Received: 6 September 2021 | Accepted: 10 November 2021

DOI: 10.1002/mcda.1775

RESEARCH ARTICLE

WILEY

Continuous manufacturing technologies in upstream pharmaceutical supply chains: Combining engineering and managerial criteria

Parminder Kaur Aulakh | **Ettore Settanni** | **Jagjit Singh Srai**

Department of Engineering, Institute for Manufacturing, Centre for International Manufacturing, University of Cambridge, Cambridge, UK

Correspondence
Ettore Settanni, Department of Engineering, Institute for Manufacturing, Centre for International Manufacturing, University of Cambridge, Alan Reece Building, 17 Charles Babbage Road, Cambridge CB3 0FS, UK.
Email: e.settanni@eng.cam.ac.uk

Funding information
Support from the Engineering and Physical Sciences Research Council (EPSRC) Future Continuous Manufacturing and Advanced Crystallization (CMAC) Research Hub (Grant No. EP/P006965/1) is gratefully acknowledged.

Abstract

The COVID-19 pandemic exposed vulnerabilities in upstream pharmaceutical supply chains (PSC). One is that the global supply of active pharmaceutical ingredients (APIs) is overly dependent on few locations and large-scale batch manufacturing. Regulators hope to enable more dependable location decisions and improved processing quality with the adoption of advanced technologies such as process intensification through continuous manufacturing (CM). Conceptual work suggests that the benefits of shifting from batch to CM accrue end-to-end across the PSC. Yet detailed quantitative information about CM is limited at an early stage of evaluation, and too specialised to inform managerial decisions about PSC reconfiguration. Supply chain and engineering criteria are rarely combined in the early-stage evaluation of alternative CM technologies. Extant CM research typically overlooks implications for supply chain managers. To address the current gap, this article evaluates, at an early stage of adoption, alternative CM reactor technologies for the synthesis of APIs in selected therapeutic areas. With evidence from secondary data, relevant technologies and criteria are identified, and their relative importance is evaluated in a semi-quantitative fashion following analytical hierarchy process (AHP) principles, ensuring that findings are intelligible to both engineers and managers. The proposed empirical work enriches previous conceptual frameworks predicated on volume-variety considerations. Specifically, findings suggest that, all things considered, microreactor technologies outperform alternatives. However, PSC managerial considerations introduce nuances in specific therapeutic areas, for example, antivirals where a tension between complex chemistry and the need for flexibility in unit operations may favour batch manufacturing. For analgesics the need to exploit the existing manufacturing base whilst addressing inventory reduction favours technologies that incorporate elements of batch and CM. The proposed analysis is in line with real-world decisions that global medicines manufacturers are increasingly facing, as governments seek to develop local health countermeasures to the COVID-19 pandemic in the absence of detailed information.

Parminder Kaur Aulakh was with the University of Cambridge at the time this research was carried out.

KEYWORDS
advanced manufacturing, analytical hierarchy process, continuous manufacturing, pharmaceutical supply chains, process intensification, reactor technologies

1 | INTRODUCTION

The 2019 coronavirus (COVID-19) pandemic exposed vulnerabilities in upstream portions of pharmaceutical supply chains (PSCs) where active pharmaceutical ingredients (APIs) are manufactured (Economist, 2020; Osterholm & Olshaker, 2020). Like most fine chemicals, API synthesis takes place in centralised, large-scale batch plants (Pollak & Vouillamoz, 2013). To develop future medical countermeasures, regulators are promoting the uptake of advanced manufacturing in PSCs (Hahn & Shah, 2020). Even prior to COVID-19, regulators looked at advanced manufacturing of pharmaceuticals to promote an increase in domestic production and prevent quality issues commonly associated with medicine shortages and recalls (Riley et al., 2019; Woodcock, 2019). A prominent example of advanced pharmaceutical manufacturing technology is process intensification via continuous manufacturing—CM (Ganesh & Reklaitis, 2020; Hahn & Shah, 2020; Lee et al., 2015). Unlike continuous processing of commodity chemicals, CM is driven by quality rather than economies of scale (Burcham et al., 2018). In principle, applications of CM technologies span 'end-to-end' unit operations along the PSC (e.g., Domokos et al., 2020). In practice, CM is most developed for drug product formulations, with fewer applications targeting the synthesis and separation/purification of APIs and intermediate chemicals (Burcham et al., 2018).

Making the case for emerging pharmaceutical processing technologies such as CM remains a complicated task (McWilliams et al., 2018). Evaluating alternative processing equipment and unit operations involves multiple, potentially conflicting criteria (Hodgett, 2016; Hodgett et al., 2014). In early process design stages, reactor technology selection is rarely based on detailed process modelling and analysis, which is usually too complex, costly, and time-consuming (Emenike et al., 2018). Alternatively, equipment selection relies solely on the intuition of experienced practitioners (Double, 2006). Intuition from experience and normative decision-making coexist to some extent, but the role of subjectivity is still debated (e.g., Wenstøp, 2005).

Extant work investigates the engineering merits of CM in depth, but rarely includes supply chain management considerations. Yet, as governments seek to develop local medical countermeasures in the wake of the recent pandemic, medicines manufacturers' decisions on technology adoption and manufacturing network configuration are often interrelated. Hence, there is an unmet need to strike a balance between specialist technical knowledge about CM and strategic managerial insights into supply chain configuration decisions. The former is often inaccessible to the non-specialist. The latter are often unstructured.

To overcome the current gap, this article provides a cross-disciplinary perspective on evaluating the potential for CM reactor technologies in upstream PSC. It addresses the following research questions:

- *RQ1*: What are the relevant criteria to evaluate at an early stage the potential of emerging CM reactor technologies for the synthesis of APIs in upstream PSC?
- *RQ2*: How does the available evidence on relevant technologies inform equipment selection decisions, when supply chain management criteria are included?

In addressing the RQs we favour well-established, semi-quantitative approaches to Multi-Criteria Decision Analysis (MCDA) that are intelligible to both managers and engineers.

The remainder of this article is as follows. Section 2 introduces the chosen methodological approach. Section 3 identifies relevant technologies and summarises secondary data for use in the analysis. Section 4 illustrates key findings. In Section 5, findings are discussed in the light of existing theoretical conceptualisations. The closing section summarises key insights, pointing to the limitations of the proposed approach and avenues for further development.

2 | MATERIALS AND METHODS

The problem of interest for this research is hierarchical in nature. It involves judgment about technological options according to technical/managerial criteria deemed relevant. Also, it seeks to establish an informed priority structure among such options and criteria. This type of problem lends itself to being formalised using techniques such as the analytical hierarchy process (AHP), a well-established framework to handle multiple, potentially conflicting criteria in decision-making. A comparative overview of AHP in the broader context of MCDA is outside scope. Interested readers are referred to Marttunen et al. (2017). The principles underpinning AHP and its extensions are extensively illustrated in Saaty (2010) and will not be repeated here. Some computational aspects of AHP that are rarely addressed will be discussed in Section 4. Whilst well-established, the original formulation of AHP is not immune from criticism or suggestions for improvement (Alvarez et al., 2021; Saaty, 2010, Ch. 14; Sushil, 2009; Donegan et al., 1992), but it affords a comprehensive theory grounded in transparent algebraic principles, which has favoured its inter-disciplinary implementation.

Technology selection problems informed by MCDA date back to the 1970s (Linstone et al., 1979). Developments in areas of interest for this article include advanced manufacturing (e.g., Sambasivarao & Deshmukh, 1997; Sobota et al., 2021); healthcare (e.g. Glaize

et al., 2019) and chemical processing including pharmaceuticals (Hodgett, 2016; Hodgett et al., 2014).

For chemical reactor technologies, several applications evaluate alternative equipment based on a range of chemistry and processing conditions (e.g., Calabrese & Pissavini, 2011; Krasberg et al., 2014; Lindeque & Woodley, 2019). Few exceptions deploy formalised MCDA approaches such as AHP (Hanratty & Joseph, 1992). Typically, the focus is on lab-scale API production, with fewer works considering managerial implications beyond equipment acquisition cost (Hall & Stoker, 2003). Peeling and Talford (2020) propose a framework but without disclosing the details in a specific application.

The approach proposed in this article consists of the following steps: (1) expert review of key CM technologies for the synthesis of APIs and their use in specific therapeutic areas; (2) engineering-driven identification of relevant attributes; (3) ranking the identified technology options and their contribution to PSC reconfiguration opportunities using analytical multi-criteria reasoning. All steps rely mainly, although not exclusively, on secondary data. To keep the scope reasonable, research is limited to APIs in the following therapeutic areas: (1) antivirals, (2) antimalarials, (3) antidiabetes and (4) analgesics. In these areas, previous frameworks suggest the adoption of CM is beneficial for PSC (Harrington et al., 2017; Srai et al., 2015). The recent pandemic has revived interest in these families of APIs due to attempts at drug repurposing and shortage issues. A subset of 14 APIs across all therapeutic areas was identified by querying Web of Science for related CM studies. Most of these APIs (~53%) are antivirals. Supplementary materials (S1) provide details.

3 | IDENTIFICATION OF TECHNOLOGY OPTIONS AND CRITERIA

This section leverages secondary data to identify relevant options and criteria for use in AHP. The technical literature is synthesised for a wider readership. In line with the chosen scope, the focus is placed on API synthesis operations in upstream PSC.

3.1 | Reactor technologies

Simplistically put, a reactor fills, holds processing material (for the time necessary to complete reactions according to specific kinetics), and then empties (either partly or completely). Batch reactor technology is the benchmark in commercial scale API synthesis, with production-to-reactor-volumes of 15–30 t/m^3 per year (Pollak & Vouillamoz, 2013). However, the scale of production may vary from milligrams to tons per year, depending on product life cycle stage (e.g., lab; clinical trials; pilot, etc.), and manufacturing strategy (Kockmann et al., 2008).

CM technology provides the following alternatives to batch reactors: (1) conventional continuous reactor technologies and their low volume counterparts, that is, plug flow reactors (PFRs), microreactors (μR), continuous stirred tanks (CSTRs), and 'miniature CSTR cascade' (cCSTR); (2) tube-in-tube reactors (TITRs), which allow gas/liquid flow reactions; and (3) packed bed reactors (PBRs), which allow the use of solid catalysts. For a technical overview see am Ende and am Ende (2019, Ch.16); Mo and Jensen (2016).

3.2 | Technology evaluation criteria

The following describes the rationale underpinning the formulation of criteria for evaluating the identified technology options. Academic literature provides the necessary evidence.

3.2.1 | Hazardous chemistry and process conditions

This set of criteria evaluates how alternative reactor technologies handle the trade-off between operational safety and process optimisation (am Ende & am Ende, 2019). At any step of API synthesis, hazardous reagents may be employed, and highly exothermic reactions may take place; also, the accumulation of heat may cause side-reactions or run-away reactions, with serious threats to safety (Barton & Rogers, 1997). Novel process conditions, typically high temperatures, pressures and concentrations, can significantly reduce the reaction time by substantially accelerating the reaction rates (Hessel et al., 2012).

3.2.2 | Reaction reagents and operational issues

Reactor technologies need to handle the so-called heterogeneous reactions in API synthesis that is, reactions involving different phases—solid, liquid and gases. Solids are present in over 60% of the reactions in the form of catalysts, reactants or products (Roberge et al., 2005). API synthesis may involve gas–liquid reactions, and the use of toxic, flammable or corrosive gases as reagents, especially at larger scales (Brzozowski et al., 2015). In addition to handling different types of reactants, reactors need to function under various operating challenges such as the formation of solids by precipitation, or the decomposition of reactants, leading to fouling problems.

3.2.3 | Energy supply

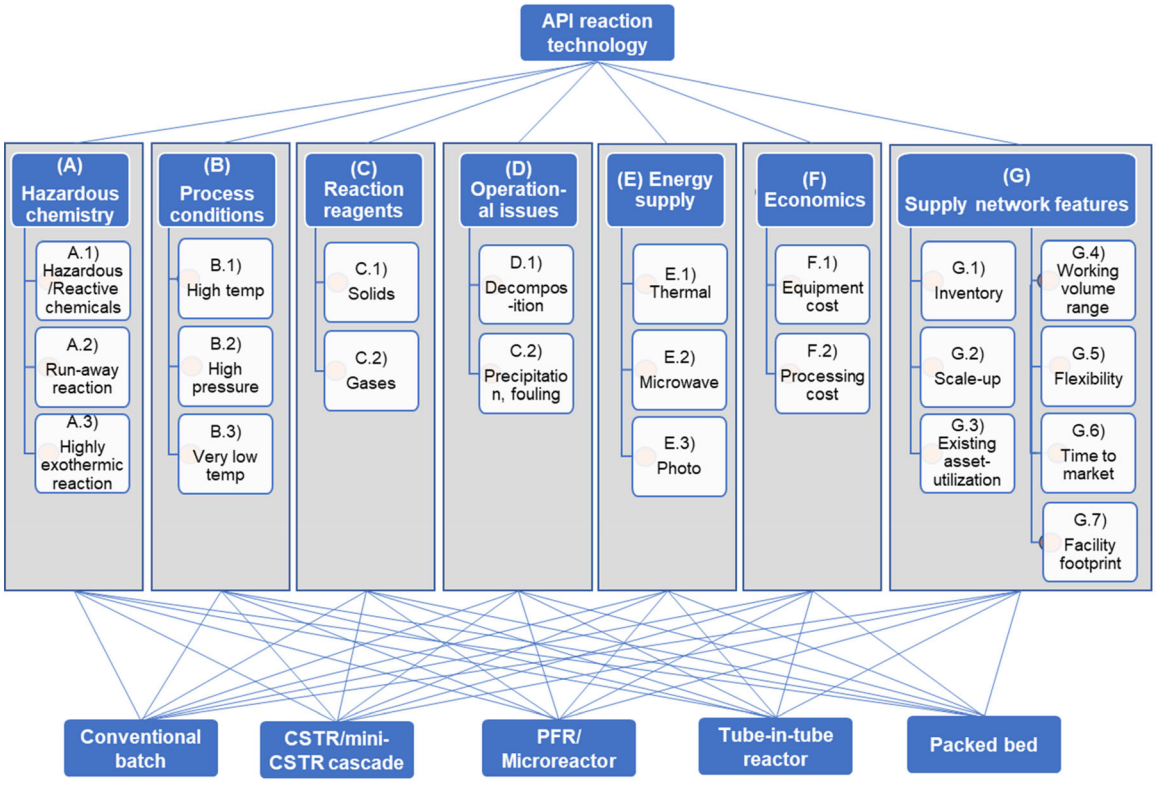
Most pharmaceutical processes are designed to run isothermally, requiring effective heat removal/addition during reaction (am Ende & am Ende, 2019, Ch. 3). The addition/removal of heat to or from the reaction mixture by heating/cooling agents is a commonplace feature in reaction technology (Kern, 1950). With the increase in energy and process intensification requirements, especially in continuous flow synthesis, innovative approaches to power supply have emerged. These include microwave irradiation, photo irradiation and inductive heating (Porta et al., 2016). Reactor technologies differ in their ability to accommodate novel energy sources, with implications for processing conditions.

3.2.4 | Economics

Technical criteria are often complemented by some knowledge of equipment acquisition cost ('CapEx'), which is promptly appraised from the required disbursements. Indeed, capital budgeting for chemical processing is a well-established topic (Brennan, 1998). The reactor technology used also affects unit production costs through the design and management of manufacturing operations. However, as API manufacture is often outsourced, unit production costs are typically approximated by purchasing prices in procurement (Friedli, 2006; Hill et al., 2018).

3.2.5 | Supply network configuration features

Few references consider managerial aspects of technology selection beyond cost (e.g., Hall & Stoker, 2003). However, the benefits of CM extend beyond the 'four walls' of individual manufacturing facilities (Woodcock, 2019). Supply chain-oriented criteria have been proposed in the literature with a focus on improving medicine inventory control, and achieving smaller, more distributed manufacturing footprints (Harrington et al., 2017; Srai et al., 2015). These criteria are agnostic towards reactor technologies, with some exceptions in other fields (e.g., Zolkaffly & Han, 2014).



(a)

	A			B			C		D		E			F		G						
	A.1	A.2	A.3	B.1	B.2	B.3	C.1	C.2	D.1	D.1	E.1	E.2	E.3	F.1	F.2	G.1	G.2	G.3	G.4	G.5	G.6	G.7
AV	●			●		●	●	●	●	●	●			●	●	○		○			○	
AM	●				●	●	●	●			●		●	●	●					○		
AD	●	●	●				●	●			●				●		○			○		
AN	●		●		●		●		●		●	●	●	●	●	○		○				

Notes:
AR: antivirals; AM: antimalarials; AD: antidiabetes; AN: analgesics.
The symbol ● denotes evidence of relevance for a given attribute in a specific therapeutic area in the technical literature. The symbol ○ denotes some evidence from conceptual research.

(b)

FIGURE 1 Hierarchical formulation for reactor technology selection for API synthesis in upstream PSC (a), with insights into specific therapeutic areas (b)

4 | FINDINGS

The problem of interest is structured consistently with AHP as shown in Figure 1(a). The diagram displays seven top-level criteria broken down in 22 sub-criteria.

In the presence of sub-criteria, AHP is implemented as described in Saaty (2008). Findings are obtained in two stages: (1) Scoring and prioritisation of identified criteria and sub-criteria within each therapeutic areas; (2) Paired comparison of reactor technologies with reference to each sub-criterion. These evaluations are combined to obtain a final priority structure by which technologies are ranked. The below sections provide details.

4.1 | Assessment of criteria by therapeutic area

As a premise to paired comparisons, insights into the relevance of each criteria for a given therapeutic area were derived from the literature. For example, work listed in Supplementary Materials S1 for antivirals shows that precipitation is likely to take place (e.g., Dolutegravir and Emtricitabine). Solids may also be involved in key synthesis steps (e.g., Atazanavir and Efavirenz). This leads to the conclusion that handling precipitation/fouling is a relevant criteria for reactor technologies targeting antivirals. As a further example, most studies on the synthesis of antimalarial APIs indicate the presence of photo-oxidation. Photo-based reactions seldom occur in other categories, with few exceptions, for example, ibuprofen. This may suggest greater need for photo energy sources in reactor technologies targeting antimalarial.

Similar evaluations were carried out for each API, yielding the table at the bottom of Figure 1. For top-level criteria, Figure 1(b) suggests that analgesics require comparatively simpler synthesis, shifting the emphasis on energy supply and process cost. Antidiabetes drugs are slightly more difficult to manufacture as multiphase reactants are often involved (e.g., Vildagliptin). Antivirals and antimalarials are the most demanding technology-wise, as they involve extreme process conditions, hazardous chemistry and operational challenges.

For supply chain criteria it was not possible to carry out a similar assessment since the literature is sparse. Insights on demand, value, variety and supply uncertainty were obtained from public domain data on representative pharmaceutical products in the therapeutic areas of interest. These include prescription data from NHS England, and regulatory data on API manufacturers and importers into the UK. Figure S3.1 in Supplementary Materials (S3), provides a visual excerpt for illustration.

Paired comparisons were carried out according to the fundamental semi-numerical scale of AHP, which ranges from 1 (as important) to 9 (extremely more important). The rationale behind this fundamental scale is extensively discussed in Saaty (2010: Ch.4). One of the authors who is a practising chemical engineer developed the standalone insights in Figure 1(b) into paired comparisons between technical criteria and sub-criteria. Comparisons between supply chain sub-criteria were performed by another author with extensive experience as a supply chain director. The relationship between top-level supply chain and technical criteria was explored by perturbation analysis instead of direct scoring. A hypothetical scenario was chosen such that supply chain features 'very strongly' dominate technical criteria. This initial scenario was perturbed at a later stage by changing the initial scores along a reduced range of the fundamental scale (1–7) deemed appropriate for the limited evidence available.

Evaluation of criteria and sub-criteria yielded 32 paired comparison matrices. In the interest of space, these are detailed in the Supplementary Materials (S2). Each therapeutic area consists of one matrix of paired comparisons between top-level criteria (Table S2.1), and seven matrices of comparisons between sub-criteria (Tables S2.2–S2.5). Each matrix of paired comparisons yields a priority vector and a ranking. These results are complemented by measures of consistency of the underpinning judgments (Table S2.6). Figure 2 provides a visual summary of priorities for criteria and sub-criteria, respectively.

For top-level criteria, Figure 2(a) shows priorities obtained from the initial scores in Table S2.1 as well as priorities obtained from perturbing the initial supply chain scores that meet the highest consistency criteria. The computation of priorities, consistency measures and perturbations are discussed further in the following sub-section.

4.2 | Numerical approximation and consistency of results

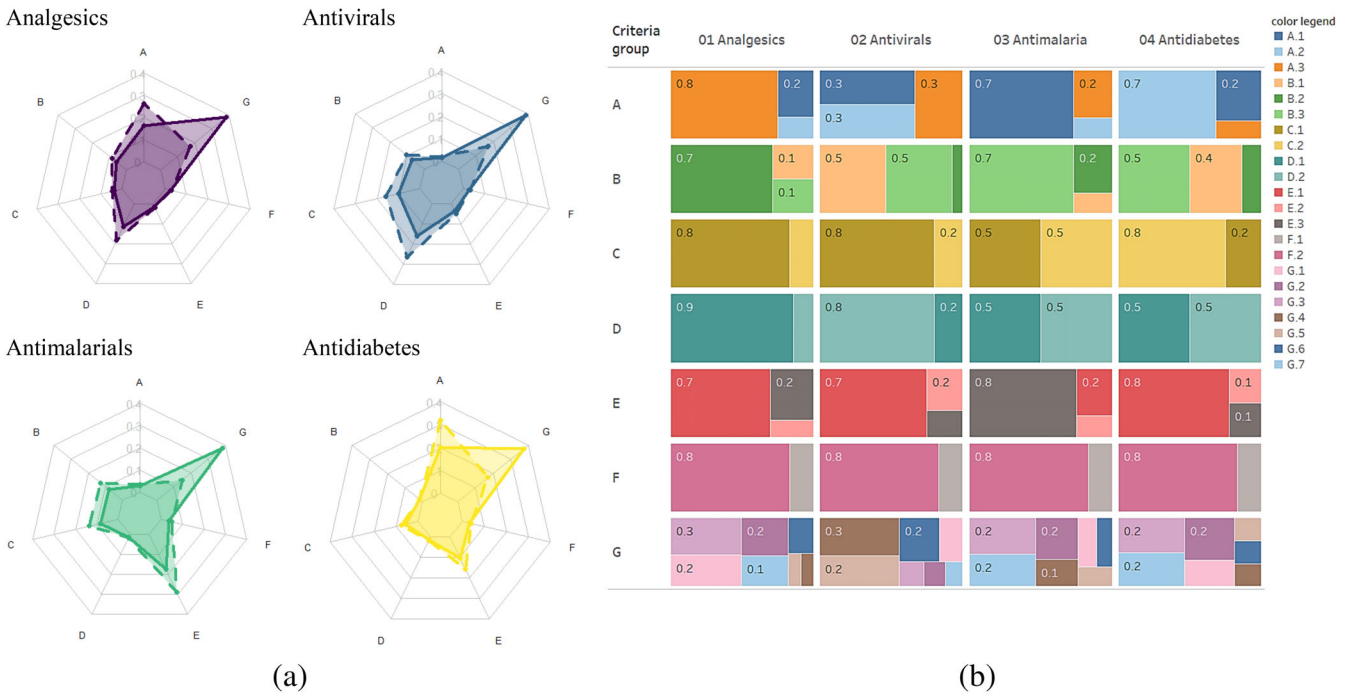
For each matrix in Tables S2.1 through to S2.5 a principal eigenvector $\mathbf{w}$ is computed by numerical approximation of the dominant eigenvalue problem:

$$\mathbf{A}\mathbf{w} = \lambda_{\max}\mathbf{w}$$

where $\mathbf{A}$ is a square, reciprocal matrix of AHP paired comparisons. Computing the dominant eigenvalue $\lambda_{\max}$ and corresponding eigenvector $\mathbf{w}$ is the preferred approach considering the theory underpinning AHP (Saaty, 2010). Yet shortcut methods are often used in practice, with the literature seldom disclosing detailed computations (Ishizaka & Lusti, 2006). In this article, the vector $\mathbf{w}$ and scalar $\lambda_{\max}$ are estimated by the power method approach (Larson & Edwards, 2000: Ch.10) with normalisation. Specifically, as $k \to \infty$ the vector sequence:

$$\mathbf{q}_k = \mathbf{A}^k\mathbf{q}_0 / \left\|\mathbf{A}^k\mathbf{q}_0\right\| \qquad (k = 1, 2, \ldots)$$

approaches the principal eigenvector $\mathbf{w}$, and the Rayleigh quotient $\lambda_k = \mathbf{q}_k^T\mathbf{A}\mathbf{q}_k / \mathbf{q}_k^T\mathbf{q}_k$ approaches the dominant eigenvalue $\lambda_{\max}$. The initial guess $\mathbf{q}_0$ corresponds to a unit vector of appropriate dimension; $\|\cdot\|$ is the Frobenius norm; and superscript T denotes transposition. The numerical approximation described above is implemented using the package *matlib* (Friendly et al., 2020) for the statistical computing software R (R Core Team, 2020). Results shown in Figure 2 refer to a priority vector, which corresponds to normalising the relevant principal eigenvector $\mathbf{w}$ so that its entries sum up to 1.



Notes, left-hand side: Solid line: initial scoring; Dashed line: lowest CR alternative identified by perturbation analysis; For consistency statistics please see Table S.6 in the Supplementary Materials.**Abbreviations - criteria:** A) Hazardous Chemistry ; B) Process conditions; C) Reaction reagents; D) Operational issues; E) Energy supply ; F) Economic; G) Supply network features.
Notes, right-hand side: **Abbreviations –sub-criteria:** A.1) Hazardous/Reactive chemicals; A.2) Run-away reaction; A.3) Highly Exothermic reaction; B.1) High temp; B.2) High Pressure; B.3) Very low temp; C.1) Solids; C.2) Gases; D.1) Precipitation/fouling; D.2) decomposition; E.1) Thermal; E.2) Microwave; E.3) Photo; F.1) Equipment cost; F.2) Processing cost; G.1) Inventory; G.2) Scale-up; G.3) Existing Asset-utilization; G.4) Working volume range; G.5) Flexibility; G.6) Time- to- market; G.7) Facility footprint.

FIGURE 2 Priority vectors by therapeutic area for (a) top-level criteria; and (b) sub-criteria by therapeutic area - under initial scoring assumptions

The choice of appropriate consistency measures is another aspect of AHP often overlooked in practical applications. For a given paired comparison matrix it is customary to compare the consistency index $CI = \lambda_{max} - n/n - 1$, where n is the number of lines in the matrix, with a 'lookup' random index (RI) for example, Saaty (2010: p. 121). Critical reviews of RI lookup values are sporadic, with Donegan and Dodd (1991) providing revised estimates. It is commonly required that the ratio between CI and RI, known as the consistency ratio (CR), should be 0.1 or less—values up to 0.2 are deemed tolerable. Dodd et al. (1993) question the use of a fixed percentage as a consistency measure. Instead, they provide an approach to assessing the level of confidence that CI values within certain thresholds are not the result of chance.Table S2.6

Table S2.6 shows some instances in which CR > 0.1. However, for scoring matrices larger than 3×3 the corresponding CI has only a 0.1% chance of coming from a random matrix, which gives a 99.9% confidence that the result is achieved by virtue of consistent judgment (Dodd et al., 1993). For a small set of 3×3 paired comparison matrices concerning sub-criteria this alternative approach could not be applied. Instead, minor changes were necessary to achieve CR ≤ 0.1. The corresponding metrics are denoted in Table S2.6 by an asterisk.

As mentioned in Section 4.1, priority structures and consistency metrics for top-level criteria were subject to sensitivity analysis. To achieve this, we perturbed the scores given to the supply chain features relative to the technical criteria (the last row in each matrix in Table S2.1), using values between 1 and 7. Exploration of all permutations ($7^6 = 117{,}649$) was deemed impractical, and only 10,000 of these were chosen at randomly. The changes observed in priority ranking of each criterion, and consistency metrics, are summarised in Supplementary Materials (S3), Figure S3.2.

Results in Figure S3.2 show that the chosen initial solutions in Table S2.1 align well with the median ranking obtained by random perturbation. As expected, given the size of scoring matrices, 'fixed percentage' consistency requirements are unlikely met. The options more likely to meet such requirements were identified and shown in Figure 2. Depending on the therapeutic area, between 79% and 91% of results obtained by perturbation meet the alternative consistency thresholds with a confidence level of 99% and above.

4.3 | Attribute-based evaluation of reactor technologies

Comparisons between relevant reactor technologies were carried out for each one of the 22 lower-level criteria discussed in the previous sections. As before, scoring took place in two steps. First, insights into the relevant literature were synthesised as shown in Table 1. Then, paired comparisons informed by these insights were carried out using

AHP's fundamental semi-numerical scale. Results from these steps are further detailed below.

4.3.1 | Hazardous chemistry

The size of a reactor affects its suitability for processes that are dangerous or difficult to control. Miniaturization allows greater efficiency in mass and heat transfer, with benefits in terms of process control, amounts of reagents handled and hence chance of hazard (Movsisyan et al., 2016). Batch reactions involve around 100–1000 kg of materials, whereas continuous reactions involve 1–5 kg (am Ende & am Ende, 2019, Ch. 8); batch reactors' volume is around 2000–10,000 L, whereas continuous reactors' is 0.1–3 L (Hessel et al., 2012).

CSTRs are medium-small size, with lower conversion rates per unit volume compared to PFRs which, in turn, are small range (Stoessel, 2020), as do cCSTRs and TITRs. Microreactor volumes do not exceed a few liters even for applications up to 2000 tons/year (Hessel et al., 2012), whereas PBRs come in all sizes from lab-scale to commercial scale (Worstell, 2014, Ch.5). The influence of reactor size on hazardous chemistry suggests the following:

TABLE 1 Summary of secondary data informing the reactor technology selection problem

Sub-criteria	Spec	Conventional	CSTR/CSTR cascade	PFR/ microreactors	Tube-in-tube reactor	Packed bed
A.1	Reactor vol.	Large	Medium/Small	Small/very small	Small	Large-small
	Head vol.	Free	Free	No	No	Free
A.2	STV	Low	Low/medium	High/highest	High	Low
A.3	STV	Low	Low/medium	High/highest	High	Low
B.1	Temperature	200	200	200–250/500	200–250	200–250
B.2	Pressure	10	10	30–150/30–150	30–150	30–150
B.3	STV	Low	Low/medium	High/highest	High	Low
C.1	Handling solids	Higher	High/medium	Small/very small	Small	Higher
C.2	Handling gases	Gas–liquid; not gas phase.	Gas–liquid; not gas phase.	Gas; and gas–liquid	Mostly for gas–liquid	Gas; and gas–liquid
D.1	Characteristic dimension	Can handle	Can handle	Cannot handle effectively	Cannot handle effectively	Cannot handle effectively
D.2		Can handle	Can handle	Cannot handle effectively	Cannot handle effectively	Cannot handle effectively
E.1	Handling thermal energy supply form	Easy	Easy	Easy	Easy	Easy
E.2	Using microwave	Possible at very low kg scale	Possible at very low kg scale	Possible at medium kg scale	Challenging	Challenging
E.3	Using photo energy	Possible at very low kg scale	Possible at very low kg scale	Possible at medium kg scale	Possible at very low kg scale	Possible at very low kg scale
F.1	Equipment cost	Low	Low/high	Low/high	High	Low
F.2	Processing cost	High	Low/low	Low/low	Low/low	Low/low
G.1	Reactor vol	High	Medium-high/low	Medium/low	Medium	Medium-high
G.2	Scaling-up capability	Difficult	Medium/low	Medium/low	Medium	Medium
G.3	Utilizing current batch asset	High	High/low	Low/low	Low	Low
G.4	Availability of various vol sizes	Low-high	Low-high/low-medium	Low-high/low-medium	Low-high	Low-high
G.5	Flex in ops	High flexibility	High flexibility	Low flexibility	Low flexibility	Low flexibility
	Flex in vols	Low flexibility	High flexibility	High flexibility	High flexibility	High flexibility
G.6	Devel. time	High	Lower	Lower	Lower	Lower
	Proc. time	High	Lower	Lower	Lower	Lower
G.7	Size of reactors	Low-high	Low-high/low	Medium/low	Medium	Low-high

Note: For a full description of sub-criteria see Figures 1 and 2. STV: surface area-to-volume.

$$R1: \{\text{Batch, PBR}\} < \{\text{CSTR}\} < \{\text{PFR, cCTSR, TITR}\} < \{\mu\text{R}\}$$

The presence of headspace above the reaction mixture may also affect safety. For example, reactions involving organic azide or tetrazole formations produce shock sensitive and explosive hydrazoic acid. Without free headspace, the hydrazoic acid formed is kept in the solution, which facilitates its immediate quenching. Batch reactors, CSTRs and PBRs provide free headspace, unlike PFRs/μR and TITRs (am Ende & am Ende, 2019, Ch. 3 and 16). Headspace may also affect hazardous chemistry in different reactors, in particular:

$$R2: \{\text{Batch, CSTR, cCTSR, PBR}\} < \{\text{PFR, }\mu\text{R, TITR}\}$$

Safety can be substantially improved with better heat transfer: allowing quick dissipation of heat prevents temperature from rising to run-away conditions (Barton & Rogers, 1997; Movsisyan et al., 2016). Usually, the higher the surface area-to-volume (STV) ratio in a reactor, the better the heat transfer. STV ratios are highest for μR and lowest for batch reactors and CSTRs (am Ende & am Ende, 2019, Ch. 14). TITRs and PFRs are similar due to their cylindrical structure; however, the larger size of TITRs reduces their STV ratios. The position of PBRs depends on diameter: when large, the heat transfer rates are poorer (Sinnott, 2005), placing PBRs closer to CSTRs. However, the presence of solid packing may favour localised elevated temperatures ('hot spots') in PBRs (Baxendale et al., 2007). Lower STV ratios make batch reactors less capable of maintaining isothermal temperatures during the highly exothermic reactions that frequently occur in API synthesis. As different reactors' STV may affect run-away and highly exothermic reactions, the following conclusion is reached:

$$R3: \{\text{Batch}\} \leq \{\text{CSTR, PBR}\} \leq \{\text{cCSTR}\} \leq \{\text{PFR, TITR}\} < \{\mu\text{R}\}$$

4.3.2 | Process conditions

Harsh or extreme process conditions enable faster kinetics, speeding up reactions by orders of magnitude (Hessel et al., 2012). Batch reactors such as those used in the pharmaceutical industry allow maximum temperature of 150°C and pressure of 10 bar. Among CM equipment, CSTRs are similar to batch reactors in this regard. PFRs allow conditions (200–250°C, and 30–150 bar) such that the reactions run above the normal boiling points of the solvents, leading to higher concentrations of dissolved gas in liquid phase for gas–liquid reactions (am Ende & am Ende, 2019, Ch. 8). Metallic microreactors operate at a maximum temperature of 500°C whereas ceramic microreactors can reach 1100°C (Hessel et al., 2013). The windows of temperature and pressure allowed by different reactor technologies are such that:

$$R4: \{\text{Batch}\} \leq \{\text{CSTR, cCSTR}\} \leq \{\text{TITR, PBR}\} \leq \{\text{PFR, }\mu\text{R}\}$$

The ability to achieve lower temperatures is likely affected by a reactor's efficiency in mass and heat transfer. This aspect was previously discussed in relation to STV ratios, concluding the following:

$$R5: \{\text{Batch, PBR}\} \leq \{\text{CSTR}\}\,\{\text{cCSTR}\} \leq \{\text{TITR, PFR}\} < \{\mu\text{R}\}$$

4.3.3 | Reaction reagents

For some CM reactor technologies issues may arise in the presence of solids (Roberge et al., 2005) and the high pressure gas–liquid reactions (Brzozowski et al., 2015) that characterise most large-scale API synthesis. For example, CSTRs and PBRs are particularly suitable for handling solids, whereas PFRs and CSTRs are best deployed for homogeneous liquid phase reactions. Also, reactor size reduction may be a drawback when using solid particles as reactants or catalysts inside a reactor. This issue is mitigated in the presence of agitation, as in batch reactors/CSTRs, or packed beds (Sinnott, 2005). Problems in handling solids may depend on the equipment diameter, with μR being most affected (Roberge et al., 2005). The potential repercussions of reactor dimensions on their ability to handle solids suggests that:

$$R6: \{\text{Batch, PBR}\} > \{\text{CSTR}\} > \{\text{cCSTR}\} > \{\text{PFR, TITR}\} > \{\mu\text{R}\}$$

Reactors also differ in their ability to handle gas/gas–liquid phases, namely:

$$R7: \{\text{Batch, CSTR, cCSTR}\} < \{\text{PFR, PBR, }\mu\text{R, TITR}\}$$

Indeed, CSTRs/batch reactors are unsuitable for gas phase reactions. However, these are commonly deployed in gas–liquid reactions where gas is bubbled into the liquid. Conversely, technologies such as PFRs, PBRs and μR/TITRs are suitable for both gas and gas–liquid reactions (Sinnott, 2005).

4.3.4 | Operational issues

Reactors with smaller dimensions are more likely to be exposed to blockage in case of precipitation, and when solid particles form due to decomposition of reagents. Indeed the characteristic dimensions of stirred vessels, tubular reactors and micro-structured reactors are in the range 1–10 m, 5–50 cm and 10 μm–1 mm, respectively (Bayer et al., 2005). Formation of solids along the walls of the reactor, that is, fouling, may cause pressure to drop, in turn leading to clogging. Also, solids tend to agglomerate into larger particles, clogging the reactors. These issues are alleviated in the presence of mechanical agitation (batch reactors/CSTRs). Miniaturised CSTRs are successfully deployed for small scale synthesis involving solids (Mo & Jensen, 2016). In PBRs leaching of solids into the solution often leads to clogging the catalysts or the void space, causing pressure drop. The influence of reactor dimensions on operational challenges suggests the following:

$$R8: \{\text{Batch, CSTR}\} > \{\text{cCSTR}\} > \{\text{PFR, PBR, } \mu\text{R, TITR}\}$$

4.3.5 | Types of energy supply

The traditional method of heat exchange using heating/cooling agents is successfully utilised in all the reactors. Some reactors, however, have elevated rates of heat transfer due to higher STV ratios and, therefore, can use the thermal energy more efficiently. The trend that can be derived for the conventional energy supply method is:

$$R9: \{\text{Batch, PBR, CSTR}\} \leq \{\text{cCSTR}\} \leq \{\text{TITR}\} \leq \{\text{PFR, } \mu\text{R}\}$$

Reactor technologies can also accommodate innovative sources of energy depending on features such as depth of the reactor. For example, microwave irradiation can be beneficial for yield/purity and solvent requirements. However, exceeding the penetration depth of microwaves would prevent uniform heating (Baxendale et al., 2007). This issue may be partially overcome by efficient stirring (Schmink et al., 2010). Smaller scale reactors are more suitable for microwave irradiation, whereas stirred reactors are limited to kilogram-scale since the maximum size that can be heated with standard magnetrons is about 2–3 L (Lehmann & La Vecchia, 2010). Microwave-assisted processing remains a challenge for TITRs due to their configuration, and for PBRs due to selective absorption in the presence of solids, thereby suggesting the following trend:

$$R10: \{\text{Batch, CSTR}\} \leq \{\text{cCSTR}\} < \{\text{PFR}\} < \{\mu\text{R}\}$$

The depth of a reactor also affects the ability to use light as a source of energy; indeed, light transmittance decreases exponentially with the distance from the light source, causing non-homogeneous irradiation. Photo irradiation can be challenging in industrial batch reactors/CSTRs/PBRs and in the presence of solids (Sambiagio & Noël, 2020). Exceptions include the use of high-intensity blue laser beam in CSTRs operating at kilogram-scale (Harper et al., 2019). Another exception is the synthesis of the antimalarial artemisinin by photogenerated singlet oxygen oxidation of *Artemisia annua* extracts in small scale PBRs (Triemer et al., 2018). In general, small scale or miniaturised reactors are more suitable for performing photochemical reactions, namely:

$$R11: \{\text{TITR, PBR}\} \leq \{\text{Batch, CSTR}\} < \{\text{cCSTR, PFR, } \mu\text{R}\}$$

4.3.6 | Managerial aspects: costs and the supply chain

Throughout the previous sections it was implied that the features contributing to the technology selection problem are built into a physical asset. Extending the analysis to more managerial aspects, whilst desirable, is less straightforward. Some managerial aspects of interest (e.g., cost, inventory) are usually expressed *in absolute quantitative terms*. Here, judgment about these criteria is expressed in *relative terms*.

Impact on cost, inventory and lead times

A traditional economic advantage of batch equipment consists of low initial setup cost. By analogy, the cost of CSTRs can be expected to be reasonably close to that of batch reactors. The equipment cost of PFRs and PBRs is also assumed to be in the same ballpark, considering that these are widely used in the chemical industry. Despite operating at a smaller scale, μR and TITRs are likely to command higher investment costs. Differences in upfront disbursement for equipment acquisition suggest the following:

$$R12: \{\text{Batch, CSTR, PFR, PBR}\} > \{\text{cCSTR, TITR, } \mu\text{R}\}$$

Processing costs may be affected by the ability of flow reactor technologies to improve reaction yield; reducing reaction time and energy requirements. In relative terms, we assume that these features drive operating cost reductions compared to batch reactors. Greater cost savings beyond the individual facility can be achieved reducing material handling, quality control and labour between processing steps (Schaber et al., 2011). Differences in the direct processing costs associated with reaction efficiency suggest the following:

$$R13: \{\text{Batch}\} < \{\text{CSTR, cCSTR, PFR, } \mu\text{R, PBR, TITR}\}$$

Inventory is one of the most widely debated and controversial aspects related to the adoption of CM in PSCs. It is estimated that the incumbent approach of manufacturing in batch campaigns generates about 1–6 months inventory in the PSC (Shah, 2004). CM were expected to bring that figure down to 70 days or less (Srai et al., 2015). However, the global disruptions in API supply linked to a recent pandemic demonstrated that the merits of cutting down on inventory are not straightforward to demonstrate in the presence of high dependency on a handful of manufacturing locations (Settanni, 2020).

Considering the focus on specific CM technologies, 'inventory' is interpreted here as the combination of starting materials, intermediate and final products of API synthesis. Batch reactors are likely to generate a higher build-up of inventory due to their characteristic sequence of operations (i.e., charging, converting, discharging, quality analysis, and storage) and the large volumes typically involved at each step. Conversely, continuous reactors are smaller in volume, thereby requiring a lower inventory of starting materials. With synthesis steps performed in flow, and 'in line' process analytical technologies (Rantanen & Khinast, 2015), it seems plausible to assume that less material storage and fewer 'end of the pipe' quality controls are required. Preliminary simulation studies also suggest similar conclusions (Srai et al., 2020). The elimination of intermediary holding stages in CM is likely to benefit the overall time required in production. The

possible influence of small-volume in flow synthesis on inventories suggests the following:

$$R14: \{\text{Batch}\} < \{\text{CSTR, PBR}\} < \{\text{TITR, PFR}\} < \{\text{cCSTR, } \mu\text{R}\}$$

Viability at scale and flexibility

Besides costs and the opportunity for lower inventory, a key issue when introducing new technologies in a PSC is their viability at commercial scale. For batch reactor technologies, heat and mass transfer phenomena occurring at lab-scale may not be achieved at larger volumes, and hence demand re-optimisation (Gutmann et al., 2015). By contrast, production in flow reactors can be increased by scaling-out or numbering-up instead of scaling-up. Scaling-out involves operating the reactor continuously for longer rather than intermittently. Numbering-up implies that the number of equipment units operating in parallel increases. Unlike scaling-up, these strategies do not require re-optimising the operating conditions, with potential savings in terms of development time (Plumb, 2005). Differences in the ease of upscaling to commercial requirements suggest that:

$$R15: \{\text{Batch}\} < \{\text{CSTR, PBR, TITR, PFR}\} < \{\text{cCSTR, } \mu\text{R}\}$$

So far it is assumed that reactor technology is consistently deployed at ideal operating conditions and scale. In practice, industry may be reluctant to endorse CM with resources committed in its current asset base. Technologies such as CSTR may provide some of the advantages of CM whilst aligning well with current technologies (Teoh et al., 2016). Reactor technologies may differ in their ability to leverage an existing asset base, specifically:

$$R16: \{\text{Batch, CSTR}\} > \{\text{cCSTR, PFR, } \mu\text{R, PBR, TITR}\}$$

As PSCs are tasked with achieving greater responsiveness (e.g., Srai et al., 2015; Woodcock, 2019), flexibility in manufacturing becomes more prominent. Flexibility may be understood as either the ability to use a single reactor type for multiple operations; or, the ability to move from one production capacity to another. In the first sense, batch reactors provide higher flexibility than continuous flow reactors (Dunn et al., 2010). However, CM provides greater flexibility in terms of changing production volumes via numbering-up or scaling-out. An interpretation of flexibility in terms of operations that equipment can carry out suggests that:

$$R17: \{\text{Batch, CSTR}\} > \{\text{cCSTR, PFR, } \mu\text{R, PBR, TITR}\}$$

However, reactors differ in their ability to switch up/down production, suggesting that:

$$R18: \{\text{Batch}\} < \{\text{cCSTR, PFR, } \mu\text{R, PBR, TITR}\}$$

Reducing time-to-market has always been one of the important aspects of PSC. Time-to-market comes from the time required in the development of a drug and after-development time required to produce the drug, plus time to reach the customer; development plus production time being more relevant to process. As discussed earlier, batch operations involve multiple stages viz. charging, operation, discharging and holding between two consecutive steps and two batches. This considerably increases the overall time required in the production of API and its final dosage form. Continuous flow reactors allow decreased time in processing, by eliminating intermediary holding stages or manual operations and time between two batches. Intensifying process by continuous flow can also lead to inherent reductions in reaction time. In addition, development time in the case of continuous flow reactors is lowered by eliminating the scale-up step (Plumb, 2005), namely:

$$R19: \{\text{Batch}\} < \{\text{cCSTR, PFR, } \mu\text{R, PBR, TITR}\}$$

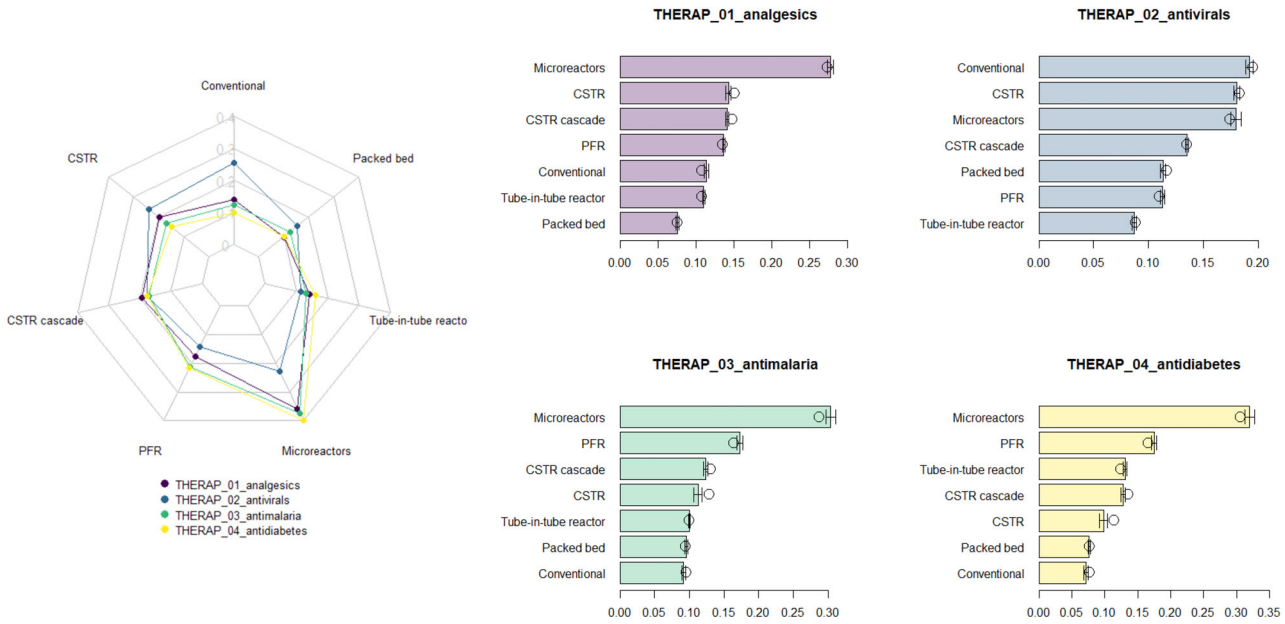
Lower plant footprint was identified by regulators as one of the important features of advanced technologies (Woodcock, 2019). Continuous reactors usually have lower volumes than batch reactors and therefore occupy less space than batch reactors. As mentioned earlier, the volume of continuous flow reactor ranges from at least two cubic meters to at most three liters (Hessel et al., 2012). CSTRs and packed beds, however, might also work at a similar volume to that of batch reactors. The miniaturisation of dimensions of PFRs/microreactors/miniaturised CSTRs leads to high efficiency in mass and heat transfer in these reactors while reducing the footprint of equipment:

$$R20: \{\text{Batch, CSTR, PBR}\} < \{\text{PFR, PBR, TITR}\} < \{\text{cCSTR, } \mu\text{R}\}$$

4.4 | Overall ranking

The above insights provided a basis for paired comparisons between the selected reactor technologies at each lower-level criterion. Similar to the process described in section 4.1, co-authors with a background in chemical engineering were responsible for the task, and the results were refined through an iterative process involving all co-authors. The process yielded 22 scoring matrices of size 7×7 capturing, for all sub-criteria, the resulting set of paired comparisons between chosen technologies. Due to space constraints, detail is provided in the Supplementary Materials. Specifically, Tables S2.7 through to S2.13 provide the scoring matrices, and priorities based on the corresponding dominant eigenvalues. Table S2.14 specifies consistency metrics for these scoring matrices. Key computational and consistency assessment procedures are as discussed in Section 4.2. Nearly all results meet the standard 'fixed percentage' criterion for acceptable CRs. For three values slightly above the acceptable range, the application of alternative tolerances (Dodd et al., 1993) suggests a 99.9% confidence that these are achieved by virtue of consistent judgment.

For a given therapeutic area, priority vectors separately obtained for criteria, sub-criteria and reactor technology options are combined into an overall ranking. This is accomplished by matrix multiplication in two steps. For a given a therapeutic area, first we compute:



(a) Overall ranking, initial scoring for SC top-level criteria

(b) Sensitivity to changes in SC top-level criteria scoring (10,000 random permutations) Histograms: means; Lines: std deviation; Circles: intial scoring (same as left-hand side)

FIGURE 3 Overall scoring for CM reactor technologies

$$\begin{bmatrix} \boldsymbol{\omega}_A & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \boldsymbol{\omega}_B & \cdots & \mathbf{0} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \cdots & \boldsymbol{\omega}_G \end{bmatrix} \times \begin{bmatrix} \omega_A \\ \omega_B \\ \vdots \\ \omega_G \end{bmatrix} = \begin{bmatrix} \boldsymbol{\upsilon}_A \\ \boldsymbol{\upsilon}_B \\ \vdots \\ \boldsymbol{\upsilon}_G \end{bmatrix}$$

where $\boldsymbol{\omega}_A = [\omega_{A.1}\ \omega_{A.2}\ \omega_{A.2}]^T$; $\boldsymbol{\omega}_B = [\omega_{B.1}\ \omega_{B.2}\ \omega_{B.2}]^T$;...; $\boldsymbol{\omega}_G = [\omega_{G.1}\ \omega_{G.2}\ \cdots\ \omega_{G.7}]^T$ corresponding to the appropriate eigenvectors for sub-criteria within A, B,..., G in Tables S.2–S.5. These vectors are normalised so that their entries sum up to 1. Similarly, $\boldsymbol{\omega} = [\omega_A\ \omega_B\ \cdots\ \omega_G]^T$ corresponds to the appropriate eigenvector in Table S.1, also normalised. Taking antimalarials as an example $\boldsymbol{\omega}_B = [0.08\ \ 0.19\ \ 0.73]^T$ and $\boldsymbol{\omega} = [0.03\ \ 0.10\ \cdots\ \ 0.48]^T$. Next we compute:

$$[\boldsymbol{\upsilon}_A\ \ \boldsymbol{\upsilon}_B\ \cdots\ \boldsymbol{\upsilon}_G] \times \begin{bmatrix} \boldsymbol{\gamma}_{1,A} & \boldsymbol{\gamma}_{2,A} & \cdots & \boldsymbol{\gamma}_{7,A} \\ \boldsymbol{\gamma}_{1,B} & \boldsymbol{\gamma}_{2,B} & \cdots & \boldsymbol{\gamma}_{7,B} \\ \vdots & \vdots & & \vdots \\ \boldsymbol{\gamma}_{1,G} & \boldsymbol{\gamma}_{2,G} & \cdots & \boldsymbol{\gamma}_{7,B} \end{bmatrix} = [\alpha_1\ \ \alpha_2\ \ \cdots\ \ \alpha_7]$$

where the vector $\boldsymbol{\upsilon} = [\boldsymbol{\upsilon}_A\ \ \boldsymbol{\upsilon}_B\ \cdots\ \boldsymbol{\upsilon}_G]^T$ is an output of the previous step.

The vectors $\boldsymbol{\gamma}_{j,A} = [\gamma_{j,A.1}\ \ \gamma_{j,A.2}\ \ \gamma_{j,A.3}]^T$; ...; $\boldsymbol{\gamma}_{j,G} = [\gamma_{j,G.1}\ \ \gamma_{j,G.2}\ \cdots\ \gamma_{j,G.7}]$ are defined for each technology $j = 1, 2,..., 7$ and correspond to the appropriate eigenvectors in Tables S2.7 through to S.13 for sub-criteria within A, B,...,G. As before, the eigenvectors are normalised so that they sum up to 1. For each therapeutic area, the result is an overall priority vector $\boldsymbol{\alpha} = [\alpha_1\ \ \alpha_2\ \cdots\ \alpha_7]^T$.

For our numerical example, values are visualised in Figure 3.

5 | DISCUSSION

The academic literature has long recognised the challenges of evaluating advanced manufacturing technologies when limited evidence is available to decision-makers (e.g., Sambasivarao & Deshmukh, 1997). For reactor technologies deployed in PSCs, analysis contributes to an early-on exploration of the performance space in which alternative options may operate. Often, approaches centered on proprietary tools and/or aimed at a specialist audience are deployed for similar tasks (e.g., Peeling & Talford, 2020). However, extant work underplays the need to combine purely technical knowledge with managerially relevant insights supporting strategic supply chain configuration decisions.

Industrial innovation policies increasingly require that end-to-end supply chain considerations for advanced manufacturing technologies are explicitly addressed. Examples include research programmes for redistributed manufacturing in healthcare (e.g., Phillips et al., 2020). In the US, programmes supporting the implementation of CM technology aim to achieve greater product quality control and flexibility of manufacturing (Lee et al., 2015).

Findings from the previous sections bridge current disciplinary silos with a view to supporting early-on strategic managerial decisions about upstream PSC reconfiguration opportunities enabled by CM. A hierarchical priority structure was obtained for different therapeutic areas linking relevant criteria and technology options. With regard to the former. Eyeball inspection of Figure 3 suggests that hazardous chemistry (criterion A) is dominant (making up 30%+ of the criteria weight) in analgesics and antidiabetes, mostly due to the possibility of exothermic and run-away reactions even though APIs in these

categories required a maximum of three reaction steps. Higher temperatures and pressures (criterion B), which form an important aspect of process intensification, were used in almost all drug categories, except the API investigated for antidiabetes. Over 60% of reactions in API synthesis involve solids, which was evident in all drug categories. The ability to handle multiphase reaction reagents (criterion C) tend to rank third for importance across the board (criterion C), except for analgesics since the APIs involved did not use any gaseous reagents. Operational issues (criterion D) are of major concern in antivirals followed by analgesics (20–30% of the criteria weight), mainly due to precipitation of intermediates or final product, although decomposition was also found in one of the antivirals. Energy supply seems to be very important (criterion E) for antimalarials and antidiabetes (also 20–30% of weight), with some antimalarials relying on photo assisted synthesis.

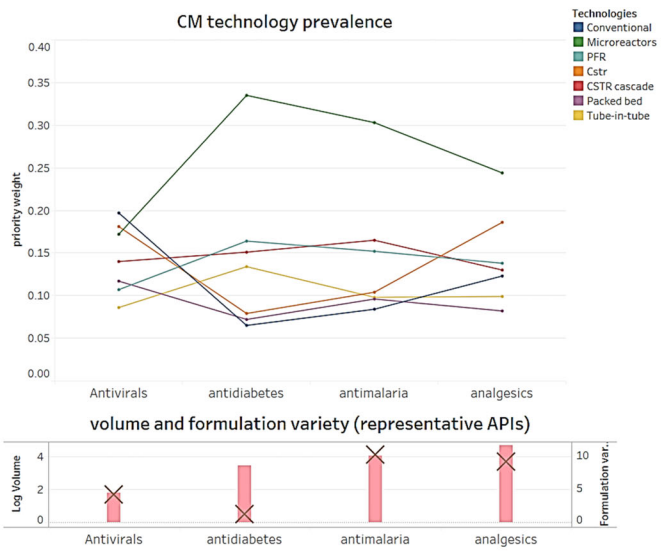
With regard to more managerial criteria, cost (criterion F) does not stand out at this level of analysis, although it tends to rank slightly higher for importance in antimalarials and antidiabetes, almost entirely in relation to CapEx. Supply chain features (criterion G) are hypothetically given high priority; however, perturbation analysis reveals that their weight (and rank) nearly halves in the alternative scenario driven by consistency ratio constraints.

For each reactor technology option, Figure 3 combines broader considerations about criteria relevance at the level of therapeutic area, and detailed technology evaluations for each sub-criterion as illustrated in Section 4.3 and Tables S2.7–S2.13. Analysis favours microreactors across almost all therapeutic areas. Antivirals provide an exception: whilst complex chemistry favours continuous microreactors, batch manufacturing remains a contender due to the need for flexibility in operations allowed by a single reactor as well as operational challenges due to fouling. In the case of analgesics, the second best option is CSTR, as this technology can help exploit the existing manufacturing base whilst addressing inventory reduction—both important features amongst supply chain sub-criteria for this therapeutic area. CSTR cascade and PFR stand out as second best in antimalarials and antidiabetes, in line with manufacturing requirements linked to handling photochemical and multiphase reactants whilst addressing inventory reduction and operational flexibility.

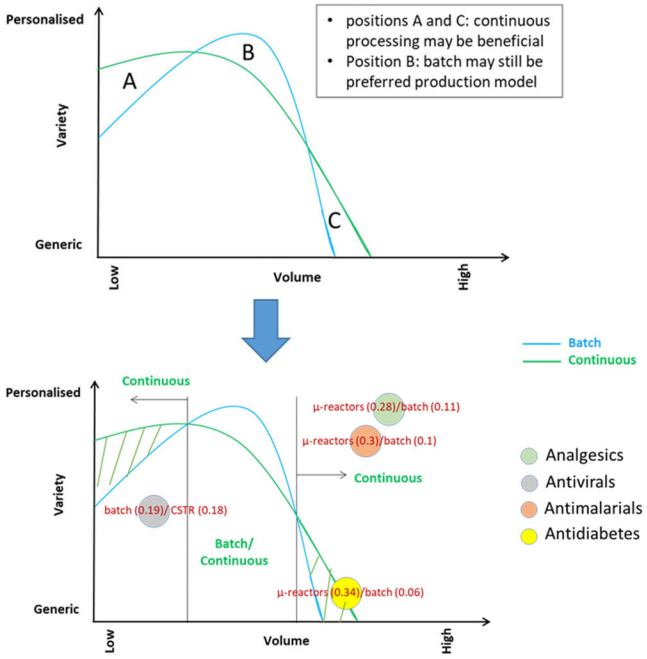
To gain a broader theoretical perspective, Figure 4 juxtaposes research findings and an existing framework that conceptualises where CM of pharmaceuticals may be beneficial based on volume-variety considerations (Srai et al., 2015).

For each therapeutic area 'volumes' were approximated by selecting representative APIs in each category and estimating the amount of APIs dispensed by NHS England in 2019–2020. Variety is approximated by the number of different dosage forms and strengths, also estimated from public domain prescription data. The overall priority weights for batch (conventional) and CM reactor technologies in each therapeutic area serve as a proxy to operationalise the benefits of alternative technologies. The original framework conceptualises these benefits as intersecting 'bell-shaped' curves, with dominance of a technology being represented by the corresponding curve laying above the other. Unlike our results, the original framework is agnostic with respect to specific CM technologies or therapeutic areas. Contrary to what is anticipated by the conceptual framework, batch and CSTR prevail on other technologies for relatively low volume, medium variety therapeutic areas such as antiviral.

For middle-range volumes nearly all CM technologies supersede batch (although CSTR and packed bed closely follow batch in terms of relevance). For high variety and high volume products such as antimalarials and analgesics, CM technologies, leading with microreactors,



(a) Re-shaped empirical results from this paper



(b) Initial conceptualisation (based on Srai et al., 2015) to current mapping

FIGURE 4 Volume-variety representation of CM technology advantages: results versus conceptualisation

gain significance over batch. The next CM technology following microreactors is CSTR for analgesics and PFR for antimalarials.

Although microreactors seem to prevail among CM technologies at high volumes, their deployment may be practical only at small-medium scale (0.1–1000 tons/year) based on the numbering-up or scaling-out approach. For example, to achieve 10,000 tons/year of production a continuous flow reactor working at 10 kg/day will need around 3000 units operating 24/7. Such high numbers can reflect negatively on the capital costs of the plant. However, use of microreactors at different scales is still an area of on-going research. This methodology helps to screen technologies at the early stages of process development. These results can feed into more detailed analysis of various process options with different reactor technologies.

The above result has no ambition to serve as a confirmatory analysis; rather, it is meant to illustrate how insights gained through semi-quantitative techniques such as AHP could provide an operational counterpart to the otherwise complex and multifaceted notion of 'benefits' conceptualised in the reference framework. Also, results may vary depending on the representative products chosen. For example, antidiabetes API such as artemisinin would dwarf analgesics such as ibuprofen in both volume and variety. However, in this work, the focus was on APIs investigated in the literature on CM. Also, the attributes considered to be relevant for selection can impact the final rankings. If flexibility is not important in a solid-free API manufacturing, then microreactors can out-do batch for antivirals.

6 | CONCLUDING REMARKS

This article applies AHP techniques to address both technological and managerial considerations in evaluating upstream PSC reconfiguration opportunities enabled by CM. During early-stage PSC configuration design and manufacturing technology selection, detailed technical knowledge is often inaccessible to managers. Furthermore, integrating multiple technical and operational information into strategic managerial decisions is challenging, and has frustrated the adoption of new technology.

This research contributes an empirical workflow for the multifaceted evaluation of alternative CM reactor technologies in PSC, enriching a thriving technical literature on CM of pharmaceuticals, with an explicit supply chain management perspective. For selected therapeutic areas, findings provide a priority structure for multiple technical and supply chain criteria, against individual reactor technology options. In particular, the research identifies 22 criteria, 13 technical and nine management-centric, to evaluate emerging CM reactor technologies within upstream PSC. Technologies such as microreactors are particularly promising, all things considered. However, supply chain considerations introduce nuances, for example with regard to antivirals where the need for flexibility in unit operations in a single piece of equipment favours batch manufacturing over numbering-up CM modules. Also, in the case of analgesics, the need to exploit the existing manufacturing base whilst addressing inventory reduction favours CSTR, which incorporates elements of both batch and CM.

This article initiates the task of providing an empirical counterpart to the conceptual framework for evaluating the benefits of CM in PSCs, predicated on volume-variety considerations. Priority structures obtained by AHP provide a concise quantification of the relative advantages afforded by alternative technological options. Analysis confirms some broader trends anticipated by the existing framework—for example, for microreactors the relative advantage of CM resembles a bell-shaped curve as volumes increase. However, the analysis provides a more nuanced view than existing frameworks. For instance, due to the tension between operational flexibility requirements and complex chemistry requirements, batch and CM may be equally viable for antivirals despite the lower volumes.

Research limitations include reliance on public domain data, and a focus limited to the upstream portion of PSC. Also, the analysis remains largely deterministic although perturbation analysis was carried out to account for the difficulty of evaluating the relative importance of supply chain over technical criteria. Future developments could extend the analysis to: (1) include judgment from a larger group of experienced practitioners; (2) additionally, evaluate CM technologies for use in post-API product formulation; (3) apply this methodology in other industry contexts where both advanced manufacturing technology and supply chain considerations influence potential adoption. Despite its limitations, this research contributes a structured approach of integrating technical and managerial insights in the early-stage evaluation of CM technologies. Also, the proposed application emphasises replicability, and addresses explicitly computational aspects of AHP that are often underplayed in practical applications. The emphasis placed on the need to address disciplinary silos, simplifying heuristics and potential biases through a structured approach to decision-making seems sensible as governments seek to develop local medical countermeasures in the wake of the recent COVID-19 pandemic.

DATA AVAILABILITY STATEMENT

Data provided as Supplementary Materials

ORCID

Ettore Settanni https://orcid.org/0000-0001-5174-9423
Jagjit Singh Srai https://orcid.org/0000-0003-2277-2127

REFERENCES

Alvarez, G. B., de Almeida, R. G., Hernández, C. T., & de Sousa, P. A. P. (2021). Some mathematical comments about the analytic hierarchy process: Part I – Theoretical analysis. *Journal of Multi-Criteria Decision Analysis. 28*, 296–310. https://doi.org/10.1002/mcda.1762

am Ende, D. J., & am Ende, M. T. (Eds.). (2019). *Chemical engineering in the pharmaceutical industry: Active pharmaceutical ingredients*. Wiley. https://doi.org/10.1002/9781119600800

Barton, J., & Rogers, R. (1997). *Chemical reaction hazards*. IChemE.

Baxendale, I. R., Hayward, J. J., & Ley, S. V. (2007). Microwave reactions under continuous flow conditions. *Combinatorial Chemistry & High Throughput Screening*, *10*(10), 802–836. https://doi.org/10.2174/138620707783220374

Bayer, T., Jenck, J., & Matlosz, M. (2005). IMPULSE-A new approach to process design. *Chemical Engineering and Technology*, *28*(4), 431–438. https://doi.org/10.1002/ceat.200407120

Brennan, D. (1998). *Process industry economics*. IChemE.

Brzozowski, M., O'Brien, M., Ley, S. V., & Polyzos, A. (2015). Flow chemistry: Intelligent processing of gas−liquid transformations using a tube-in-tube reactor. *Accounts of Chemical Research*, *48*(2), 349–362. https://doi.org/10.1021/ar500359m

Burcham, C. L., Florence, A. J., & Johnson, M. D. (2018). Continuous manufacturing in pharmaceutical process development and manufacturing. *Annual Review of Chemical and Biomolecular Engineering*, *9*, 253–281. https://doi.org/10.1146/annurev-chembioeng-060817-084355

Calabrese, G. S., & Pissavini, S. (2011). From batch to continuous flow processing in chemicals manufacturing. *AICHE Journal*, *57*(4), 828–834. https://doi.org/10.1002/aic.12598

Dodd, F. J., Donegan, H. A., & McMaster, T. B. M. (1993). A statistical approach to consistency in AHP. *Mathematical and Computer Modelling*, *18*(6), 19–22. https://doi.org/10.1016/0895-7177(93)90123-G

Domokos, A., Nagy, B., Gyürkés, M., Farkas, A., Tacsi, K., Pataki, H., Liu, Y. C., Balogh, A., Firth, P., Szilágyi, B., Marosi, G., Nagy, Z. K., & Nagy, Z. K. (2020). End-to-end continuous manufacturing of conventional compressed tablets: From flow synthesis to tableting through integrated crystallization and filtration. *International Journal of Pharmaceutics*, *581*, 119297. https://doi.org/10.1016/j.ijpharm.2020.119297

Donegan, H., Dodd, F., & McMaster, T. (1992). A new approach to AHP decision-making. *Journal of the Royal Statistical Society (The Statistician)*, *41*(3), 295–302. https://doi.org/10.2307/2348551

Donegan, H. A., & Dodd, F. J. (1991). A note on Saaty's random indexes. *Mathematical and Computer Modelling*, *15*(10), 135–137. https://doi.org/10.1016/0895-7177(91)90098-R

Double, J. M. (2006). Project IMPULSE: Equipment selection methodology. *17th international congress of chemical and process engineering*. Prague, 27–31 August.

Dunn, P. J., Wells, A., & Williams, M. T. (2010). *Green chemistry in the pharmaceutical industry*. Wiley-VCH. https://doi.org/10.1002/9783527629688

Economist. (2020). The covid-19 virus is teaching the world hard lessons about China-only supply chains. Feb 29th. *434*(9183):50.

Emenike, V. N., Schenkendorf, R., & Krewer, U. (2018). A systematic reactor design approach for the synthesis of active pharmaceutical ingredients. *European Journal of Pharmaceutics and Biopharmaceutics*, *126*, 75–88. https://doi.org/10.1016/j.ejpb.2017.05.007

Friedli, T. (2006). *Operational excellence in the pharmaceutical industry*. Cantor-Verl.

Friendly, M., Fox J., & Chalmers P. (2020). Matlib: Matrix functions for teaching and learning linear algebra and multivariate statistics. https://CRAN.R-project.org/package=matlib

Ganesh, S., & Reklaitis, G. V. (2020). Basic principles of continuous manufacturing. In Z. Nagy, A. El Hagrasy, & J. Litster (Eds.), *Continuous pharmaceutical processing*. Springer. https://doi.org/10.1007/978-3-030-41524-2

Glaize, A., Duenas, A., Di Martinelly, C., & Fagnot, I. (2019). Healthcare decision-making applications using multicriteria decision analysis: A scoping review. *Journal of Multi-Criteria Decision Analysis*, *26*(1–2), 62–83. https://doi.org/10.1002/mcda.1659

Gutmann, B., Cantillo, D., & Kappe, C. O. (2015). Continuous-flow technology—A tool for the safe manufacturing of active pharmaceutical ingredients. *Angewandte Chemie, International Edition*, *54*(23), 6688–6728. https://doi.org/10.1002/anie.201409318

Hahn, S.M., & Shah, A. (2020) Investing in advanced manufacturing to support public health preparedness. https://www.fda.gov/news-events/fda-voices/investing-advanced-manufacturing-support-public-health-preparedness

Hall, S., & Stoker, A. (2003). API chemical synthesis trends in reactor system design APIs: Reactor considerations. *Pharmaceutical Engineering*, *23*(5), 1–9.

Hanratty, P. J., & Joseph, B. (1992). Decision-making in chemical engineering and expert systems: Application of the analytic hierarchy process to reactor selection. *Computers and Chemical Engineering*, *16*(9), 849–860. https://doi.org/10.1016/0098-1354(92)80037-A

Harper, K. C., Moschetta, E. G., Bordawekar, S. V., & Wittenberger, S. J. (2019). A laser driven flow chemistry platform for scaling photochemical reactions with visible light. *ACS Central Science*, *5*, 109–115. https://doi.org/10.1021/acscentsci.8b00728

Harrington, T. S., Phillips, M. A., & Srai, J. S. (2017). Reconfiguring global pharmaceutical value networks through targeted technology interventions. *International Journal of Production Research*, *55*(5), 1471–1487. https://doi.org/10.1080/00207543.2016.1221541

Hessel, V., Gürsel, I. V., Wang, Q., Noël, T., & Lang, J. (2012). Potential analysis of smart flow processing and micro process Technology for Fastening Process Development: Use of chemistry and process design as intensification fields. *Chemical Engineering and Technology*, *35*(7), 1184–1204. https://doi.org/10.1002/ceat.201200038

Hessel, V., Renken, A., Schouten, J. C., & Yoshida, J.-I. (2013). *Micro process engineering* (Vol. 1). Wiley-VCH. https://doi.org/10.1002/9783527631445

Hill, A. M., Barber, M. J., & Gotham, D. (2018). Estimated costs of production and potential prices for the WHO essential medicines list. *BMJ Globalization and Health*, *3*(1), e000571. https://doi.org/10.1136/bmjgh-2017-000571

Hodgett, R. E. (2016). Comparison of multi-criteria decision-making methods for equipment selection. *International Journal of Advanced Manufacturing Technology*, *85*(5), 1145–1157. https://doi.org/10.1007/s00170-015-7993-2

Hodgett, R. E., Martin, E. B., Montague, G., & Talford, M. (2014). Handling uncertain decisions in whole process design. *Production Planning and Control*, *25*(12), 1028–1038. https://doi.org/10.1080/09537287.2013.798706

Ishizaka, A., & Lusti, M. (2006). How to derive priorities in AHP: A comparative study. *Central European Journal of Operations Research*, *14*(4), 387–400. https://doi.org/10.1007/s10100-006-0012-9

Kern, D. Q. (1950). *Process heat transfer*. McGraw-Hill.

Kockmann, N., Gottsponer, M., Zimmermann, B., & Roberge, D. M. (2008). Enabling continuous-flow chemistry in microstructured devices for pharmaceutical and fine-chemical production. *Chemistry–A European Journal*, *14*, 7470–7477. https://doi.org/10.1002/chem.200800707

Krasberg, N., Hohmann, L., Bieringer, T., Bramsiepe, C., & Kockmann, N. (2014). Selection of technical reactor equipment for modular, continuous small-scale plants continuous small-scale plants. *PRO*, *2*(1), 265–292. https://doi.org/10.3390/pr2010265

Larson, R., & Edwards, B. H. (2000). *Elementary linear algebra* (4th ed.). Houghton Mifflin.

Lee, S. L., O'Conor, T. F., Yang, X., Cruz, C. N., Chatterjee, S., Madurawe, R. D., Moore, C. M. V., Yu, L. X., & Woodcock, J. (2015). Modernizing pharmaceutical manufacturing: From batch to continuous production. *Journal of Pharmaceutical Innovation*, *10*(3), 191–199. https://doi.org/10.1007/s12247-015-9215-8

Lehmann, H., & La Vecchia, L. (2010). Scale-up of organic reactions in a pharmaceutical kilo-lab using a commercial microwave reactor. *Organic Process Research and Development*, *14*(3), 650–656. https://doi.org/10.1021/op900269y

Lindeque, R. M., & Woodley, J. M. (2019). Reactor selection for effective continuous biocatalytic production of pharmaceuticals. *Catalysts*, *9*(3), 262. https://doi.org/10.3390/catal9030262

Linstone, H. A., Lendaris, G. G., Rogers, S. D., Wakeland, W., & Williams, M. (1979). The use of structural modeling for technology assessment. *Technological Forecasting and Social Change*, *14*(4), 291–327. https://doi.org/10.1016/0040-1625(79)90032-5

Marttunen, M., Lienert, J., & Belton, V. (2017). Structuring problems for multi-criteria decision analysis in practice: A literature review of method combinations. *European Journal of Operational Research*, *263*(1), 1–17. https://doi.org/10.1016/j.ejor.2017.04.041

McWilliams, J. C., Allian, A. D., Opalka, S. M., May, S. A., Journet, M., & Braden, T. M. (2018). The evolving state of continuous processing in pharmaceutical API manufacturing: A survey of pharmaceutical companies and contract manufacturing organizations. *Organic Process Research and Development*, *22*(9), 1143–1166. https://doi.org/10.1021/acs.oprd.8b00160

Mo, Y., & Jensen, K. F. (2016). A miniature CSTR cascade for continuous flow of reactions containing solids. *Reaction Chemistry & Engineering*, *1*, 501–507. https://doi.org/10.1039/C6RE00132G

Movsisyan, M., Delbeke, E., Berton, J., Battilocchio, C., Ley, S., & Stevens, C. (2016). Taming hazardous chemistry by continuous flow technology. *Chemical Society Reviews*, *45*, 4892–4928. https://doi.org/10.1039/C5CS00902B

Osterholm, M. T., & Olshaker, M. (2020). Why we are so ill-prepared for a possible pandemic like coronavirus. *TIME Magazine (Online)*, Feb 4. www.time.com/5777923/america-prepared-pandemic-coronavirus/

Peeling, R. H., & Talford, M. (2020). Chemical reactors: Whole process based approaches to reactor design and selection. *Chemistry Today*, *38*(1), 32–24.

Phillips, W., Kapletia, D., Dalgarno, K., Hunt, P., Bibb, R., Makatsoris, H., & Benge, J. (2020). Innovation in healthcare manufacturing: Transforming deployed medical care. *Proceedings of the XXXI ISPIM innovation conference*, Berlin, 7–10 June. https://hdl.handle.net/2134/12571010.v1

Plumb, K. (2005). Continuous processing in the pharmaceutical industry changing the mindset. *Chemical Engineering Research and Design*, *83*(6), 730–738. https://doi.org/10.1205/cherd.04359

Pollak, P., & Vouillamoz, R. (2013). Fine chemicals. In *Ullmann's encyclopedia of industrial chemistry*. Wiley-VCH Verlag. https://doi.org/10.1002/14356007.q11_q01

Porta, R., Benaglia, M., & Puglisi, A. (2016). Flow chemistry: Recent developments in the synthesis of pharmaceutical products. *Organic Process Research and Development*, *20*(1), 2–25. https://doi.org/10.1021/acs.oprd.5b00325

R Core Team. (2020). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. https://www.R-project.org/

Rantanen, J., & Khinast, J. (2015). The future of pharmaceutical manufacturing sciences. *Journal of Pharmaceutical Sciences*, *104*(11), 3612–3638. https://doi.org/10.1002/jps.24594

Riley, D. L., Strydom, I., Chikwamba, R., & Panayides, J.-L. (2019). Landscape and opportunities for active pharmaceutical ingredient manufacturing in developing African economies. *Reaction Chemistry & Engineering*, *4*(3), 457–489. https://doi.org/10.1039/C8RE00236C

Roberge, D. M., Ducry, L., Bieler, N., Cretton, P., & Zimmermann, B. (2005). Microreactor technology: A revolution for the fine chemical and pharmaceutical industries? *Chemical Engineering and Technology*, *28*(3), 318–323. https://doi.org/10.1002/ceat.200407128

Saaty, T. L. (2008). Decision making with the analytic hierarchy process. *International Journal of Services Sciences*, *1*(1), 83–98. https://doi.org/10.1504/IJSSci.2008.01759

Saaty, T. L. (2010). *Mathematical principles of decision making*. Pittsburgh, RWS.

Sambasivarao, K. V., & Deshmukh, S. G. (1997). A decision support system for selection and justification of advanced manufacturing technologies. *Production Planning and Control*, *8*(3), 270–284. https://doi.org/10.1080/095372897235325

Sambiagio, C., & Noël, T. (2020). Flow photochemistry: Shine some light on those tubes! *Trends in Chemistry*, *2*(2), 92–106. https://doi.org/10.1016/j.trechm.2019.09.003

Schaber, S. D., Gerogiorgis, D. I., Ramachandran, R., Evans, J. M. B., Barton, P. I., & Trout, B. L. (2011). Economic analysis of integrated continuous and batch pharmaceutical manufacturing: A case study. *Industrial and Engineering Chemistry Research*, *50*(17), 10083–10092. https://doi.org/10.1021/ie2006752

Schmink, J. R., Kormos, C. M., Devine, W. G., & Leadbeater, N. E. (2010). Exploring the scope for scale-up of organic chemistry using a large batch microwave reactor. *Organic Process Research and Development*, *14*, 205–214. https://doi.org/10.1021/op900287j

Settanni, E. (2020). Those who do not move, do not notice their (supply) chains—Inconvenient lessons from disruptions related to COVID-19. *AI & Society*, *35*, 1065–1071. https://doi.org/10.1007/s00146-020-00988-y

Shah, N. (2004). Pharmaceutical supply chains: Key issues and strategies for optimisation. *Computers and Chemical Engineering*, *28*(6–7), 929–941. https://doi.org/10.1016/j.compchemeng.2003.09.022

Sinnott, R. K. (2005). *Chemical engineering design* (4th ed.). Butterworth.-Heinemann.

Sobota, V. C. M., van de Kaa, G., Luomaranta, T., Martinsuo, M., & Ortt, J. R. (2021). Factors for metal additive manufacturing technology selection. *Journal of Manufacturing Technology Management*, *32*(9), 26–47. https://doi.org/10.1108/JMTM-12-2019-0448

Srai, J., Harrington, T., Alinaghian, L., & Phillips, M. (2015). Evaluating the potential for the continuous processing of pharmaceutical products—A supply network perspective. *Chemical Engineering and Processing*, *97*, 248–258. https://doi.org/10.1016/j.cep.2015.07.018

Srai, J. S., Settanni, E., & Aulakh, P. K. (2020). Evaluating the business case for continuous manufacturing of pharmaceuticals: A supply network perspective. In Z. K. Nagy, A. El Hagrasy, & J. Litster (Eds.), *Continuous pharmaceutical processing* (pp. 477–512). Springer International Publishing. https://doi.org/10.1007/978-3-030-41524-2_14

Stoessel, F. (2020). *Thermal safety of chemical processes*. Wiley-VCH.

Sushil. (2009). Interpretive ranking process. *Global Journal of Flexible Systems Management*, *10*(4), 1–10. https://doi.org/10.1007/BF03396567

Teoh, S. K., Rathi, C., & Sharratt, P. (2016). Practical assessment methodology for converting fine chemicals processes from batch to continuous. *Organic Process Research and Development*, *20*(2), 414–431. https://doi.org/10.1021/acs.oprd.5b00001

Triemer, S., Gilmore, K., Vu, G. T., Seeberger, P. H., & Seidel-Morgenstern, A. (2018). Literally green chemical synthesis of artemisinin from plant extracts. *Angewandte Chemie, International Edition*, *57*(19), 5525–5528. https://doi.org/10.1002/anie.201801424

Wenstøp, F. (2005). Mindsets, rationality and emotion in multi-criteria decision analysis. *Journal of Multi-Criteria Decision Analysis*, *13*(4), 161–172. https://doi.org/10.1002/mcda.384

Woodcock, J. (2019). *Safeguarding pharmaceutical supply chains in a global economy*. https://www.fda.gov/news-events/congr essional-testi mony/safeg uardi ng-pharm aceut ical-suppl y-chain s-global-econo my-10302019

Worstell, J. (2014). *Adiabatic fixed-bed reactors*. Butterworth-Heinemann.

Zolkaffly, M. Z., & Han, K. (2014). Reactor technology assessment and selection utilizing systems engineering approach. *International nuclear science, Technology & Engineering Conference*, Kuala Lumpur, 30 Sept-2 Oct. doi:https://doi.org/10.1063/1.4866099

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Aulakh, P. K., Settanni, E., & Srai, J. S. (2021). Continuous manufacturing technologies in upstream pharmaceutical supply chains: Combining engineering and managerial criteria. *Journal of Multi-Criteria Decision Analysis*, 1–15. https://doi.org/10.1002/mcda.1775