compared and contrasted with incumbent supply network configurations.

Along with challenges and opportunities, capturing value across the E2E supply chain through continuous manufacturing suggests new developments, some of which have been demonstrated through collaborative, industry-led projects; see, for example, Badman and Srai (2018):

- Digital-technology-enabled, reconfigurable, and adaptive supply networks, whereby response to demand fluctuations is increasingly driven by product demand requirements captured directly between the patient and drug provider through Patient Diagnostic and Management Systems
- Convergence between continuous-processing-based and other medical technologies such as "smart packaging" and additive manufacturing (3D printing) to support more integrated and patient-centric product-service solutions, for example, facilitating product assurance, as well as compliance and adherence to treatment
- More decentralized models of supply and derisked technical transfer earlier in the development timeline through continuous supply centers and reconfigurable assets

In particular, digitally enabled production technologies such as continuous processing with advanced process analytics are now regarded by industry and policy makers alike as viable alternatives to "monolithic" centralized production of medicines in pharmaceutical supply, both commercial (UNCTAD 2017) and clinical (Made Smarter Review 2017).

Demonstrating end-to-end benefits across the pharmaceutical supply chain, however, is not a trivial task. For example, while the use of continuous-flow chemistry, in particular microreactor technology, represents one of the few radical improvements to fine chemical plants in over 25 years, only 10–15% of chemical reaction that could be carried out in microreactors are deemed economically justified by experts (Pollak and Vouillamoz 2012). Also, existing business case for continuous processing seldom extends beyond the four walls of the individual manufacturing plant—see, e.g., Schaber et al. (2011). The following sections focus on how to address these gaps, providing a framework as well as analytical insights.

14.3 Identification of Strategic Targets Through Product Category Analysis

A credible conceptualization of the relative benefits potentially arising at the system level—not just at the manufacturing plant level—from the continuous processing of pharmaceutical products should follow a four-staged analytical framework (Srai et al. 2015b):

1. *Identification of opportunities and barriers to adopting potential alternative product-process technologies*: the first step is to explore which existing markets can be served more effectively and which unmet end-user needs can be targeted through continuous processing. *Volume* and *complexity* play a crucial role in identifying E2E opportunities. Two major questions that arise at this stage are as follows: "What is the volume-scale where the transition from batch to continuous becomes attractive?" and "Which arrangement of batch and continuous processing can achieve the desired volume flexibility?" The resulting

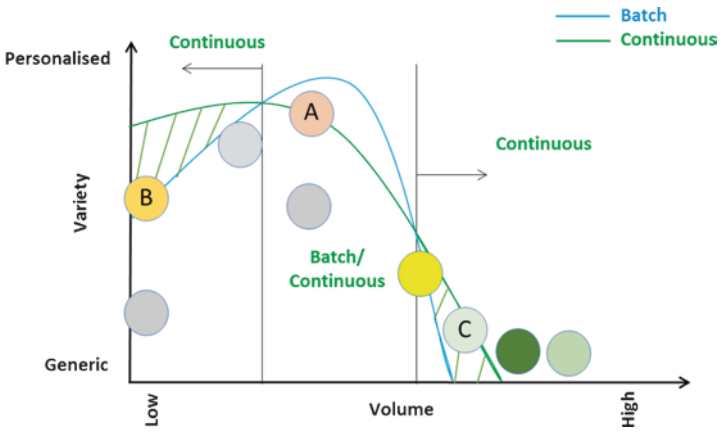


Fig. 14.2 Conceptual volume-variety matrix for pharmaceutical products. (Based on Srai et al. (2015b))

"volume-variety matrix" conceptualization is represented in the central portion of Fig. 14.2: three hypothetical "dots" denote where continuous processing may be beneficial (points "B" and "C" in Fig. 14.2) while considering areas where batch can still be a viable option (point "A"). This stage leads to the identification of *product-process archetypes* that are best candidates for network reconfigurations (i.e., transformative changes in unit operations and actors) enabled by targeted technology interventions, possibly resulting in the emergence of new products.

2. *Subsystem identification and mapping of "current state"*: the incumbent configuration of pharmaceutical supply networks reflects the fact that extensive regulatory requirements operate to a large extent by segregated manufacturing steps, namely, primary manufacturing (i.e., synthesis of active pharmaceutical ingredients/drug substances), secondary manufacturing (formulation of drug products as dose forms), packaging and distribution, and finally dispensing to the patient. Relevant network configuration design rules and trade-offs between them are identified at this stage for each semi-independent subsystem. Value network mapping techniques are particularly useful for defining the overall industrial landscape, as well as actors, technologies, and processes operating within the landscape and its subsystems—Srai (2017) provides a detailed methodology.
3. *Alternative, "future state" supply network scenario formulation and analysis*: alternative scenarios involving continuous technology processing options may be considered and their technology readiness levels assessed. Understanding emerging technologies is crucial at this stage, bringing into the picture scales of production, reordering policies and routes to market that were previously thought unfeasible in a pharmaceutical context (e.g., direct-to-patient e-commerce last-mile delivery, advanced patient diagnostics, close-to-market low-scale integrated manufacturing plant, etc.). Typically, alternative scenarios will

challenge the incumbent supply network configurations for the identified product-process archetypes and introduce new possibilities in terms of product, process, and service offering.

4. *End-to-end supply network system analysis*: the final step consists of E2E network performance analysis, defining potential benefits for the most promising scenarios previously identified. At this stage, existing subsystems are reevaluated from a business perspective as part of a more integrated network reconfiguration agenda considering targeted technological interventions. For example, potential benefits may accrue in terms of revenue/margins, inventory/service levels, etc. against the required capital investments and the technological feasibility of potentially disruptive technologies.

Figure 14.2 shows at a conceptual level the opportunity in the batch-continuous context for particular processing models. The conceptual framework described above has been implemented extensively through case study research for representative products from different regimes of Fig. 14.2, with data being gathered from expert informants during workshops and interviews, as well as secondary data (see, for example, Harrington et al. 2017; Srai et al. 2015b). The potential integration between the framework and technical workflows developed for the implementation of continuous crystallization technologies has also been demonstrated, leading to the identification of critical "attributes" for product-technology screening (Brown et al. 2018). For illustrative purposes, Table 14.3 summarizes insights from the application of the framework to prescreen candidate product segments within specific therapeutic areas for the future application of continuous processing.

14.4 A Multilayered Approach to Analytical Supply Network Modeling

Proceeding from left to right in Fig. 14.1, the last step of the proposed approach to making the business case for continuous processing is the incorporation of quantitative data and analytical tools to complement the conceptual framework discussed in the previous section. Previous work reviews the extant literature, suggesting that incumbent approaches to pharmaceutical supply chain modeling exhibit the following features (Settanni et al. 2017a):

- Quantitative data and analytical tools tend to be applied to specialist subsystems (e.g., plant-level manufacturing scheduling, especially for APIs; clinical trial multiechelon inventory positioning; distribution and logistics; etc.), suggesting difficulties in overcoming functional silos.
- Most pharmaceutical supply chain models are agnostic to specific technologies and market/patient dynamics. In particular, knowledge about specific manufacturing and information technologies is typically a secondary aspect in pharmaceutical supply chain models, rarely contributing to model formulation. Similarly, knowledge of medicine demand/prescription profiles is often exogenous to these models.

Table 14.3 Exemplar results from the application of the conceptual framework

Framework step	Case-specific insights by framework step (nonexhaustive)			
	Case 1: lipid lowering agent[a]	Case 2: antiretroviral[b]	Case 3: antimalarial[b]	Case 4: diabetes[b]
1: Barriers and opportunities	Recommended for high cardiovascular-risk subjects but debated relationship between mortality and LDL cholesterol levels, technical challenges arising from particles with needle-like morphology	Complexity and adherence management, affordability of new combination drugs in least developed countries	Highly subsidized product with target population expected to increase, posing security issues	Mostly "type 2" with greater concerns for treatment affordability/accessibility, major healthcare cost
2: Current-state mapping	Synthetic statins among top 200 most prescribed drugs, decline of natural statin lovastatin market: low cost (~4 USD/kg)[c], very high volume (~17,000 t/a)[c] manufactured via batch/semi-continuous biosynthetic route	High variety (50+ combination), low volumes (<100 t/a), and high cost (>1000 USD/kg); multistage batch characterized by low yield and high wastage	Chiefly artemisinin, multiple combinations, high volume (up to 250 t/a), medium cost (~400 USD/kg), high counterfeit risk, high yield variability due to plant-based active ingredient	Chiefly metformin, very high volumes (tens of thousands t/a), low cost (<20 USD/kg) with wide choice of nonproprietary equivalents, low variety (<10 combinations), simple chemistry
3: Future-state scenario	Potential repurposing to reduce the growth/metastatic spread of melanomas, prevention of Alzheimer and treatment of some types of muscular dystrophy, particle engineering improvement through continuous processing in secondary manufacturing	Service improvement opportunities through greater API control enabling novel, high-leading combination products using continuous formulation	Potential for continuous manufacturing in alternative synthetic routes with lower capex on newly installed capacity to meet increasing demand	Continuous processing enabled by alternative chemistry with improved kinetics, potential capacity gains with lower manufacturing footprint

(continued)

Table 14.3 continued

Framework step	Case-specific insights by framework step (nonexhaustive)			
	Case 1: lipid lowering agent[a]	Case 2: antiretroviral[b]	Case 3: antimalarial[b]	Case 4: diabetes[b]
4: E2E benefits	Better response to demand flexibility under a repurposing scenario through distributed manufacturing, reduction of manufacturing steps through direct compression enabled by continuous crystallization and spherical agglomeration	Better demand matching through continuous processing can reduce complexity, with a positive impact on inventory levels and lead time; limited scale-up opportunities due to complex synthesis; regulator's priority might not align	Lower dependency on harvesting, better quality control and more consistent purity, reduced risk of counterfeiting through "continuous printing" and "serialization," rapid and local response to outbreaks/ emergency situations leveraging available precursors[d]	Greater benefits under high-volume/flexibility scenarios (e.g., doubling global capacity and novel combinations), demanding asset reconfiguration, and ability to relocate closer to specific markets

[a]Based on secondary data/desk research by the authors
[b]Based on published works (Harrington et al. 2017; Srai et al. 2015b)
[c]Based on Clarivate Analytics' Newport estimates
[d]Based on Bio (2018)

The literature provides little guidance on how to carry out early-on quantitative assessment of future supply network configuration scenarios enabled by intensified, continuous processing technologies. Partly, this could be due to the conservativism with regard to manufacturing technologies discussed in the previous sections. However, exploring the future performance space in which an emerging technology may operate is inherently difficult because it is typically carried out before quantitative evidence is available for specific product-process-market contexts: at best, available data are limited to experimental proof of concepts or partial validation at lab scale (Cucurachi et al. 2018).

Some of these challenges can be addressed by moving away from the incumbent silo approach: as multiple layers of analysis are brought together, a richer picture of the pharmaceutical supply chain and the underpinning technologies can be gained (Settanni and Srai 2018b). These layers are represented schematically in Fig. 14.3 and summarized as follows:

- Analysis of country- or sector-level data on, e.g., markets, interorganizational networks and resource availability ("macro" layer)
- Global supply network configuration optimization and analysis, multiechelon inventory simulation ("meso" layer)

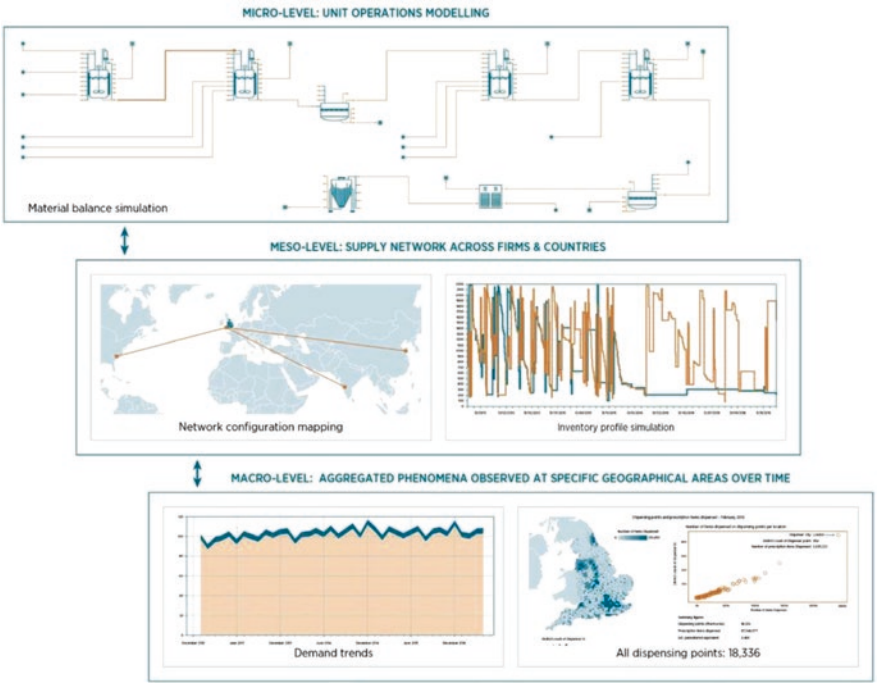


Fig. 14.3 A multilayered approach to pharmaceutical supply chain modeling (expanded detail from Fig. 14.1). (Source: Srai and Christodoulou (2017))

- Formulation of technology intervention scenarios in unit operations/business processes ("micro" layer)

For example, continuous manufacturing technologies are likely evaluated by process engineers at the microlayer (upper slice in Fig. 14.3), emphasizing whether alternative equipment or synthesis routes reduce the number of processing steps, improve yield, and make reactions more consistent. Flowsheet diagrams are the tool of choice at this stage of analysis. However, a purely technical focus could easily lead to a locally optimized system, whereby the benefits of "polishing" a specific factory might be offset by poor (or oversimplified) understanding of the wider supply network behavior downstream in terms of responsiveness to the market dynamics and/or upstream in terms of interactions with the supply base.

Carrying out a technology assessment beyond the four walls of the production plant requires moving towards the mesolayer (intermediate slice in Fig. 14.3) while ensuring that relevant insights from the analysis of unit operations are appropriately "plugged into" network-level configuration and inventory analysis tools. In so doing, difficulties may arise due to the streamlined and "discretized" representation of unit operation technologies that supply chain analysts typically work with due to assumptions that are implicit, such as the following:

- Supply network design is prevalently used in the assembly industry.
- The scope of the analysis is more likely to include site locations than unit operations.

Although without specific application to pharmaceuticals, these assumptions are challenged to an extent by the concept of enterprise-wide process optimization (Quaglia et al. 2012). In practice, the main implications for the specific assessment of continuous manufacturing technologies is that widely used off-the-shelf network design tools are unlikely to provide an adequate technical representation of the corresponding unit operations, thus calling for bespoke analysis.

The third layer of analysis, shown in Fig. 14.3 (bottom slice), represents the analytical exploration of key dynamics in resource availability and demand patterns through, e.g., visual and data-driven analytics. The analysis carried out at the macrolayer can be descriptive and predictive in nature. The latter is perhaps most valued in its own right because big data and digitalization narratives typically suggest that telling associative relationships between unstructured variables can be quickly and effortlessly identified (Waller and Fawcett 2013).

A key link between macro- and mesolayer is the analytical representation of demand signals—actual or forecasted—as well as resource constraints across multiple locations. As in the case of operation technology, the macrolayer is often a black box to the supply chain analyst. For example, in clinical trial supply chains, comprehensive statistical analysis of patient enrollment and dispensing events is common practice; however, insights from field data analysis are rarely integrated in clinical supply network design models, and so are scenarios including alternative technological interventions—with a few exceptions (Settanni and Srai 2018a).

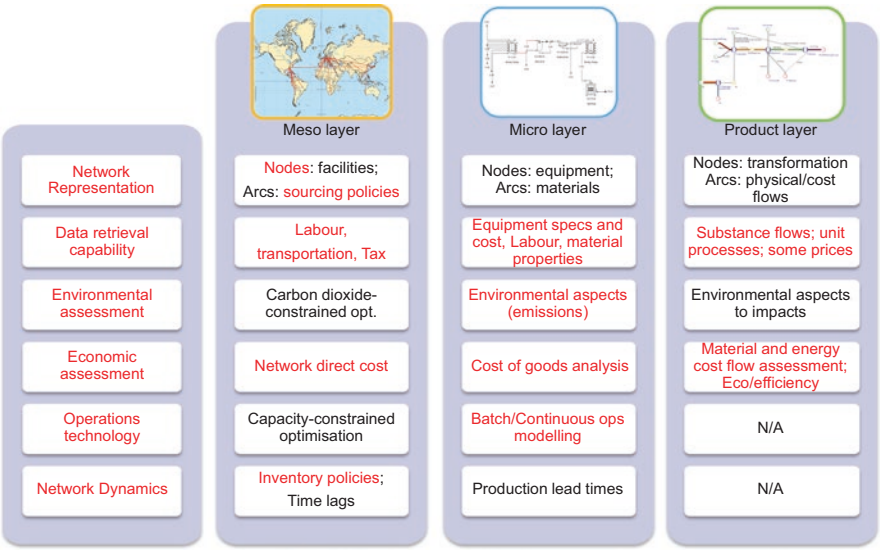
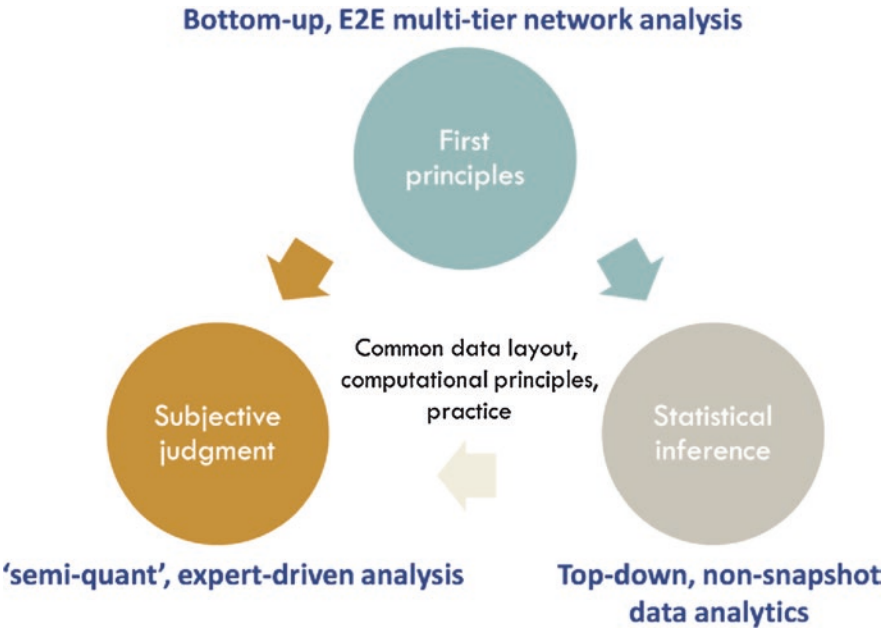


Fig. 14.4 Exemplar evaluation of selected digital network design tools operating at different layers of analysis. (Source: Settanni and Srai (2018b))

From a practitioners' perspective, each layer is readily operationalized through specific digital tools that are commonly employed by most multinationals for technology assessment and supply network design. This operationalization can greatly facilitate bridging different layers of analysis within an organization—and, potentially, the corresponding functional silos. However, in doing so, it also exposes inconsistencies that may arise in the way specialists operating at each layer approach and solve the same problem situation. For example, Fig. 14.4 shows an evaluation of industry-grade, commercial-off-the-shelf tools commonly deployed at the micro- and mesolayer. Despite apparently similar capabilities claimed by specific software vendors in terms of generating optimal supply chain network configurations that jointly reduce costs and environmental burdens, the comparison shown in Fig. 14.4 helps identify whether and to what extent individual tools align in terms of underpinning conceptual models, computational structures, required data, visualization facilities, and data retrieval capability.

Finally, at each layer of analysis described so far, different approaches and tools may be deployed depending on the nature of the data available at specific stages of technology development. Figure 14.5 summarizes which "families" of analytical approaches are typically used with different data—quantitative "snapshot" data, longitudinal/time series data, or hybrid/"semi-quant" (e.g., categorical); it also exemplifies which analytical insights can be generated through each approach to support early-on exploration of a given technology's performance space.



Analytical purpose	First principles	Statistical inference	Subjective judgment
● Explore likely scenarios of future performance for a technology at scale. ● Compare the performance of emerged technology with incumbent technology.	For example, flowsheet simulation informing multi-tier supply network modelling	For example, unsupervised segmentation to quantify 'similarities' between existing technologies	For example, structural modelling, to provide analytical structure to expert opinions and secondary data to reduce subjective bias

Fig. 14.5 Taxonomy of approaches for data-driven, ex ante assessment of emerging technologies. (Based on Settanni et al. (2017b), with additions and modifications)

14.5 Illustrative Applications of the Multilayered Approach

Key concepts introduced in the previous section are further exemplified here using streamlined applications to medicine manufacturing, highlighting specific implications in terms of business case for continuous processing technologies. In the interest of space, the illustration is kept concise and descriptive without disclosing analytical details.

14.5.1 Macrolayer: Data-Driven Industrial System Mapping

Analysis carried out at the macrolayer is concerned with systematically capturing fundamental aspects in mapping supply network configurations, such as the following (Srai 2017): top-level structure of international manufacturing networks, aggregated material flows, indicative product structure and variety, and key actors and transactional relationships.

For example, Fig. 14.6 provides data-driven insights for paracetamol, one of the largest-selling nonproprietary drugs worldwide and the most widely used and prescribed first-line analgesic in the UK (also known as acetaminophen and, by its chemical name, *N*-(4-hydroxyphenyl)acetamide). The focus is on the UK, all data being obtained by leveraging resources in the public domain.

The top half (Fig. 14.6a) looks closer to the point of dispensing to the patient providing a foundation for estimating demand signal at specific geographies in the absence of business-specific data. Proceeding from left to right in Fig. 14.6a, location-specific "hotspots" in terms of prescription dispensing are identified regardless of specific products and trends for specific product formulations in terms of the number of script, expenditure, and units dispensed (500 mg tablets can be considered a typical formulation for this drug), both in absolute terms and relative to total prescriptions across all prescribed medicines in a month. These aggregate, sector-level figures can then be used to simulate more granular demand patterns such as those required at the mesolayer to evaluate alternative supply network designs.

The bottom half (Fig. 14.6b) leverages a completely different set of data (regulatory API registration certificates across the EU) to highlight that, at present, no manufacture of paracetamol as an active pharmaceutical ingredient (API) takes place in the UK or Europe. The likely supply base for crude paracetamol API is located in the USA, China, and India, shipping API varieties (color coded in Fig. 14.6b) toward UK activities that qualify as either importers (17) or distributors (5). Indicative capacity is summarized through a box plot to emphasize the variability in the scattered data disclosed by manufacturers. From a practitioner's perspective, the insights summarized in Fig. 14.6 can be particularly valuable, considering the limited coverage of APIs in published chemical market reports, such as from the early 2000s, and the increasing commercial interest in healthcare data, especially with regard to prescription records (Steinbrook 2006).

Besides buyer–supplier relationships defined in terms of material flows, analysis carried out at the macrolayer can shed some light on contractual relationships between key actors fostering collaboration on specific technologies. For example, Fig. 14.7 visualizes a network of collaborative agreements concerning two natural statins, lovastatin and simvastatin, considered in Table 14.3.

Within this specific network, hubs (nodes with the greatest number of inbound/outbound connections) can be determined by visual inspection to include Kos Pharmaceuticals (acquired by Abbott in 2006) and, rather expectedly, Merck (appearing as multiple nodes due to changes that occurred over time in the

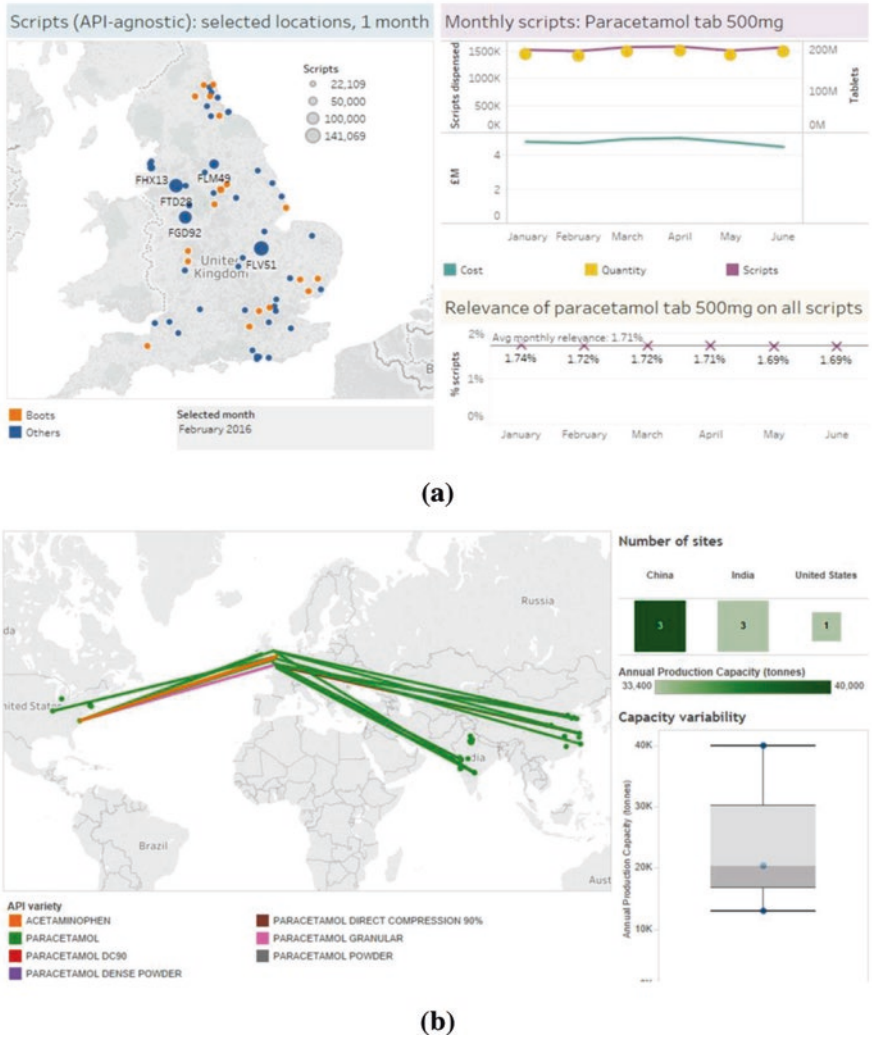


Fig. 14.6 (**a**) Product-specific dispensing estimate in England (raw data: NHS digital: https://digital.nhs.uk/), (**b**) authorized manufacturing footprint based on authorized API importers (raw data: EudraGMP: http://eudragmdp.ema.europa.eu)

company's structure), which pioneered natural statins in the late 1970s (Barrios-González and Miranda 2010). A closer inspection of the edges in the graph highlights the following aspects:

- Only 10% of the captured relationships concern manufacturing and supply agreement of API and/or formulation—over half of which concern Merck's outsourcing of its statin manufacturing activities.

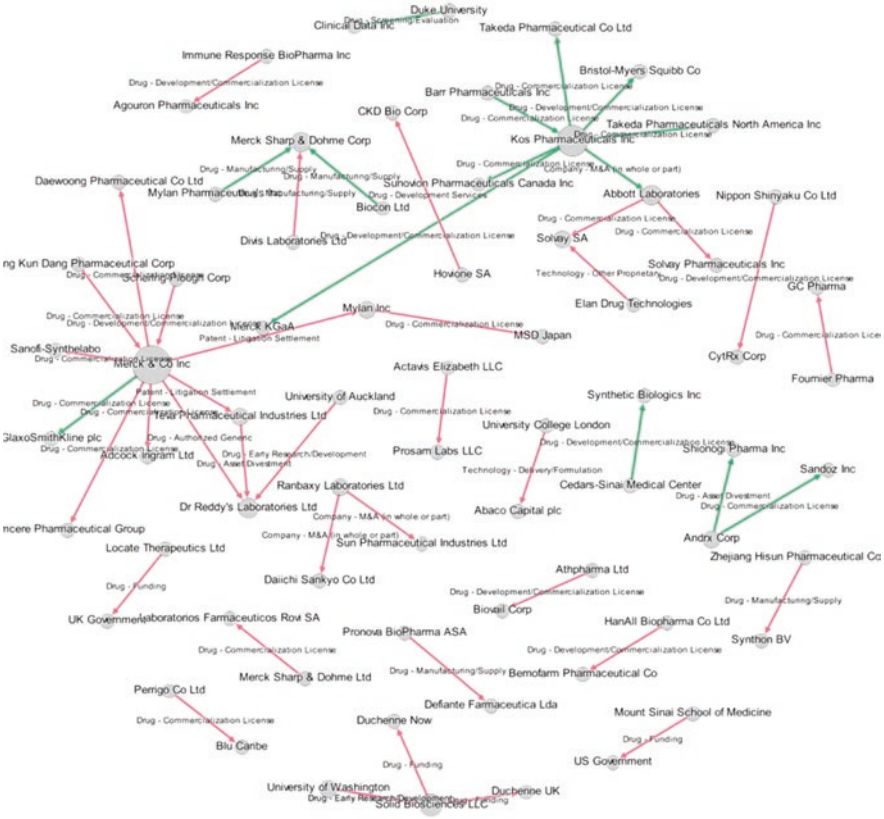


Fig. 14.7 Network representation of collaborative agreements concerning natural statins lovastatin (green arcs) and simvastatin (red arcs)—including combinations. (Authors' elaboration based on Clarivate Analytics' Cortellis data (as of February 2018))

- Twelve percent of arcs (labeled "early research development" or "funding") concern collaborations on simvastatin being repurposed for the treatment of certain types of muscular dystrophy or atherosclerotic plaques.

The above application shows an industrial landscape where potential users of continuous technologies are most likely contract manufacturing organizations seeking to provide greater flexibility through scaling up/numbering up within exclusive supply agreements (Pollak and Vouillamoz 2012). Continuous processing may also play a role in the possible reshoring of key intermediates to protect against disruptions of highly prescribed medicines due to, e.g., foreseeable changes in international trade agreements. With specific regard to simvastatin, opportunities for lab-scale continuous manufacturing may arise from repurposing as novel combinations are developed in adjacent therapeutic areas such as musculoskeletal and cardiovascular.

14.5.2 *Microlayer: Assessment of Current and Perspective Unit Operations*

Models developed at the "micro" layer (upper slice in Fig. 14.3) generate analytical insights into relevant manufacturing technologies and how these are, or could be, implemented under specific supply network configuration scenarios. Following the scheme presented in Fig. 14.5, it is possible to implement distinct modeling approaches at this layer, depending on which type of data is available as the technology of interest develops. In what follows, examples illustrate different principles that can be used to model unit operations depending on what is known about the underpinning technology. Numerical results from an overarching exemplar application are shown in Table 14.4, with a focus on the paracetamol current-state example introduced earlier and selected environmental performance indicators (Settanni et al. 2017b).

Case 1: Chemistry and Manufacturing Technologies Are Fairly Well Understood In the presence of sufficient evidence from a theoretical and experimental viewpoint, it is possible to deploy data-driven models of unit operations using computer-aided flowsheet simulation diagrams. Flowsheet simulation of fine chemical synthesis and pharmaceutical product formulation are supported by fairly well-established modeling platforms available off the shelf and typically yield "first principle" estimates of the following (Petrides et al. 2010):

- Cycle time and throughput estimate
- Bill of material generation from known kinetics/stoichiometry
- Equipment sizing and corresponding resource demand (labor, energy, utilities, etc.)
- Manufacturing cost analysis (typically through a direct costing approach)
- Campaign scheduling feasibility analysis and debottlenecking

In general, a "first principles" approach to unit operation modeling can be used to replicate the actual behavior of an installed base operating, e.g., at the commercial scale for incumbent batch technologies or at lab scale for continuous processing technologies; the same insights can also be helpful to explore the likely behavior of novel operation technologies under scale-up/number-up scenarios. This approach has been used, for example, to compare the economics of batch and continuous technologies for an existing commercial API all the way through tablet formulation (Schaber et al. 2011; Gerogiorgis and Jolliffe 2015). Flowsheet simulation often plays a major role in the environmental life-cycle assessment (LCA) of medicines, LCA being now regarded as a key engineering research area supporting the industry-wide adoption of "green chemistry" practices (Jiménez-González et al. 2011).

When developing a business case for the shift to continuous technologies, the first challenge is to create a flowsheet simulation for existing as well as new technology-based processes using process simulators, e.g. Aspen Plus, SuperPro

Table 14.4 Example results for the environmental assessment of paracetamol obtained from multiple approaches shown in Fig. 14.5

Modeling approach	Unit op data	Approach/tool	Unit of measure	Manufacturing supply chain stage			
				Raw materials	API manufacture	Formulation	Packing
"First principles"	Snapshot quantitative data on material flows based on secondary evidence (literature, patents)	Combined flowsheet diagram simulation and life-cycle assessment (LCA)—see right-hand side of Fig. 14.4 for details	$kgCO_2$-eq/pack	33.35	44.48	0.06	0.91
"Subjective judgment"	Environmental aspect scoring via categorical data based on secondary evidence (literature)	Multicriteria ranking of life-cycle stages by impact category using analytical hierarchy process (AHP)	Dimensionless rank	N/A	0.663	0.259	0.078
Statistical inference	Industry-driven data set on ~30 APIs linking carbon footprint to process characteristics (e.g., annual production volume, no. of synthesis steps, chirality, etc.)	Multivariate regression and supervised segmentation, visual analytics	$kgCO_2$-eq/kg API	N/A	>900	N/A	N/A

Based on Settanni et al. (2017b)

Designer, gPROMS Process Builder, or to make own process models using MATLAB, gPROMS Modelbuilder, etc. The process needs to incorporate all the steps involved in manufacturing a drug, i.e. API synthesis, API separation and purification, and tablet manufacturing so as to conduct an end-to-end case study. Each of these steps consists of an integration of individual unit operations. For the existing process, generally, these unit operations are performed in the form of batches, while for the new process, we consider a part/all of these processes being performed in continuous flow, depending upon which the new process can be either integrated continuous and batch (Schaber et al. 2011) or completely continuous (Jolliffe and Gerogiorgis 2015). The development of flowsheet simulation for the existing process requires data related to process diagram, process conditions, recycling, energy integration, batch sizes, and scheduling. In most situations, these data have to be collected based on extensive/exhaustive search. Different products, however, may present specific challenges. For example, "white biotechnology" products, such as lovastatin, are more widely discussed in terms of API manufacturing technologies, with comparative analyses focused on solid-state versus liquid-submerged fermentation, either batch or semi-continuous—see, e.g., Goswami et al. (2012). Thus, one has to use secondary data and his/her process engineering expertise to make up for the missing information. For the new process, the data requirement remains the same with some alterations: residence times and equipment sizes instead of batch sizes and details of new technology and additional unit operations added/removed from the new process, which can be detailed in a process flow diagram.

Figure 14.8 shows an example of a current-state/future-state unit operation map based on paracetamol as a demonstrator—a detail process description is provided elsewhere (Aulakh et al. 2018b). The existing/current-state flowsheet was developed based on secondary data collected from the literature search; however, due to limited information, scheduling was carried out using in-house simulation in SuperPro Designer. Also, where possible, the process was linked to specific supply geographies within the network configuration presented in Fig. 14.6. The flowsheet simulation for current-state manufacturing would, for example, take into account the fact that central or nearly all the paracetamol manufacturing routes currently exploited commercially involve a reduction-acetylation system where *p*-nitrophenol is reduced to *p*-aminophenol, and the result is acetylated to *N*-acetyl-*p*-aminophenol (Mitchell and Waring 2000), and that in such countries as India, where a large part of the UK paracetamol supply base is located, the *p*-nitro chlorobenzene (PNCB) route is estimated to account for 80% of production (NIIR 2004). With specific regard to environmental assessment metrics, flowsheet simulation on secondary data is sufficient to generate detailed results for each manufacturing stage, as shown in Table 14.4. For the new paracetamol process, a conceptual process flow diagram and experimental, lab-scale data were obtained as a part of research collaboration by CMAC (Continuous Manufacturing and Crystallization) Future Manufacturing Research Hub. Flowsheet simulation was deployed to connect the newly developed and individually optimized processes to form a complete process.

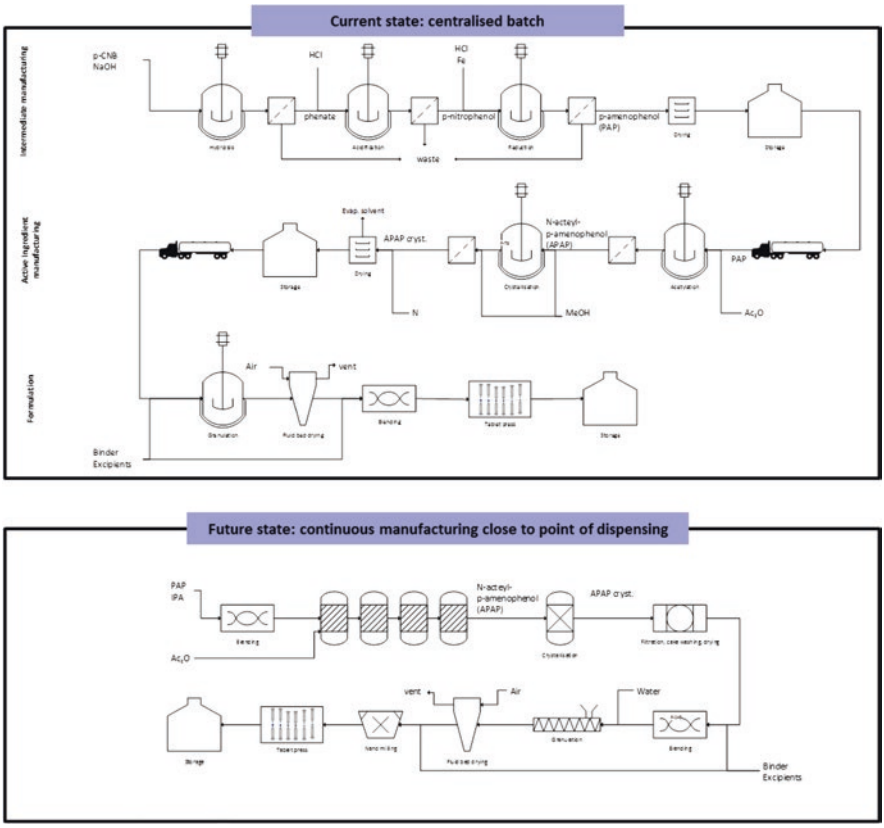


Fig. 14.8 Current- and future-state unit operations using process flowsheet diagrams (details omitted) for paracetamol API manufacturing. (Based on Aulakh et al. (2018b) and Brown et al. (2017))

From a continuous processing perspective, sometimes greater attention is paid to specific unit operations due to manufacturability implications, e.g., lovastatin crystals' characteristic high aspect ratio needle-like morphology or seeded cooling continuous crystallization of paracetamol (Brown et al. 2018). In such situations, the process engineer needs to use secondary data and his/her process engineering knowledge to connect the individual unit operations and respective material and energy flows to develop a continuous process that uses the experimental data as its foundation. For the continuous paracetamol process, similar exercise was performed for developing a process flowsheet that was simulated in SuperPro Designer. Further to note is that while comparing the existing and new processes, one might have to scale up the continuous processes from lab scale to the desired scale of comparison with batch unless data exist for both at similar scales of operation. This also depends upon the type of manufacturing set-up we are considering while developing the business case. In case of paracetamol, a process flowsheet for a

small/microfactory was used to compare it with batch process while setting it up in a distributed manufacturing scenario, as will be discussed in Sect. 14.5.3.

Case 2: Extensive Data (Longitudinal/Historical) Available for Fielded Technologies With the advancement of predictive analytics, the discovery of relevant measures of association from past observations across a variety of products is believed to greatly simplify the cumbersome task of understanding the "mechanics" of specific manufacturing processes in detail.

As in the case of first-principle flowsheet modeling, the cost and environmental footprint of medicine manufacturing are example performance metrics where the principle of statistical inference from an extensive data set of historical or longitudinal observations is extensively used. For example, de Soete et al. (2014) identify potential explanatory variables to predict environmental hotspots from 40 batch "recipes" for 5 APIs covering almost 3000 tasks performed by unit operations. Basu et al. (2008) use historical trend analysis to estimate the cost of goods sold across different types of pharmaceutical manufactures—research driven, generics, biotech—as well as the relationship with R&D effort.

With specific reference to the paracetamol example, results in Table 14.4 were obtained by analyzing excerpts from an industry-contributed data set covering circa 30 undisclosed APIs obtained in confidence. The excerpt covering only primary manufacturing results could be obtained only for one stage of the paracetamol manufacturing chain. No significant association could be found; however, a supervised segmentation approach was deployed to predict whether the product's carbon footprint would be greater than a certain threshold, rather than its magnitude.

The application of statistical inference principles to evaluate alternative manufacturing technologies has been less extensive so far. Adjacent application includes possible synergies between flexible synthesis workstations based on continuous manufacturing and automated selection of optima synthesis paths for a given molecule based on predictive analytics (Peplow 2014). Lapkin et al. (2017) reported the generation of multiple possible reaction routes to convert a biowaste feedstock, limonene, to paracetamol through data mining using Reaxys and a network analysis of the combined literature and in-house reaction set. The approach was based on combining data mining with heuristics and using network representation of chemical knowledge for automating the analysis to evaluate possible routes for paracetamol. The routes were analyzed based on the criteria of mass and energy efficiency, along with route reliability and the selected criteria of environmental importance. Finally, based on the literature and additional in-house data, a complete process flowsheet for manufacturing paracetamol from limonene was developed and modeled (Fig. 14.9). Such advances in automated synthesis planning and automated process design in future might also be extended to flexible and transformative augmentation of optimal supply chain configurations and of the corresponding underpinning technologies.

Case 3: Emerging Technologies Are Only Described Through Secondary Data and Expert Opinion A final case concerns situations where quantitative data

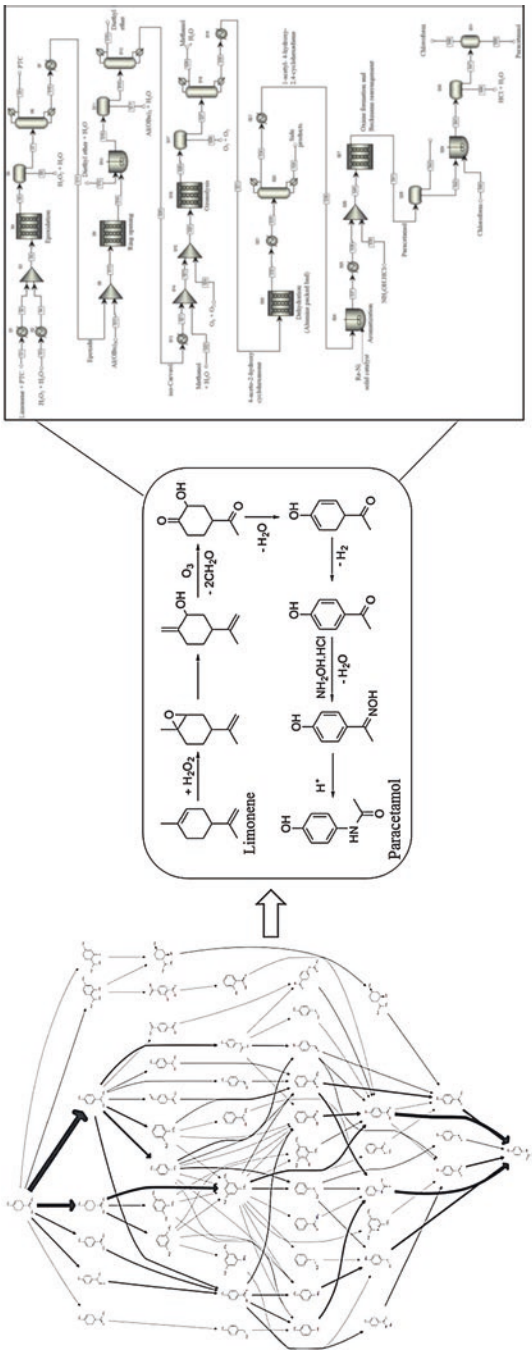


Fig. 14.9 A network of possible synthetic routes from limonene to paracetamol and process flowsheet of one selected route. (Based on Lapkin et al. (2017))

describing the performance of a given technology is not readily available. It is fairly common to elicit expert knowledge for ranking the relative importance of alternative technology options with respect to given criteria. Unlike the previously examined approaches, this type of analysis requires scoring the examined options and criteria with respect to each other, leveraging evidence available through secondary data or elicited from experts. For example, Choudhury et al. (2004) combine expert judgment and quantitative data to estimate the relative priority of different stock-keeping units in balancing the workload of pharmaceutical packaging lines. Another example closer to the chemical processing operations is provided by Manipura et al. (2013), who use expert knowledge to identify lowest risk/highest capability reaction schemes available at the early stage of process development, considering a range of criteria that include the application of continuous flow reactors for an improved process control.

In the paracetamol example, the performance metric shown in Table 14.4 under the subjective judgment approach was derived by gathering evidence from the literature to score resource intensities in a two-step process: first, by evaluating the relative importance of four criteria representing classes of environmental aspects (direct emissions and emissions embedded in resources, energy, and waste) and, second, by assessing three aggregated manufacturing supply chain stages (API, formulation, and packing) with respect to each criteria.

Other applications of the subjective judgment principle include the design of multicriteria decision-making tools to prioritize technological interventions from subject expert knowledge and/or systematic secondary data analysis. The following example is based on Aulakh et al. (2018a), who suggest a multicriteria decision-making approach to support the comparative evaluation of emerging technologies; considering multiple criteria, however, can be a challenge in the absence of detailed and specific quantitative data. In this study, the analytical hierarchical process (AHP) was used to support early-stage assessment of five representative API manufacturing reactor technologies: conventional batch, microreactor, microwave, supercritical fluid (SCF), and continuous stirred-tank reactor (CSTR) cascade. AHP allowed for a set of attributes, which have an impact on technology selection, to be compared with the importance of each attribute relative to its impact on the selection.

The typical steps involved in AHP are as follows: (1) identify multiple criteria/attributes, (2) identify multiple technology solutions, (3) determine the ranking/weights of attributes, and (4) evaluate the ranking of alternatives. In the specific case of rector technologies for the manufacture of pharmaceuticals, each technology's performance was evaluated qualitatively based on secondary data with regards to a range of 11 criteria through a rigorous scoring system.

To illustrate the scoring process using reports from the literature and industrial expert opinions, an example is shown in Table 14.5. The example refers to scoring microreactor and microwave reactor against batch reactor based on the attributes of solids handling capability; batch reactor was scored the highest since it could handle all solids, whereas as per the reports, only 38% of reactions could be handled in microreactor, and microwave was demonstrated to handle slurries above 30%. On the other hand, microreactor was scored higher than microwave reactor when the

Table 14.5 Example of the literature used for reactor technology selection based on attribute scoring (Aulakh et al. 2018a)

	Solid handling	Process cost	Continuous processing
Microreactor	Fifty percent of the reactions can benefit from microreactor technology. However, 62% of these reactions cannot be performed in microreactors due to the presence of solid (Lonza).	The investment costs for a continuous multipurpose microreactor plant were calculated to be as high as or even higher than that of a conventional batch plant (Lonza).	Demonstrated since two decades. It is a commercial product of AzurChem GmbH, 4-cyanophenylboronic acid, made by microprocess technology (1 production period = 10 kg of product).
Microwave	CamWave technology made continuous flow applicable to handling slurries and suspensions in microwave reactors. This opens up continuous flow to virtually all reactions of pharmaceutical interest, well beyond the estimated 30% that is or can be made homogeneous (Cambrex).	Selective heating can significantly increase efficiency and decrease operating cost (AstraZeneca).	Cambrex CaMWave KiloLAB reactor was operated continuously for 32 h, giving 22.3 kg of product.
Summary	All these reactions can be/are being carried out in conventional batch reactors.	Yield improvements compared to conventional technology will be necessary to justify higher investment costs.	Continuous processing is quite well established in microreactors.

continuous manufacturing capability was considered for which batch was scored the least. Through the use of AHP, a larger number of, perhaps individually less important, indicators do not get ignored in the final decision during a simplification that relies too heavily on a small number of key criteria.

The findings of the study highlighted that the ability of a specific emerging technology to replace conventional batch technology depends on the relative importance that experts assign to specific performance areas (Fig. 14.10). The importance of specific attributes is ought to change for specific product segments/therapeutic areas, and therefore the analysis not only needs to be performed individually on different products but also needs to be updated as technology improvements take place. The repeated deployment of the tool for a range of products can define the feasible zones for a given technology within the volume-variety matrix. A possible mapping of technology on volume-variety matrix is shown in Fig. 14.10 (for illustrative purpose only). However, such a multicriteria decision-making tool allows an early-stage assessment of processing technology options for given product-process-market contexts prior to detailed modeling and full supply network configuration design.

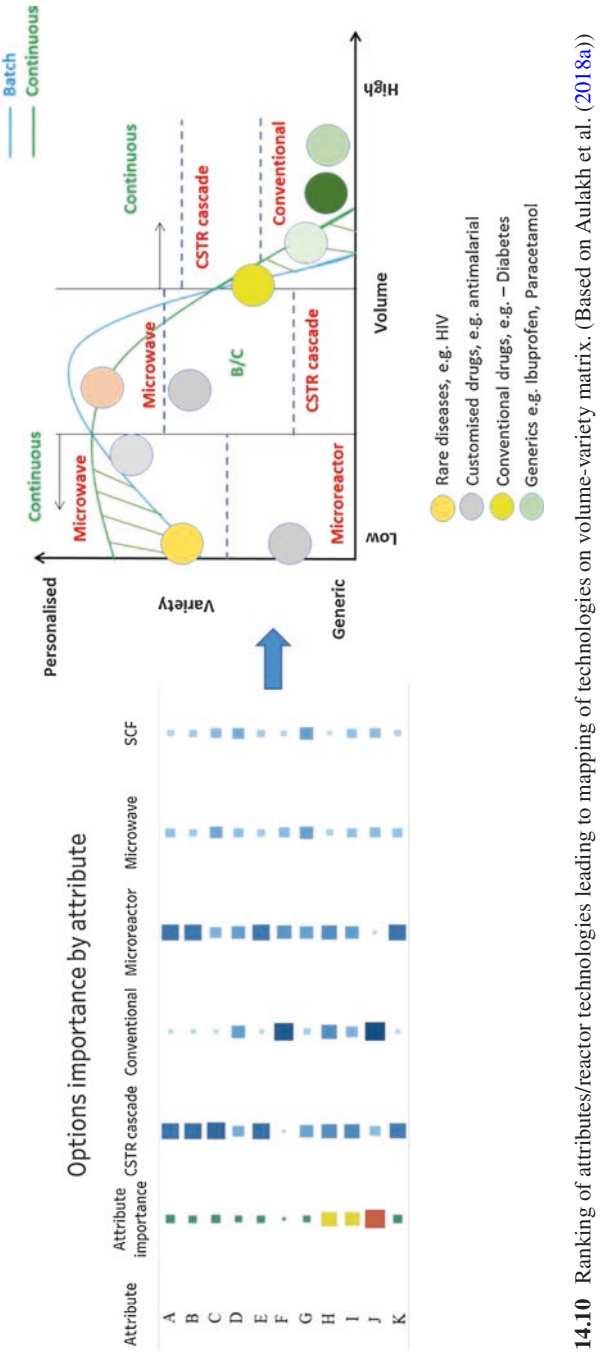


Fig. 14.10 Ranking of attributes/reactor technologies leading to mapping of technologies on volume-variety matrix. (Based on Aulakh et al. (2018a))

14.5.3 *Mesolayer: Network Optimization and Inventory Modeling*

The intermediate layer in Fig. 14.3 combines insights from the other layers (macro and micro) to enable supply network configuration design. In general, the pillars of data-driven supply network design typically require detailed representation of site locations, product architecture, and demand signals (Watson et al. 2013). Considered jointly, these elements define a "superstructure" whose behavior is determined by current and envisaged flows of information and materials through the network, governance relationships between key organizations, and product-process technological intervention scenarios (Srai and Gregory 2008).

Figure 14.11a, b shows a typical structure for a generalized, commercial pharmaceutical supply network configuration; it also maps against such the figure shows example techonlogy interventions at specific supply chain stages, based on evidence from a recently concluded, industry-led UK research program (Badman

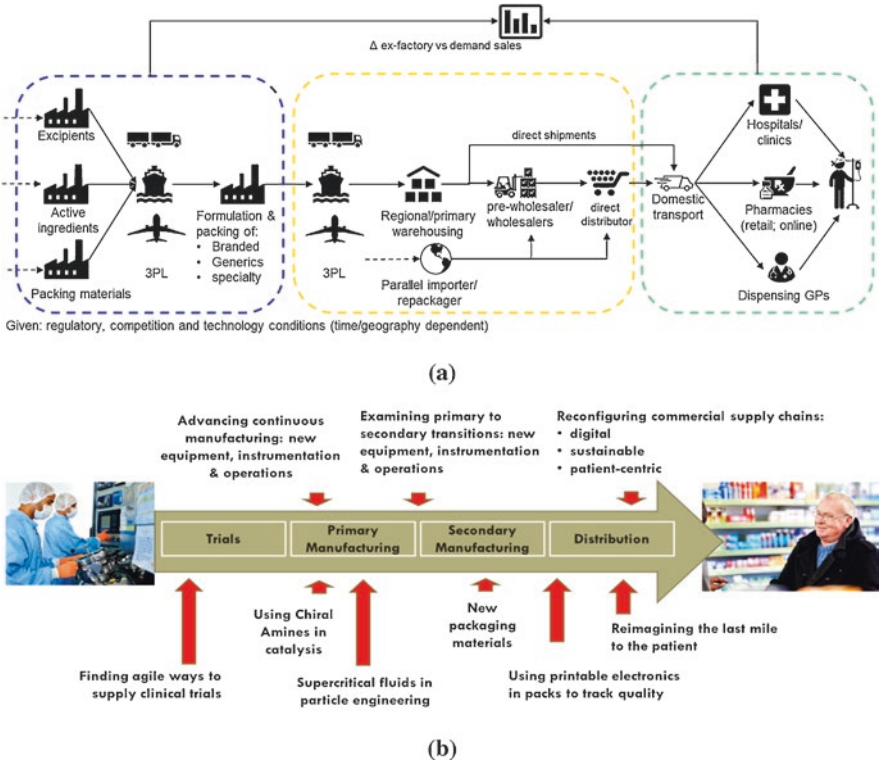


Fig. 14.11 (**a**) "Linear view" of a streamlined pharmaceutical supply chain, (**b**) exemplar interventions at each stage based on outcomes from the industry-led, UK-based ReMediES research program (www.remiediesproject.com)

and Srai 2018). The supply chain structure displayed in Fig. 14.11 is linear as it "follows the pill," rather than mirroring a geographically dispersed manufacturing footprint. Within this typical supply chain structure, one distinguishes the following actors: manufacturing organizations delivering APIs (primary), intermediates and formulated pharmaceutical products (secondary), packaging and leaflets, and nonmanufacturing organizations, including (at minimum) third-party logistics providers (3PL), medicine distributors (prewholesale, wholesale, and direct retail), and dispensing points—e.g., pharmacies, hospitals, dispensing physicians, and even fast-moving consumer goods (FMCG) retailers for some medicines sold over the counter. Moving beyond the physical flows, additional actors emerge. For example, country-specific context such as the US may have a wider range of intermediaries, such as payers and controllers (Rees 2011).

In principle, demand signals for in-market product are generated at the point of dispensing; in practice, misalignment between these signals and product ex-factory forecasts is typically due to intermediaries' behaviors, such as speculation, pipeline fill-and-bleed policies, etc. (Cook 2015). The distinction between generics, branded, and speciality pharmaceutical, as well as the possibility of parallel imports and repackaging in Fig. 14.11, adds to the behavioral complexity of the pharmaceutical supply chains.

Specialized approaches and tools can be deployed at the mesolayer to evaluate the operational performance of novel manufacturing network configurations building on insights generated by the early-on characterizations of relevant technologies carried out at the microlayer. For illustrative purposes, the interplay between knowledge of the operating conditions of an emerging technology and supply-network-level repercussions of deploying continuous processing can be illustrated through hypothetical scenarios of particular relevance for continuous processing, such as those arising from the following network design requirements:

- Capacity flexibility through the use of small-scale modular production concepts with the possibility of "numbering up" or decoupling container-scale devices as required capacity (see, e.g., Bieringer et al. 2013)
- Responsiveness to local demand fluctuation through a "pharmacy on demand" concept enabled by miniaturized and mobile "reaction toolboxes," achieving fully integrated multistep synthesis, purification, and formulation (see, e.g., Lewin et al. 2016)

Continuous technology alone cannot formulate a business case; it is imperative to consider which manufacturing scenario might be credible for a product and technology combination. Figure 14.12 illustrates possible scenarios to evaluate potential repercussions of supply chain configuration redesigns that leverage continuous manufacturing in terms of the necessary scale to respond to specific volume/variety market requirements (high/low) and location (distributed/centralized). When considering the products that are manufactured in medium-to-high volumes, the current-state-of-art manufacturing, followed by the pharmaceutical industry is batch. The possible replacement manufacturing strategy at this scale could be pro-

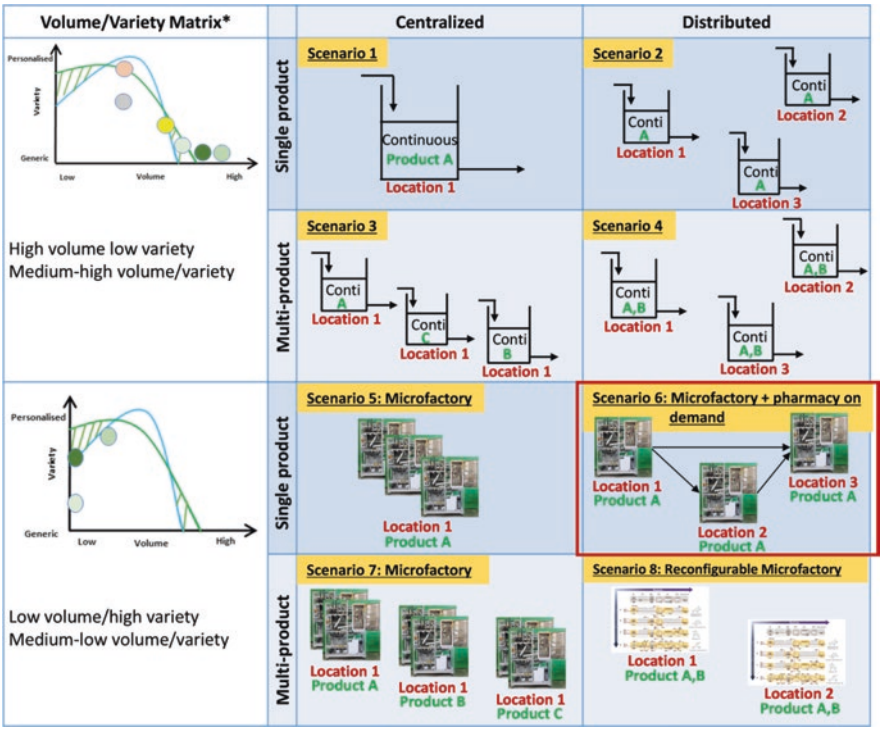


Fig. 14.12 Manufacturing network scenarios enabled by continuous processing technologies. Volume/variety matrix concept as per Fig. 14.2

ducing the products at the same scale in a continuous fashion in single location or in multiple locations, as depicted by scenarios 1 and 2 in Fig. 14.12. The same manufacturing regime can be followed for multiple products (scenarios 3 and 4). For small-scale products, the current batch manufacturing can be substituted by modular units or small/microfactories centralized at a single location (scenario 5) or distributed geographically over multiple locations for on-demand production (scenario 6). A similar strategy can be applied for multiple products (scenario 7) wherein, in scenario 8, there exists an additional future opportunity of exploiting reconfigurable modular units (Lewin et al. 2016). These are highly adaptable small pieces of equipment, which implement real-time monitoring that demonstrates the concept of continuous, small-scale, on-demand production of pharmaceuticals (Adamo et al. 2016).

Scenario 6 (combining the concepts of microfactory and pharmacy on demand) will be further considered for the sake of example. In this scenario, a "microfactory" technology, including an integrated one, such as the one described in Sect. 14.5.2, is deployed in a distributed manufacturing network configuration scenario whereby production activities of a pharmaceutical product are located closer to, or even colocated with, key dispensing points and hence closer to the patient. In the hypothetical

paracetamol demonstrator case used so far, a microfactory unit can plausibly achieve integrated continuous operations from acetylation of intermediate material *p*-aminophenol, through crystallization and filtration, to tablet formulation.

Figure 14.14 shows results obtained when, for a simplified numerical example, considering only six hypothetical dispensing points located in England, underpinned by actual data on high-prescribing points of dispensing, shown in Fig. 14.6, consistently with which a 30-day random demand signal is generated for each location. The same demand signal would drive both current- and future-state scenarios, shown in Fig. 14.13. For each scenario, lead times (in the case of batch manufacturing) or residence times (in the case of continuous processing), bill of materials, and manufacturing cost were obtained by flowsheet simulation (as explained in Sect. 14.5.2). The current-state supply base was mapped from public-domain data, as explained in Sect. 14.5.1.

Insights from unit operation modeling were integrated into a broader network design/optimization model using off-the-shelf tool Supply Chain Guru (Llamasoft, Ann Arbor, MI). To define the network structure, policies were declared for each product in the estimated bill of material and for each manufacturing or distribution node in a specific network configuration with regard to sourcing (multiple/single), transportation (e.g., less than truckload), and inventory replenishment (e.g., RQ—fixed reorder point/order quantity).

With regard to the final product (paracetamol tablets), the right-hand side of Fig. 14.13 shows production and final inventories over time. For the "current-state" scenario, an inventory of the final product is recorded at three echelons (distribution centers and secondary manufacturing facility), whereas for the distributed manufacturing case, an inventory is held at each dispensing point.

The hypothetical future-state scenario in Fig. 14.13 is underpinned by two "penalizing" assumptions about the continuous technology: (1) the microfactories hold no initial inventory at the beginning of the time window, and (2) the minimum run length is 24 h during the time window considered. While different microfactories have been allowed to operate below full capacity while meeting peak demand locally, once production started, it was not allowed to stop and restart. To compensate for the first assumption, in the network optimization step, the microfactories were allowed to meet each other's excess demand if capacity was insufficient. The results in Fig. 14.13 show that, under the abovementioned penalizing assumptions, both scenarios have comparably similar inventory positions at the end of the time window.

To demonstrate the sensitivity of network-wide performance to the level of understanding of the operational conditions for an emerging technology, a second iteration was carried out, allowing a less stringent run size of 5 days, strictly consecutive, with the possibility to operate at any point between minimum and maximum capacity during such time window. Also, microfactories were only allowed to respond to local demand while introducing one-day equivalent initial inventories at each location to prevent infeasibility. As shown in Fig. 14.14, under these revised

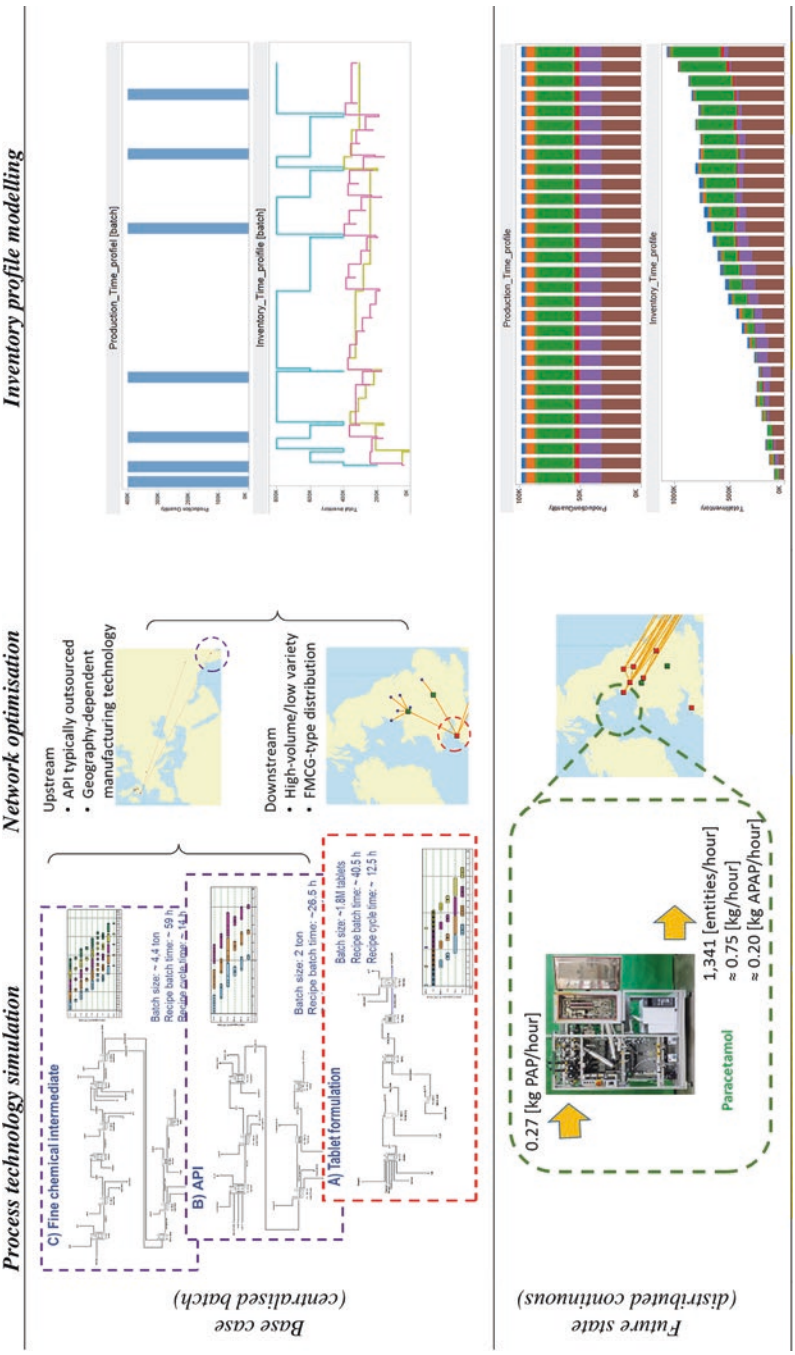


Fig. 14.13 Pharmaceutical supply chain network configuration and inventory modeling for a centralized batch current state (above) versus future state (below) involving distributed continuous microfactories

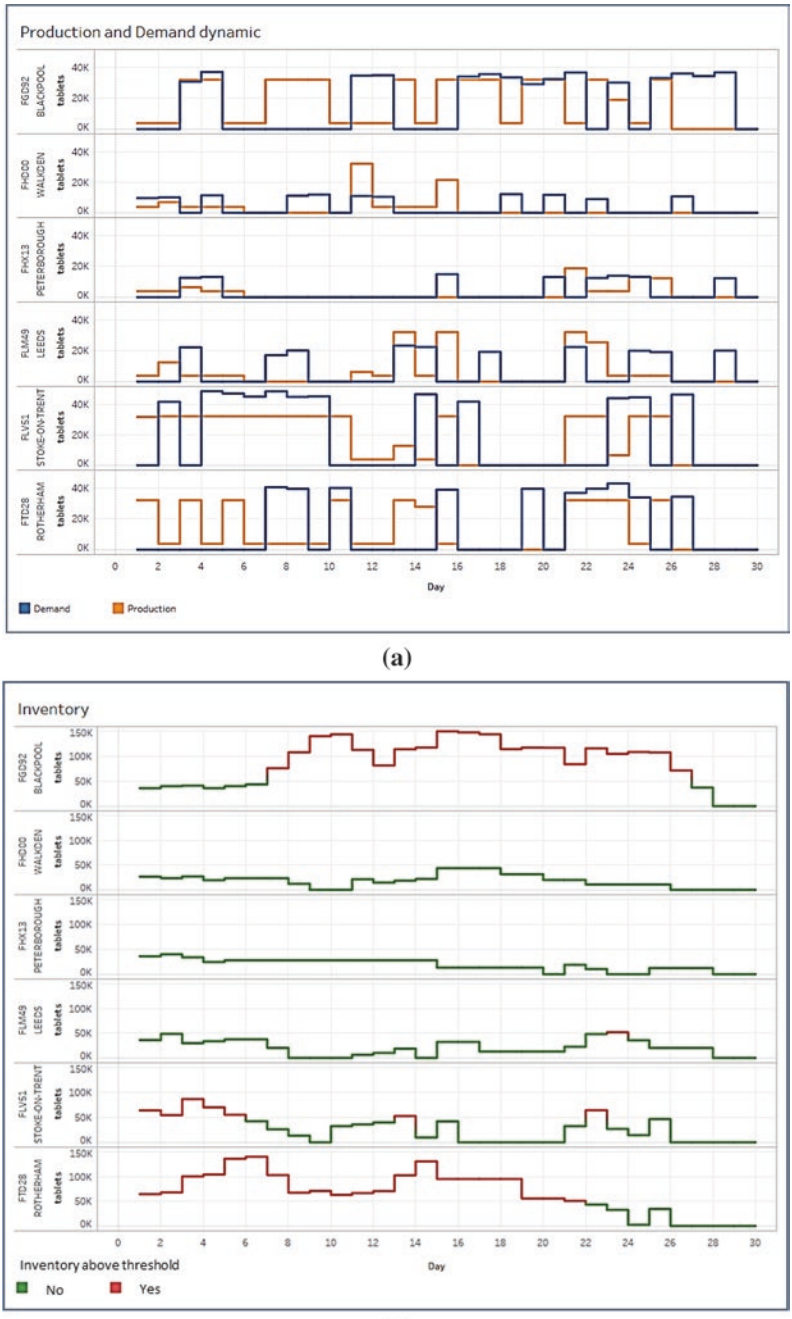


Fig. 14.14 Revised network-level production (**a**) and inventory (**b**) profile simulation for the distributed microfactory scenario (run size of 5 days, one-day-worth initial inventory)

assumptions, the distributed microfactory scenario operates very close to the concept of "on demand pharmacy" with zero inventory at the end of the time period at each location.

14.6 Concluding Remarks

This chapter has provided an overview of the key concepts, approaches, and tools to assess opportunities enabled by targeted technological interventions such as continuous medicine manufacturing from an end-to-end pharmaceutical supply network configuration perspective. It recommends that a "multi-layered" analysis is adopted when evaluating a business case for continuous manufacturing. With the aid of numerical examples based on outcomes from leading UK research programs, we demonstrate how to achieve greater integration between product/process technologies and supply chain dimensions for the evaluation of emerging technologies for specific product categories/therapy areas.

Modeling principles for the exploration of their operational space have been discussed, with an emphasis on the nature of the data that may be available as emerging technologies are developed.

Identification of "feasible zones" for a given technology for desired levels of volume and variety requires that the analysis is iterated for a range of products and under specific hypothesis with regard to the technology's operating conditions. Throughout this chapter, it is emphasized that early-stage production process design is a crucial input to a detailed evaluation of manufacturing and supply chain benefits for specific product-technology configurations through a multilayer system modeling platform.

Achieving a realistic understanding of the operating conditions for chosen continuous technologies enables the supply network designer to evaluate alternative configurations and select those that better support network-level performance improvements in terms of inventory reductions and manufacturing responsiveness. Particular emphasis is placed on the potential for achieving enhanced product flexibility (in terms of volume and variety) and, depending on scale, the optimum number and location of manufacturing operations to support speed to market and system-level cost benefits. In the case of multiple manufacturing operations using continuous production process technologies, where production facility replication through digital twins is becoming a key enabler, the chapter sets out a supply network design and analysis approach that evaluates the commercial and operational viability of alternative manufacturing supply network scenarios.

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References

Adamo A, Beingessner RL, Behnam M, Chen J, Jamison TF, Jensen KF, Monbaliu J-CM, Myerson AS, Revalor EM, Snead DR, Stelzer T, Weeranoppanant N, Wong SY, Zhang P. On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system. Science. 2016;352(6281):61–7.

Aulakh PK, Settanni E, Srai JS. Application of analytical hierarchy process (AHP) for comparative evaluation of API manufacturing technologies. In: 22nd Cambridge International Manufacturing Symposium, September 27–28, 2018, Cambridge. 2018a.

Aulakh PK, Settanni E, Srai JS. Unit process modelling of pharmaceuticals using public domain data: the case of paracetamol. Unpublished working paper. Institute for Manufacturing, University of Cambridge, Cambridge, UK. 2018b.

Badman C, Srai JS. ReMediES: collaborative research in action. White Paper. 2018. Available at: https://remediesproject.com/wp-content/uploads/2018/11/ReMediES-Collaborative-Research-in-Action.pdf.

Barrios-González J, Miranda RU. Biotechnological production and applications of statins. Appl Microbiol Biotechnol. 2010;85(4):869–83.

Basu P, Joglekar G, Rai S, Suresh P, Vernon J. Analysis of manufacturing costs in pharmaceutical companies. J Pharm Innov. 2008;3(1):30–40.

BBC News. Public may have to stockpile drugs in no-deal Brexit. 2018. Accessed 23 Oct 2018.

Bieringer T, Buchholz S, Kockmann N. Future production concepts in the chemical industry: modular – small-scale – continuous. Chem Eng Technol. 2013;36(6):900–10.

Bio MM. Flow chemistry as an enabling technology for essential medicine. Pharma Horiz. 2018;2(1):38–9.

Boswell C. Western manufacturers buy in China. Chem Mark Rep. 2004;265(23):FR4, FR6.

Boswell C. Drug deals go east. ICIS Chem Bus. 2007;272(16):23–5.

Brown CJ et al. MicroFactory prototype report V1.0 10-07-17. Unpublished technical report. CMAC, University of Strathclyde. 2017.

Brown CJ, McGlone T, Yerdelen S, Srirambhatla V, Mabbott F, Gurung R, Briuglia ML, Ahmed B, Polyzois H, McGinty J, Perciballi F, Fysikopoulos D, MacFhionnghaile P, Siddique H, Raval V, Harrington TS, Vassileiou AD, Robertson M, Prasad E, Johnston A, Johnston B, Nordon A, Srai JS, Halbert G, ter Horst JH, Price CJ, Rielly CD, Sefcik J, Florence AJ. Enabling precision manufacturing of active pharmaceutical ingredients: workflow for seeded cooling continuous crystallisations. Mol Syst Des Eng. 2018;3(3):518–49.

Choudhury AK, Tiwari MK, Mukhopadhyay SK. Application of an analytical network process to strategic planning problems of a supply chain cell. Case study of a pharmaceutical firm. Prod Plan Control. 2004;15(1):13–26.

Cook AG. Forecasting for the pharmaceutical industry: models for new product and in-market forecasting and how to use them. Aldershot/Burlington: Gower; 2015.

Cucurachi S, van der Giesen C, Guinée J. Ex-ante LCA of emerging technologies. In: 25th CIRP life cycle engineering (LCE) conference, 30 April – 2 May 2018, Copenhagen, Denmark, vol. 69. 2018. p. 463–468.

de Soete W, Debaveye S, de Meester S, van der Vorst G, Aelterman W, Heirman B, Cappuyns P, Dewulf J. Environmental sustainability assessments of pharmaceuticals: an emerging need for simplification in life cycle assessments. Environ Sci Technol. 2014;48(20):12247–55.

Dell'Orco P, Tix M. The state of continuous processing: thirteen companies share their experiences. Presented at the 3rd international symposium on continuous manufacturing of pharmaceuticals (ISCMP). 2018.

FDA – U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for industry: PAT – a framework for innovative pharmaceutical development. Manufacturing, and Quality Assurance. 2014.

Friedli T, Basu P, Bellm D, Werani J, editors. Leading pharmaceutical operational excellence: outstanding practices and cases. Heidelberg: Springer; 2013.

Gerogiorgis DI, Jolliffe HG. Continuous pharmaceutical process engineering and economics. Chim Oggi. 2015;33(6):29–32.
Goswami S, Vidyarthi AS, Bhunia B, Mandal T. A review on lovastatin and its production. J Biochem Technol. 2012;4(1):581–7.
Harrington TS, Phillips MA, Srai JS. Reconfiguring global pharmaceutical value networks through targeted technology interventions. Int J Prod Res. 2017;55(5):1471–87.
Jiménez-González C, Poechlauer P, Broxterman QB, Yang B-S, Am Ende D, Baird J, Bertsch C, Hannah RE, Dell'Orco P, Noorman H, Yee S, Reintjens R, Wells A, Massonneau V, Manley J. Key green engineering research areas for sustainable manufacturing: a perspective from pharmaceutical and fine chemicals manufacturers. Org Process Res Dev. 2011;15(4):900–11.
Jolliffe HG, Gerogiorgis DI. Process modelling and simulation for continuous pharmaceutical manufacturing of ibuprofen. Chem Eng Res Des. 2015;97:175–91.
Lapkin AA, Heer PK, Jacob P-M, Hutchby M, Cunningham W, Bull SD, Davidson MG. Automation of route identification and optimisation based on data-mining and chemical intuition. Faraday Discuss. 2017;202:483–96.
Lewin JJ, Choi EJ, Ling G. Pharmacy on demand: new technologies to enable miniaturized and mobile drug manufacturing. Am J Health Syst Pharm. 2016;73(2):45–54.
Made Smarter Review. 2017. Available at: https://www.gov.uk/government/publications/made-smarter-review.
Manipura A, Martin EB, Montague GA, Sharratt PN, Houson I. Risk-based decision making in early chemical process development of pharmaceutical and fine chemical industries. Comput Chem Eng. 2013;55(Supplement C):71–82.
McWilliams JC, Allian AD, Opalka SM, May SA, Journet M, Braden TM. The evolving state of continuous processing in pharmaceutical API manufacturing: a survey of pharmaceutical companies and contract manufacturing organizations. Org Process Res Dev. 2018;22(9):1143–66.
Mitchell SC, Waring R. Aminophenols. In: Ullmann's encyclopedia of industrial chemistry. Weinheim: Wiley-VCH; 2000.
NIIR – National Institute of Industrial Research. Drugs & pharmaceutical technology handbook. Delhi: Asia Pacific Business Press; 2004.
Peplow M. Organic synthesis: the robo-chemist. Nature. 2014;512(7512):20–2.
Petrides D, Koulouris A, Siletti C, Jiménez JO, Lagonikos PT. The role of simulation and scheduling tools in the development and manufacturing of active pharmaceutical ingredients. In: am Ende DJ, editor. Chemical engineering in the pharmaceutical industry. Hoboken: John Wiley & Sons, Inc; 2010. p. 521–41.
Pollak P, Vouillamoz R. Fine chemicals. In: Ullmann's encyclopedia of industrial chemistry. Weinheim: Wiley-VCH; 2012.
Quaglia A, Sarup B, Sin G, Gani R. Integrated business and engineering framework for synthesis and design of enterprise-wide processing networks. Comput Chem Eng. 2012;38:213–23.
Rantanen J, Khinast J. The future of pharmaceutical manufacturing sciences. J Pharm Sci. 2015;104(11):3612–38.
Rees H. Supply chain management in the drug industry: delivering patient value for pharmaceuticals and biologics. Hoboken: John Wiley & Sons, Inc; 2011.
Schaber SD, Gerogiorgis DI, Ramachandran R, Evans JMB, Barton PI, Trout BL. Economic analysis of integrated continuous and batch pharmaceutical manufacturing: a case study. Ind Eng Chem Res. 2011;50(17):10083–92.
Settanni E, Srai JS. Combining field data analysis and simulation to evaluate an alternative Just-In-Time clinical trial supply strategy. In: 22nd Cambridge International Manufacturing Symposium, September 27–28, 2018, Cambridge. 2018a.
Settanni E, Srai JS. Towards a new approach to modelling pharmaceutical supply chains in a changing technological landscape. Pharma Horiz. 2018b;2(1):26–8.
Settanni E, Harrington TS, Srai JS. Pharmaceutical supply chain models: a synthesis from a systems view of operations research. Oper Res Perspect. 2017a;4:74–95.

Settanni E, Srai JS, Yatskovskaya E, Harrington TS. Exploring generalisations for sustainability assessment in medicine manufacturing networks. In: 24th International Annual EurOMA Conference, July 3–5, 2017, Edinburgh. 2017b.

Shah N. Pharmaceutical supply chains: key issues and strategies for optimisation. Comput Chem Eng. 2004;28(6–7):929–41.

Srai JS. Mapping industrial systems – a supply network perspective on enabling technologies, processes and actors. Int J Manuf Technol Manag. 2017;31(1/2/3):82–99.

Srai JS, Christodoulou P, Settanni E. Next generation supply chains: making the right decisions about digitalisation. Institute for Manufacturing, University of Cambridge, 2017. Available online at https://www.ifm.eng.cam.ac.uk

Srai JS, Gregory M. A supply network configuration perspective on international supply chain development. Int J Oper Prod Manag. 2008;28(5):386–411.

Srai JS, Badman C, Krumme M, Futran M, Johnston C. Future supply chains enabled by continuous processing – opportunities and challenges. May 20–21, 2014 Continuous Manufacturing Symposium. J Pharm Sci. 2015a;104(3):840–9.

Srai JS, Harrington TS, Alinaghian L, Phillips M. Evaluating the potential for the continuous processing of pharmaceutical products – a supply network perspective. Chem Eng Process. 2015b;97:248–58.

Stegemann S. The future of pharmaceutical manufacturing in the context of the scientific, social, technological and economic evolution. Eur J Pharm Sci. 2015;90:8–13.

Steinbrook R. For sale: physicians' prescribing data. N Engl J Med. 2006;354(26):2745–7.

UNCTAD – United Nations Conference on Trade and Development. World investment report: investment in the digital economy. 2017.

Waller MA, Fawcett SE. Data science, predictive analytics, and big data: a revolution that will transform supply chain design and management. J Bus Logist. 2013;34(2):77–84.

Watson M, Lewis S, Cacioppi P, Jayaraman J. Supply chain network design: applying optimization and analytics to the global supply chain. Upper Saddle River: FT Press; 2013.