Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations (2021)

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Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations

Committee to Identify Innovative Technologies to Advance Pharmaceutical Manufacturing

Board on Chemical Sciences and Technology

Division on Earth and Life Studies

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report, nor did they see the final draft before its release. The review of the report was overseen by Babatunde A. Ogunnaike (NAE) and Stephen W Drew (NAE) who were responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

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Summary

Ensuring patient access to safe and efficacious drugs is a primary public-health mission of the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER). To accomplish its mission, CDER has a critical role in fostering manufacturing innovations that can improve product quality and prevent drug shortages that have become all too frequent. The coronavirus pandemic has also highlighted the need to modernize pharmaceutical manufacturing so that drugs can be produced swiftly and reliably. The current status compromises the ability to harness the power of science and technology fully and make vital products as available and accessible as possible. Many innovative technologies have been developed in recent years to advance pharmaceutical manufacturing, but much remains to achieve an agile, flexible pharmaceutical manufacturing sector that can produce high-quality drugs reliably without extensive regulatory oversight—a goal that FDA leadership has promoted. To assist its efforts to realize that goal, CDER asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to identify emerging technologies—such as product technologies, manufacturing processes, control and testing strategies, and platform technologies—that have the potential to advance pharmaceutical quality and modernize pharmaceutical manufacturing in the next 5–10 years for products regulated by CDER.[1] The agency also asked that technical and regulatory challenges be identified and suggestions provided to overcome the regulatory challenges.[2] It is important to note that the committee was not asked to recommend what innovations should be pursued but rather was asked to identify innovations that FDA is likely to see in the next 5–10 years. As a result of the request, the National Academies convened the Committee to Identify Technologies to Advance Pharmaceutical Manufacturing, which prepared this report. Here, the committee highlights some key innovations, identifies underlying regulatory constraints and potential impediments at FDA to foster manufacturing innovations, and provides some overarching recommendations and concluding statements.

KEY MANUFACTURING INNOVATIONS ON THE HORIZON

In this report, the committee has described many innovations to modernize the manufacture of drug substances and drug products,[3] to advance new control approaches, and to develop integrated, flexible, and distributed manufacturing networks. The technologies highlighted here perhaps represent the most probable and extensive opportunities to advance pharmaceutical manufacturing within 5–10 years. The committee has represented many of these innovations as classes rather than individual technologies; it is likely that diverse innovative technologies within a class will be implemented on similar timelines. Details of these and other innovations are provided in the report's chapters with a discussion of technical and regulatory challenges that they would face.

- *New routes to drug substances*. Innovations in manufacturing technology to synthesize active pharmaceutical ingredients (APIs) or drug substances include photochemical and electrochemical approaches, biocatalysis, cell-free protein synthesis, and cell-based biosynthesis that uses alternative hosts. All those technologies are gaining traction and are motivated by product innovations and by

[1] The committee notes that products regulated by CDER do not include vaccines, blood products, and cell and gene therapy products.

[2] The full task statement is provided in Chapter 1 of this report.

[3] A d*rug substance* (or active pharmaceutical ingredient) is any substance or mixture of substances that is intended to be used in the manufacture of a drug product. A *drug product* is the physical form in which drug substances are delivered to patients; common types are tablets, capsules, injections, and infusions.

opportunities to improve process efficiency, speed, cost, throughput, safety, and environmental sustainability. They also have the potential to improve the assurance of product quality by reducing the risk of byproduct formation or other undesired variants.

- *Co-processed APIs*. An innovation in the manufacture of APIs is the addition of a nonactive excipient or carrier to improve yields or to manipulate attributes of a process stream to achieve a desired outcome. For example, co-processed APIs might be advantageous in particle formation, crystallization, or drying operations to improve the stability of a desired solid state or to tailor physical properties of the drug substance.
- *Process intensification*. Technologic innovations that create more efficient, higher-yielding processes and enable smaller manufacturing footprints and reduced capital and operating costs are characterized as process intensification. Anticipated innovations include the integration or reduction of multiple traditional unit operations, the replacement of batch processes with continuous formats, and the incorporation of recirculation and recycle approaches. Such innovations afford improvements that are also foundational to the development of modular systems and flexible, distributed manufacturing networks. They will also help to overcome some of the most difficult impediments in supply-chain investment and decision-making and make it more feasible for redundant and surge capacity to be created and thus improve overall capability and security of the pharmaceutical supply.
- *Additive manufacturing*. Product formation by three-dimensional printing (additive manufacturing) is a radical alternative for manufacture of drug products in comparison with conventional tablet production. There are various approaches, but all use precise layering of materials in a successive, specific pattern to arrive at the final dosage form. The technologies can tailor the desired characteristics of a drug product—for example, its geometry, porosity, and API composition—and customize them for a specific indication or an individual patient requirement. Additive manufacturing also enables monitoring and acceptance or rejection of a product at the individual-dose level and can be scaled down to a compact size and thus potentially support highly distributed manufacturing.
- *Advanced process control and automation*. Important advances are being made in sensor technology, data analytics, and system modeling, and manufacturers will increasingly rely on these innovations to design, understand, and control complex processes. The combined capabilities of various sensors will create an unprecedented ability to measure process variables and product attributes. To use the enormous quantity and resolving power of such data effectively, sophisticated analytics, models, and artificial intelligence will be required to support advanced process-control strategies, continued process verification, and ultimately real-time process optimization and automated operation and management of manufacturing.
- *Modular systems*. Modular systems are composed of interconnected unit-operation "modules" that can be arranged and adapted to enable a single facility to manufacture a large array of drug products. They present an opportunity to reshape the very nature of manufacturing facilities and the global supply chain and offer the possibility of creating integrated, flexible, and distributed manufacturing networks. These modular systems can be easily replicated and deployed quickly in an existing facility or to other locations and thus provide the ability to respond rapidly to patient and health-care system needs that range from personalized therapies to varying patient needs across geographic and demographic boundaries. It is important to note that integrated, flexible, and distributed manufacturing networks will be extremely difficult to achieve through traditional quality-management systems that were built around large, centralized facilities and supply-chain networks. The ability to achieve consistency of operations and quality in smaller, more modularized operations will depend heavily on integrated advanced process control and automation.

The innovations described here represent exciting opportunities to modernize pharmaceutical manufacturing, but many challenges must be overcome for them to achieve widespread adoption. The following sections highlight some of the overarching issues that challenge adoption of innovative technology.

THE EFFECT OF PRODUCT REVIEW AND APPROVAL AS THE BASIS OF ACCEPTANCE AND IMPLEMENTATION OF MANUFACTURING TECHNOLOGY

An important factor in the pace of manufacturing innovation is the reality that formal regulatory review of technology occurs only in the context of an individual product. That is, technology is evaluated for its suitability to deliver a high-quality product consistently and is not approved outright on its own. That regulatory approach places a large burden on any manufacturer that wants to use an innovative technology in support of product approval for the first time. Even if regulators have had exposure to and are generally supportive of a particular manufacturing innovation, only when a product that uses it has been fully subjected to detailed review and approval can an initial understanding of its genuine regulatory status be achieved. It is entirely incumbent on the manufacturer to satisfy all requirements that regulators might need to approve the product, and introducing an innovative technology might result in unanticipated activities, costs, and time that could affect the financial viability of the product. Unless there is sufficient incentive for a manufacturer to bear that burden on behalf of a particular product, it often makes business sense to use more conventional technology for the product. Thus, the overall potential of a manufacturing innovation to influence many products or the global supply chain is not easily built into the value proposition for a single product. Even when a first such approval is achieved, it will take much time and effort—through the review and approval of other products—before a particular manufacturing technology is broadly and successfully adopted.

THE NEED FOR ALIGNMENT OF INCENTIVES TO ADVANCE TECHNOLOGY INNOVATION

Strong and consistent views have been expressed regarding the effect of incentives and disincentives on innovation. The committee concludes that although technical and regulatory challenges described in this report pose hurdles, none likely presents a greater barrier than insufficient, conflicting, or countervailing incentives. In some cases, there is a strong incentive for a manufacturing innovation, as when a pharmaceutical product depends on the technology for its production. However, many cases are not so clear-cut, for example, when a manufacturing innovation is a central feature of a potentially disruptive business model, such as small-scale, automated, integrated, and portable drug-manufacturing systems. In that situation, the business incentive is the potential to create and participate financially in a new drug-supply paradigm, but the disincentives begin to surface when one considers how to get the technology reviewed, approved, and accepted. In the current regulatory framework, the technology has to be part of a drug-approval process. If it is attached to an innovative product, there is a risk that the product could be delayed because of a slower, more complex, expensive, and riskier development program. If it is attached to established products, the effort and cost of gaining approvals for products manufactured with the innovative technology might negate a positive return on investment. Other scenarios can provide similar examples of competing incentives and disincentives. Ultimately, there is always a question of whether the incentives for the industry to invest in innovative technologies are sufficient.

This discussion assumes that the responsibility for proposing and justifying innovative technologies rests entirely with manufacturers. The committee finds that incentives need to be sufficiently aligned among all stakeholders and concludes that the work of aligning incentives should be broadly shared and not wait for industry-centric incentives alone to evolve and prevail. A more active, strategic, and system-focused effort will be required if the desired agility and flexibility of the manufacturing sector are to be achieved.

THE NEED FOR GLOBAL CONVERGENCE AND HARMONIZATION

Differences in regulatory expectations and requirements of international health authorities pose considerable challenges. Given that pharmaceutical companies often aspire to register and commercialize

their products in multiple geographic regions, often globally, the cost, effort, and complexity of this endeavor can be daunting. International guidelines have been developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). However, even in the case of well-established product categories that are manufactured by using proven technologies, companies regularly experience substantial differences in how guidelines are interpreted by regulatory authorities. The industry experience is that queries, interests, and concerns of individual reviewers and institutional health authorities remain highly variable and seemingly often arbitrary and inflexible. In the best case, the process can be resource- and time-intensive; manufacturers are often trying to achieve business-critical approvals without creating a patchwork of commitments and quality standards to suit different markets. Thus, the burden of seeking approvals for multiple geographic areas is great, and including novel manufacturing methods in the approval process increases the effort and cost and carries a greater risk of delays or an inability to register products in some countries. Any progress that can be made to enhance or accelerate regulatory harmonization and consistency will reduce disincentives for global implementation of innovative manufacturing technology.

POST-APPROVAL CHANGES: ESSENTIAL FOR ACCELERATING INNOVATION

The regulatory requirements concerning changes in the manufacturing process after a product has been approved or licensed are an impediment to advancing innovative technologies. To create wide-scale change, commercial pharmaceutical products—many of which were developed and registered years or even decades ago—need legitimate, viable access to post-licensure manufacturing improvements after the product is approved. Otherwise, the implementation and impact of innovation will lag profoundly behind the state of technology with little overall effect on the stability and security of the global supply chain. Conversely, if innovations in manufacturing technology can be expected to apply only to *future* products, the ability to realize value and return on investments will be constrained by the risks and potentially long timelines associated with research and development.

ICH has developed guidance (Q12) that is directed explicitly to the commercial phase of the product life cycle and constitutes a major effort to address issues that have hindered the full realization of the vision of a more flexible and agile pharmaceutical-manufacturing sector that has been advocated for the last 2 decades. The ultimate success of the guidance will hinge not only on the specific merits and comprehensiveness of the guidance itself but on an intensive, sustained effort on the part of the industry and regulators to agree on how the guidance will be used in practice. With consistent support and a genuine sense of partnership, experimentation, and continuous adaptation and improvement of the process, the ICH guidance has a chance to make a lasting difference.

CHALLENGES IN THE FOOD AND DRUG ADMINISTRATION

FDA leadership has acknowledged and emphasized its role in supporting manufacturing innovation in presentations and various reports, and CDER has taken important steps to foster innovation by creating the Emerging Technology Program and the associated Emerging Technology Team (ETT) in 2014. However, the views expressed in the workshops that were held by the committee to gather information indicate that the role of CDER in enabling innovation is underdeveloped, and this underdevelopment jeopardizes its ability to ensure access to safe and efficacious drugs reliably. The committee identified two areas in which the agency can play a prominent role in addressing impediments: (1) the expertise, capacity and culture of CDER and (2) the external perception of risks and benefits associated with implementing innovative technologies. The committee emphasizes that it is fully aware that CDER cannot advance innovation without efforts by other stakeholders in the pharmaceutical manufacturing ecosystem; success will depend on the concomitant actions of other critical stakeholders, especially the industry and policy-makers. However, the committee's task was to recommend actions that FDA should undertake to prepare for and accelerate adoption of innovative technology in pharmaceutical manufacturing

The ability of CDER to evaluate the risks to patient safety that are associated with innovative manufacturing technology is related directly to its technical expertise, capacity, and culture in supporting manufacturing innovation. The agency faces several challenges. First, the breadth of innovation in products, manufacturing processes, analytic technology, and control approaches present staffing and training challenges for CDER to ensure that it has the necessary expertise to evaluate new technologies. Second, there appear to be capacity constraints that affect consistency in evaluating innovative technologies. Views expressed in the committee's workshops suggest that the Emerging Technologies Program lacks sufficient capacity to sustain external engagement with industry, cultivate internal expertise necessary to inform that interaction, and support the transfer of the expertise to reviewers and inspectors. The inconsistencies lead to industry's hesitation to implement innovative technologies because of the expectation that reviewers and inspectors will need to be educated through iterative information requests throughout the life cycle of a product. Third, there appears to be dissonance between the oversight and facilitation roles. Although FDA leadership has encouraged the use of novel technologies to strengthen the robustness of pharmaceutical-manufacturing processes, a disconnect between the podium and the practice of front-line regulators erodes the industry's confidence that an investment in innovative technology will not derail planned regulatory-review timelines. The Prescription Drug User Fee Act (PDUFA) provides the agency with substantial funding through user fees paid by industry and requires reviewers to conform to aggressive review timelines to meet performance benchmarks. The iterations of information requests and reviewer education associated with the first use of an innovative technology create a highly stressful environment in light of PDUFA deadlines for both the industry and regulators. Prior reviewer experience with or exposure to new technologies offers important advantages during the review cycle, but such learning opportunities appear to be rare.

Industry decisions to implement innovative technologies clearly do not depend solely on the maturity and readiness of a specific technology itself. Rather, a key consideration is the risk that implementing an innovation might disrupt product timelines to market, and the uncertainties associated with the regulatory-review timelines and resource burdens appear to pose a substantial disincentive to innovate. The committee identified three specific concerns that appear to be critical factors in business decisions to innovate. First, there is the question of what data will be needed for regulatory filings to demonstrate the identity, safety, purity, and potency of a drug that is manufactured with innovative technology. Second, there is no clarity or consistency in the evaluation of residual risk to product quality. An innovation might introduce new uncertainties regarding product quality that cannot be fully eliminated, especially for complex drug products, and it is unclear how regulators will weigh risks and benefits associated with innovations that greatly enable flexibility and agility and thus address public-health needs but might present a theoretical quality concern with no clear and cost-effective path to resolution. Third is the issue of the global regulatory environment. As discussed, the resource-intensive effort to satisfy regulators in multiple geographic areas is a disincentive to implement innovation, and the committee perceives that a commitment from CDER to lead the development of international guidance would heavily influence the industry's risk–benefit evaluation in favor of innovation.

OVERARCHING COMMITTEE RECOMMENDATIONS

As noted, CDER's public-health mission to ensure patient access to safe and efficacious drugs drives the strategic need to facilitate innovation in manufacturing pharmaceuticals. The committee commends CDER for its willingness to examine mechanisms to strengthen its important role in changing the status quo, which often appears immutable given the industry's perception of risk. However, the committee's overall observation is that the center's resources, culture, and practices are tilted so heavily toward its oversight role that it is challenging to support innovation. Unless CDER addresses the challenges raised in the previous section, industry will continue its risk avoidance with respect to innovation unless innovation is necessary to bring a new product to market. Thus, the committee offers five overarching recommendations to strengthen FDA's role in fostering the use of innovative technologies to improve the quality and consistency of pharmaceutical manufacturing. The committee

emphasizes that its task was to focus on the role of FDA in preparing for and facilitating innovation to reach this future state. Accordingly, this report does not make recommendations to other stakeholders in the pharmaceutical ecosystem, but the committee acknowledges the critical need for them to also undertake actions in support of shared goals. Details associated with these recommendations are provided in Chapter 6.

- *Strengthen expertise in innovative technology throughout CDER*. The committee concludes that expertise in innovative manufacturing technology should be cultivated not only within the ETT but throughout CDER to ensure consistency in review and inspection. It recommends that CDER examine internal practices to increase technical fluency among its scientists through such actions as evaluating priorities in hiring and retention practices and ensuring that staff-development plans support continuous education on innovative technologies.
- *Advance innovative mechanisms for evaluating technology outside product approvals*. It is clear to the committee that any substantial acceleration in the pace of implementation of innovative technology requires CDER to engage earlier and more broadly in considering the suitability of novel enabling technologies. Therefore, the committee recommends that *CDER create new mechanisms and evaluate, expand, and consolidate existing pilot programs that allow consideration of innovative technology outside individual product submissions*. Although the committee is aware of limitations of the center's authority for formally reviewing technology outside the context of individual products, finding a path forward for other types of evaluation is a critical strategic action that should be undertaken by the agency.
- *Expand the scope and capacity of the Emerging Technology Program and the Emerging Technology Team*. In the committee's workshops, stakeholders expressed appreciation for the Emerging Technology Program as an effective pilot-scale effort and agreed that it would have a greater impact if capacity and scope constraints were lessened. The committee recommends expanding the influence of the ETT through the following actions: (1) dedicate independent funding to the ETT; (2) expand the number of dedicated full-time employees in the ETT; (3) broaden the criteria for entry into the program to include innovations that are neutral to product quality but enable agility, flexibility, and efficiency in the manufacturing process, control strategy, or supply chain; and (4) increase transparency of the capacity of the ETT and program outcomes.
- *Increase external engagement to facilitate innovation and increase awareness of readiness of CDER to evaluate innovative technology*. The committee concludes that increased external engagement speeds the exchange of knowledge between regulatory and industry scientists and lessens both parties' uncertainty in the assessment of risk. The committee recommends that CDER strengthen its external engagement through the following efforts: increase engagement of regulatory scientists with public–private partnerships, nonprofits, and academic institutions in technical activities; increase visible leadership in organizing, planning, and conducting open technical meetings and less structured "listen-and-learn" sessions; and leverage agency investments, extramural-research funding mechanisms, and partnerships with nonprofit consortia and academia to define research and development priorities, create affordable workforce-development training courses, and facilitate short-term sabbaticals for reviewers and inspectors.
- *Expand the leadership role in global regulatory harmonization efforts*. The heterogeneity of regulatory requirements in various regions is a disincentive to the industry to implement innovative technology and impedes CDER's strategic objective to foster innovation. As noted, the committee concludes that guidelines, such as those being developed by ICH, are highly effective in reducing real and perceived barriers to post-approval modifications but require sustained leadership by the United States to align global practices. Therefore, the committee recommends that CDER increase dedicated resources and incentives to support greater emphasis on consistency in implementation of existing ICH guidelines and to enable leadership in ICH working groups to accelerate harmonization. To complement ICH-focused efforts, CDER should consider and pursue more direct interaction with key regulatory agencies through

information exchange, training, and mechanisms to support mutual recognition programs for inspections. Where possible, FDA should emphasize advancement of innovative manufacturing technology as an explicit purpose and benefit of harmonization activities.

CONCLUDING STATEMENT

A common concern expressed throughout this study was that the agility, robustness, and overall maturity of the pharmaceutical-manufacturing sector need attention and investment to overcome the many potential vulnerabilities that could threaten access to products essential to public health. There is a strong consensus that advanced manufacturing technologies can and must play a central role in creating this future agile, flexible industry that can produce high-quality drugs reliably. However, what became evident to the committee in conducting its analysis is that many stakeholders have a role to play and can influence the adoption of innovative technology. Reflecting on the various parties and the overall system responsible for delivering high-quality medicines, the committee concludes that no single organization or entity—however well-financed, large, powerful, or influential—has either the capability or the mandate to lead the broader community to this desired future state on its own.

The historical pace of improvement arguably has suffered at the whole-system level because of the fundamental structural barriers and the roles and incentives of the various key participants in the pharmaceutical-manufacturing ecosystem. In particular, the predominant drivers of value for the industry and the public are the pharmaceutical products—not the technologies deployed to manufacture them. That reality has important implications both for industrial developers and manufacturers of products and for regulatory authorities that review and oversee them. Thus, neither manufacturers nor regulators are able to take a fully strategic, system-focused approach to the implementation of advanced manufacturing technology. Even if each organization acts responsibly and effectively within the expectations, motivations, and incentives of its mandate, no concerted driving force or "invisible hand" is guiding the system toward an overall desirable end point. A dramatic change in the relationship and collective leadership among entities most able to affect the outcome will be required. The committee concludes that FDA, as a critical participant and node of influence, can and should play a direct leadership role and emphasizes that FDA needs to support the ability and willingness of manufacturers to lead and drive innovative change.

1

Introduction

In 2002, the U.S. Food and Drug Administration (FDA) launched the Pharmaceutical Quality for the 21st Century Initiative to encourage adoption of innovative technologies that would lead to an agile, flexible pharmaceutical manufacturing sector.[1] The goal was to encourage a transition to manufacturing processes and approaches that could produce high-quality drugs reliably without extensive regulatory oversight (NASEM 2020a). Much progress has been made toward that goal as the industry has developed and advanced new technologies, but more progress is required as recent natural disasters and the coronavirus pandemic have revealed vulnerabilities in supply chains and highlighted the need to modernize pharmaceutical manufacturing further. To facilitate that modernization, the FDA Center for Drug Evaluation and Research (CDER) strives to foster adoption of innovative technologies by the pharmaceutical industry. To assist those efforts, CDER asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to identify emerging technologies—such as product technologies, manufacturing processes, control and testing strategies, and platform technologies—that have the potential to advance pharmaceutical quality and modernize pharmaceutical manufacturing for products regulated by CDER. In response to that request, the National Academies convened the Committee to Identify Innovative Technologies to Advance Pharmaceutical Manufacturing, which prepared this report.

THE PHARMACEUTICAL INDUSTRY TODAY AND INNOVATION

The pharmaceutical industry is a heterogeneous ecosystem that consists of five broad categories of organizations:

1. Large multinational, research-intensive companies represented by trade associations, such as the Pharmaceutical Research and Manufacturers of America and the Biotechnology Innovation Organization, which traditionally have developed and brought to market patented drug products.
2. Generic-drug companies, represented by the Association for Accessible Medicines, that supply the huge number of medicines whose patents have expired, for which a market is established, and which account for nearly 90% of the prescriptions written in the United States (IQVIA 2019).
3. A broad spectrum of start-up and medium-size companies that innovate in the discovery of novel therapies, especially biologics, and innovative drug-delivery technologies.
4. A variety of contract organizations that offer pharmaceutical-product development and manufacturing services to the first three categories of organizations.
5. Established and start-up technology vendors that provide the process equipment, sensors, analytic tools, and information technology; associated services; and next-generation technology in this space.

Although FDA and regulatory agencies in the European Union and Japan have encouraged manufacturing innovations throughout the entire industry, the innovations in pharmaceutical manufacturing that are the focus of this study are generated largely by categories 1 and 3. The generic companies (category 2) have not generally been the source of manufacturing innovations because they

[1] See https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/pharmaceutical-quality-21st-century-risk-based-approach-progress-report#intro.

need to replicate the product performance achieved by the originators of patented products and to do so at as low a cost as possible. Those constraints limit the time and resources allotted for the development of innovative manufacturing processes. The contract organizations (category 4) generally do not lead with innovations; rather, they offer such technologies in response to customer demands or, in a few cases, in partnership with innovators in category 1. Although technology vendors (category 5) also typically operate in response to market pull, the rising interest in manufacturing innovations has led to a growing technology push by technology providers, especially those of sensing and process equipment.

Collaborative efforts to foster innovation have resulted in industry consortia, such as BioPhorum,[2] and in university–industry–government consortia, such as the National Institute for Innovation in Manufacturing Biopharmaceuticals[3] and LyoHub.[4] Those consortia have produced technology roadmaps that have identified manufacturing technology gaps—for example, for the biopharmaceutical industry[5] and for such specific technologies as lyophilization[6]—and offer promising solutions. Technology gaps have also been identified and research funded by philanthropic organizations, such as the Bill & Melinda Gates Foundation, typically to address needs of health care in underdeveloped countries.[7]

The innovations identified by the roadmaps, other scientific literature, and the committee's expertise typically fall into four categories:

- Specific operations in drug-substance manufacturing, including integration of steps through intensification, use of microfluidic formats, replacement of traditional separation and purification processes with membrane technologies, new synthesis routes involving electrochemistry or photochemistry, and co-processing of active and excipient components.
- Specific technologies in drug-product manufacturing, such as additive manufacturing modes, continuous lyophilization, highly automated and robotics-enabled aseptic filling, microwave-based drying, microparticle formation, and nanoparticle-based delivery systems.
- Process sensing and control, modeling, and data-analytics technologies, including multiattribute sensing, sensors that exploit a wide range of wavelengths, model-predictive and plantwide control strategies, integrated use of digital twins in manufacturing operations, and condition-based monitoring and management of processes.
- Organization of manufacturing processes, including integration of all the processing steps from synthesis of an active pharmaceutical ingredient to final drug product (end-to-end), use of continuous manufacturing, modularization of manufacturing operations, and downsizing of manufacturing scale to personalized production at point of sales or administration.

Those and other innovations are discussed further in the chapters that follow.

THE FOOD AND DRUG ADMINISTRATION AND INNOVATION

CDER approves drug-product applications, and the technologies and processes used to manufacture the products are evaluated solely as part of the application process for the specific products. CDER does not regulate or approve technologies outside the scope of product submission. Thus, the pharmaceutical industry has traditionally been hesitant to pursue innovations, given the perception that introducing new technologies could delay, impede, or complicate the approval process. To address that tension, CDER created the Emerging Technology Program and Team (ETT), which works with

[2] See https://www.biophorum.com/.
[3] See https://niimbl.force.com/s/.
[4] See https://pharmahub.org/groups/lyo/about.
[5] See https://niimbl.force.com/s/niimbl-roadmaps and https://www.biophorum.com/download/executive-summary/.
[6] See https://pharmahub.org/groups/lyo/lyohub_roadmapping.
[7] See https://www.gatesfoundation.org/What-We-Do/Global-Health/Innovative-Technology-Solutions.

pharmaceutical companies that are considering innovations at the early stages to try to reduce barriers to adoption of innovative technologies.[8] Also as part of its efforts, CDER tries to stay abreast of technologies that it might see within the timeframe of 5–10 years and asked the National Academies to assist it in that effort.

STATEMENT OF TASK

The committee that was convened as a result of the CDER request included experts in innovative pharmaceutical manufacturing, process engineering, formulations and drug delivery, data science and machine learning, and regulatory compliance. (Appendixes A and B provide biographic and disclosure information, respectively, on the committee.) The committee was asked to identify emerging technologies and challenges that might prevent their adoption and to recommend ways of overcoming any regulatory challenges. It is important to note that the committee was not asked to recommend what innovations should be pursued but rather was asked to identify innovations that FDA is likely to see in the next 5–10 years. The verbatim statement of task is provided in Box 1-1.

THE COMMITTEE'S APPROACH TO ITS TASK

To accomplish its task, the committee held two large public workshops to inform the study process and drew speakers from categories 1, 3, and 4 noted above and academic contributors who represent research groups that work in partnership with the various industrial organizations. Workshop agendas are provided in Appendix C, and the proceedings are freely available on the National Academies Press website (NASEM 2020a,b) and are provided in Appendixes D and E. The committee also held two webinars to get further input from FDA staff and from the generics-manufacturing sector. It considered technology roadmaps and other scientific literature and held six committee meetings to deliberate on its findings and recommendations and prepare its report.

The committee recognizes that various terms in the pharmaceutical industry have often been used inconsistently. To ensure clarity, the committee has defined, in Box 1-2, several terms that are used throughout this report. Also, the terms *pharmaceutical industry* and *biopharmaceutical industry* are often used to distinguish between small-molecule manufacturers and biologics manufacturers. For simplicity in this report, the committee generally uses the term *pharmaceutical industry* as an all-encompassing term; distinctions are made where needed.

BOX 1-1 Statement of Task

The Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration fosters the adoption of innovative technologies by pharmaceutical companies. To assist CDER in those efforts, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will produce a consensus report that identifies emerging and upcoming technologies (e.g., product technologies, manufacturing processes, control and testing strategies, and platform technologies) that have the potential to advance pharmaceutical quality and modernize pharmaceutical manufacturing for products regulated by CDER (small and large molecules up to monoclonal antibodies or therapeutic proteins). For the technologies for which the FDA will need to be prepared in the 5-10 years following the report, the committee will describe (1) potential pharmaceutical applications of emerging technologies, (2) key technical issues that will affect innovation, (3) regulatory issues for which the agency might want to prepare, and (4) suggestions for how to overcome those regulatory issues to facilitate the adoption of promising novel technologies in the pharmaceutical industry. The committee's approach will include collection of information, workshops on innovation and on technical and regulatory hurdles with highlights captured in workshop proceedings, and expert analysis that culminates in a peer-reviewed consensus report. The report will describe promising innovation areas and insights on key regulatory and technical challenges that the FDA and the pharmaceutical industry will need to address to realize the benefits of the innovation.

[8] See https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program.

BOX 1-2 Definitions of Key Terms

Active Pharmaceutical Ingredient: "Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product" (FDA 2006, p. 48). This term is sometimes restricted to refer to active ingredients produced only via synthetic organic chemistry routes; however, for this report, it is used interchangeably with *drug substance*.

Additive Manufacturing: A manufacturing mode in which a three-dimensional object is formed by the layer-by-layer deposition of material, usually under computer control, and that relies on a digital three-dimensional representation of the object to guide the deposition. Also called 3D printing.

Advanced Manufacturing: Manufacturing developments in which innovative technologies are used to upgrade or replace existing manufacturing systems so as to improve product quality and process performance.

Batch Processing: A manufacturing mode in which transformation of input materials occurs in a series of discrete unit operations; each operation involves charging of the unit with input material, processing over some period, releasing the resulting processed material at the end of that period, possibly testing it, and then transferring it in bulk to the next operation. See Figure 1-1.

Campaign: A period during which a drug substance or drug product is manufactured in a specific manufacturing line. In the case of batch processing, it consists of a sequence of batches of the same drug substance or product that is made in the selected manufacturing line.

Continuous Manufacturing: An integrated process that consists of a series of two or more unit operations in which materials are continuously fed into and continuously processed in the unit operations and the output materials are continuously removed. See Figure 1-1.

Data Analytics: Methods for examining large datasets that originate from a system of interest by using visual, mathematical, and statistical tools to extract insights and draw conclusions about the information they contain.

Digital Twin: The virtual representation of a physical asset or process that uses mathematical relations, real-time data, and other information sources to replicate the behavior of the actual asset or process with sufficiently high fidelity.

Distributed Manufacturing: A manufacturing strategy in which manufacturing assets are replicated and geographically dispersed to shorten supply chains and increase supply reliability.

Drug Product: The physical form in which drug substances are delivered to the patient. The most common types are tablets, capsules, injections, and infusions.

Drug Substance: An active pharmaceutical ingredient.

End-to-End Manufacturing: A manufacturing system in which the drug substance and drug product manufacturing steps are fully integrated into a single continuous process with no isolation of drug substance or intermediates.

Portable Manufacturing: A manufacturing system design in which integrated manufacturing assets are reduced in scale, modularized, and made largely site-independent so as to allow transport and operation of the system at any desired location.

Semi-Batch Processing: A semi-batch operation is an inherently batch operation in which there is some addition or removal of material as the batch operation progresses. A special case is the so-called fed-batch mode in which there is input flow of material during the course of batch execution, such as addition of oxygen or nutrient solutions to a fermentor during the fermentation step.

(Continued)

BOX 1-2 Continued

Semi-Continuous Processing: Processing that is inherently continuous but operates intermittently; that is, it is started up, operated at some fixed constant rate, and then shut down. An example is a tablet press that when active is operated at a selected constant rate (rpm) and is then shut down once the available input of powder blend is consumed.

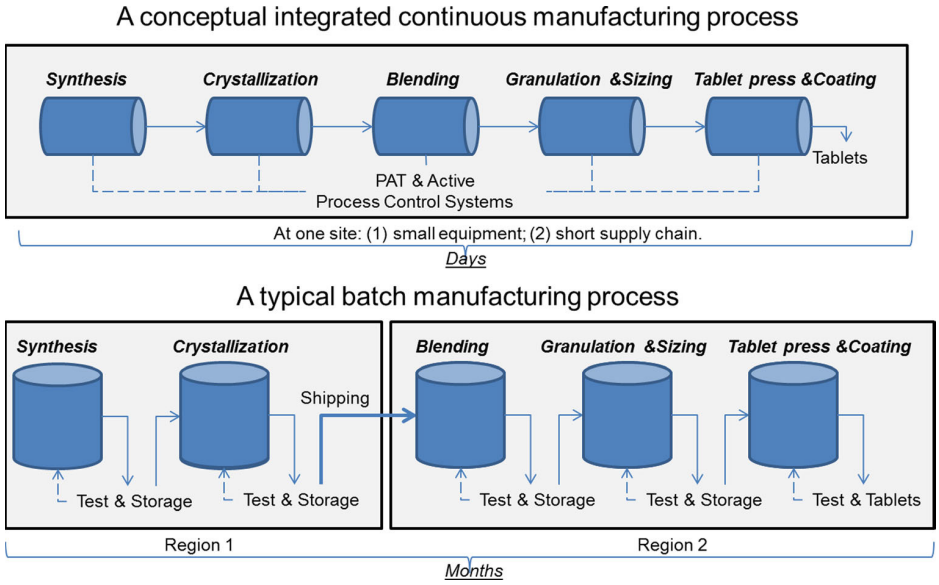

FIGURE 1-1 Comparison of batch and continuous operations for a hypothetical small-molecule manufacturing process. Abbreviation: PAT, process analytic technology. Source: Lee et al. 2015. Reprinted with permission; copyright 2015, *Journal of Pharmaceutical Innovation*.

ORGANIZATION OF THIS REPORT

This report is organized into six chapters and four appendixes. Chapters 2 and 3 describe innovations in manufacturing of drug substances and drug products, respectively. Chapter 4 discusses innovations in control approaches. Chapter 5 describes innovations in organizing manufacturing networks. Each chapter briefly describes various technologies and possible technical and regulatory challenges specific to each and provides suggestions for overcoming the regulatory challenges. Chapter 6 provides some general observations, describes some overarching challenges, and concludes with some recommendations for overcoming the challenges. Appendixes A and B provide biographic and disclosure information, respectively, on the committee, Appendix C provides workshop and webinar agendas, Appendix D provides the proceedings of the innovations workshop, and Appendix E provides the proceedings of the workshop on technical and regulatory barriers to innovation.

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2

Innovations in Manufacturing Drug Substances

Production of the nation's drug supply involves manufacture of drug substances—the active pharmaceutical ingredients (APIs)—and ultimately the drug products that are delivered to patients. In this chapter, the committee explores innovations for manufacturing bulk, purified APIs. Specifically, the committee discusses innovations in unit operations, process intensification, and process stream compositions that are associated with the upstream and downstream processing of APIs. Here, *upstream* refers to the portion of the process in which an API is first generated by reaction or from a host organism, and *downstream* refers to the portion of the process dedicated to the isolation and purification of the API. The innovations discussed here are likely to arise in filings of investigational new drugs in the next 5–10 years. Technical and regulatory challenges are also discussed with suggestions for overcoming the regulatory challenges in drug-substance manufacturing.

UNIT OPERATIONS

Unit operations refers to individual manufacturing steps and their associated equipment, such as a stirred tank reactor for synthesis of a small-molecule API from chemical precursors, a cell culture for producing monoclonal antibodies (mAbs), a harvest operation that uses a filtration unit to separate a biologic API from host cells and host-cell debris after cell culture, a crystallizer for final purification and generation of a solid form of a small-molecule API, or a polishing purification operation that uses a column chromatography unit to remove residual contaminants to yield a highly purified biologic API stream from a stream of intermediate purity. Innovations in unit operations arise when traditional, expected operations are replaced with atypical alternatives, when technologies are adopted from other industries, when new formats or operating strategies are instituted for existing unit operations, or when completely new process equipment and technologies are created. The following sections describe innovations for those situations.

Replacement of Traditional Process Technologies with Atypical Alternatives

The physicochemical or biophysical properties of new APIs and changes in the composition of process streams are likely to drive the replacement of traditional technologies. The inability to crystallize small-molecule APIs of increased molecular complexity and the production of amorphous forms of API solids that have desirable release kinetics might lead to the replacement of typical crystallization operations with chromatographic purification operations and leave the formation of the solid phase to a later drying step. Column chromatography, although long the mainstay of the downstream purification of biologics, is much less familiar in the context of small molecule APIs.

For biologics that are produced by secreting host cells, substantial increases in API titers during upstream processing have been made possible by host-cell engineering, adoption of alternative hosts, cell-growth media and feeding-strategy innovations, and bioreactor engineering. Those advances have pushed the limits of capacity and mass-transfer kinetics of traditional column chromatography. For mAbs—the largest class of biopharmaceuticals by number of approved drugs, production scale, and sales volume—fed-batch production titers (currently 5–10 g/L, Shukla et al. 2017; Xu et al. 2020) are expected to grow to 40 g/L within 10 years (BPOG 2017a). At such high protein concentrations, bulk-separation alternatives to the traditional protein A affinity column-chromatography capture step—such as

precipitation, aqueous two-phase extraction, and crystallization—become attractive with respect to throughput, cost, and complexity. In fact, for high-titer proteins, the development of purification trains[1] completely devoid of column chromatography is likely.

Adoption of Process Technologies from Other Industries

The similarities between the properties of process streams in biologic-drug production and product streams in other industries—such as the food and beverage, industrial enzyme, plasma fractionation, and wastewater-processing industries—provide opportunities for the adoption of alternative unit operations. Harvest operations for biologics have long been conducted by centrifugation or filtration operations, and cell flocculation and flotation-based harvest strategies that could be adopted from wastewater processing might provide low-fouling alternatives. The precipitation-based capture purification of mAbs is an example of a technology borrowed from long use in the plasma-fractionation industry. New continuous-processing unit operation formats, discussed further below, illustrate the diffusion of technology and processing approaches from the oil, gas, and chemical-process industries, and more recently the food industry, to the pharmaceutical industry. Here, the drivers for the adoption are decreased operational complexity and costs and increased throughput.

New Formats and Operating Strategies for Existing Process Technologies

New formats and operating strategies are being created for existing unit operations to increase efficiency and throughput, decrease the cost of goods and complexity, and address scalability concerns. The manufacture of biologics provides several innovative examples (Coffman 2020; Jagschies 2020). The need to limit lactate and ammonia accumulation can lead to batch operations that have new feeding strategies in which glucose is fed to the culture in a controlled manner to increase cell densities and product titers. Further advances are likely to link feeding strategies directly to sensed critical quality attributes. Cell-perfusion operations can greatly increase productivity provided that long-term cell growth can be maintained. Expectations are that perfusion-reactor productivities will grow from 0.05–1 g/L-day to 0.5–10 g/L-day (BPOG 2017a) within 10 years. Such increases will be facilitated by innovations in current cell-retention devices, such as the incorporation of new low-fouling membranes in tangential flow filtration (TFF) and alternating tangential flow (ATF) filtration, and in the application of new process technologies, such as scalable acoustic separators and hydrocyclones described below.

Multicolumn periodic continuous chromatography formats have been developed to address the capacity and throughput limitations of traditional column chromatography for high-titer protein products. Next-generation chromatographic formats, such as counter-current tangential chromatography that uses chromatographic media slurries in place of packed beds and rapid cycling adsorptive membranes, are under development to address the mass-transfer limitations of fixed beds. Single-pass tangential flow filtration, an alternative developed for traditional batch ultrafiltration-based concentration operations, might be used in new configurations to accomplish sequential concentration and diafiltration or in cascades to form a purification train. Examples of new formats and operating strategies that span both biologic and small-molecule drugs are microfluidic unit-operation formats for small-scale production of individualized therapies and continuous formats for many batch unit operations. The development of continuous formats is discussed further below.

New Process Technologies

Beyond the extension and elaboration of existing technologies, completely new types of unit operations that exploit physical phenomena that have not previously been harnessed in traditional manufacturing processes are emerging. In the synthesis of small-molecule drugs, new types of reactors

[1] *Trains* are defined here as sequences of unit operations.

that enable photochemical and electrochemical reactions are being developed (Tom 2020). In upstream operations for biologics, the use of membrane-based microcarriers for culturing adherent cells introduces a different process from the one used for culturing suspension cells. Methods to retain individual cells or microcarriers in perfusion cultures are likely to be the subject of substantial innovation. In general, such methods must be neutral with respect to cell viability and effective in retaining cells or microcarriers in the bioreactor. Alternatives to now-conventional TFF and ATF cell-retention devices—such as acoustic separators that work by concentrating cells at the nodes of a three-dimensional low-frequency standing wave and hydrocyclones that exploit density differences between cells and the suspending medium in a centrifugal-flow field to concentrate cells—might see application. In addition, precipitation methods that use various types of decanters and cell filtration and recycling have been used for cell retention in processes that involve perfusion cultures. Acoustic separators might also replace primary depth filtration in cell-harvest operations.

Other new technologies in the downstream processing of biologics have incorporated sequential membrane-based chromatographic operations that remove trace impurities while allowing high-concentration target species to flow through for the polishing purification of biologics. Such sequential membrane-based operations have arisen because of the availability of new membrane media and the increasing ability to predict target and contaminant binding behaviors as a function of media properties and solution conditions (Crowell et al. 2018). These new unit operations can have operational and performance advantages over traditional technology and might allow the rearrangement or elimination of surrounding operations in the overall manufacturing process.

Technical Challenges

Adoption of new unit operations can pose several technical challenges. First, new unit operations can have unfamiliar mechanisms and create uncertainty regarding the relationships between critical process parameters and critical quality attributes of the API. New process analytic technologies (PATs) and control strategies might be needed to operate new unit operations. Second, the introduction of a new unit operation can alter the composition or impurity profile of a process relative to a conventional process; for example, a novel, high-throughput capture step during purification might have lower selectivity than typical capture operations and transfer a greater share of the purification burden to later polishing steps. Third, the robustness of new unit operations to accommodate variations in feed stream flows while maintaining consistent output stream characteristics and to provide long-term operability at needed scales with associated failure modes needs to be demonstrated if the industry is to adopt them. Fourth, validation protocols for a new unit operation might not be well established or might need to be developed from scratch. Finally, new unit operations must integrate well within the broader process in which they are embedded with respect to processing timescales, transient time constants, equipment footprints, process-stream holdup volumes, and resource needs.

Regulatory Challenges

New and unfamiliar unit operations will lack the historical operating records and institutional experiences that instill confidence in established validation protocols and previously identified critical process parameters and performance characteristics and their connections to critical quality attributes of drug substances. In the absence of specific guidance, the first to introduce a new unit operation in an investigational new drug application, a new drug application, or a biologic license application will bear the burden of demonstrating that the new process and its mechanism of operation, performance characteristics, and critical quality attributes are well understood and that the validation protocol and results are sufficient to establish robustness. Both applicants and regulators will need to be convinced that the unknown risks have been minimized such that the product and patient-safety risks associated with deploying an innovative unit operation are commensurate with or smaller than those posed by the established unit operation that it is replacing.

PROCESS INTENSIFICATION

Process intensification can be defined as "the development of novel apparatuses and techniques that, compared to those commonly used today, are expected to bring dramatic improvements in manufacturing and processing, substantially decreasing equipment-size/production-capacity ratio, energy consumption, or waste production, and ultimately resulting in cheaper, sustainable technologies" (Stankiewicz and Moulijn 2000). In its roadmap for biomanufacturing technologies, the BioPhorum Operations Group (BPOG) has classified process intensification according to how it is achieved—by manipulating the supporting infrastructure of an existing process without changing unit operations or operating parameters, by changing operating parameters within existing unit operations, by changing raw-material use in existing unit operations, or by substantially changing process flow with disruptive technologies (BPOG 2017b). In the context of anticipated innovations in the manufacture of APIs, the committee discusses intensification in terms of the last category, the one with the greatest effects, specifically addressing the integration or reduction of multiple traditional unit operations, the replacement of traditionally batch unit operations with continuous formats, and the incorporation of recirculation and recycle in unit operations and processes.

Integrated Unit Operations

By analogy with the chemical-process industries in which efficiency considerations have driven the integration of reactor-separator unit operations, such as reactive distillation and reactive extraction, the pharmaceutical industry is developing new combinations of unit operations that have enhanced performance and efficiency. For example, in the upstream processing of biologics, novel seed trains that use high-density cell lines with high-nutrient inoculation media and N-1 perfusion can shrink the number of discrete cell-expansion operations and substantially shorten overall culture times. Innovations are also expected in product harvest and capture operations, which are critical steps at the interface between upstream and downstream processes. Here, specific innovations include the use of precipitants in bioreactors to remove cell debris, host-cell proteins, and host DNA before supernatant harvest and the introduction of combined clarification and product-capture devices. Furthermore, viral filters that contain filter media with viral-inactivating coatings combine two orthogonal modes of viral clearance that are traditionally conducted in separate unit operations (viral filtration and viral inactivation) into a single unit operation.

An important element of integrative intensification for the manufacture of biologics that bears mentioning separately is solution preparation. This seemingly mundane aspect of bioprocessing is a substantial process-time, labor, and complexity bottleneck and a controlling factor in setting a facility or process footprint. Intensified cell-culture operations place increased demands on media-solution preparation in that fed-batch bioreactor media needs to scale with cell-number density, and a perfusion bioreactor needs to scale with perfusion rate. Buffer use in the downstream process scales with titer, and many buffer solutions are required, particularly to support chromatographic operations. Although traditional batch solution preparation is giving way to in-line dilution of concentrates, further intensification is expected. A unit for on-demand preparation of buffer solutions that consolidates all downstream process buffer preparation into a single unit operation is under development as part of a collaboration between the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and BPOG with broad industry participation. Given the intensity of industry interest, it is likely to be deployed soon (BPOG 2019), and the concept is likely to be extended to on-demand cell-culture media preparation.

Continuous Unit Operations

Unit operations that have a long history of use in batch or semi-batch modes are being converted to continuous mode in an effort to capture all the benefits of continuous operations: smaller footprint,

decreased material use, higher throughput and yield, and, ultimately, cost efficiencies. Continuous operation also provides the potential for achieving true steady-state conditions that ensure consistent attainment of critical quality attributes of the product during operation. For small-molecule APIs, flow chemistry offers many additional benefits in upstream processing given the often complex and hazardous reactions that are involved in API generation. It can decrease the volumes of hazardous reactants and solvents that are handled in a process at a given time, restrict extreme reaction conditions to short residence times, avoid the isolation of hazardous intermediates, control the formation of products and side-products by manipulating serial and parallel reactions, and enable more efficient reactor designs (Burcham et al. 2018). For biologics, there is precedence for continuous unit operations given the long-standing upstream use of perfusion cell culture to enable production of labile APIs that would otherwise be substantially degraded if batch operations were used. Another continuous-processing example can be found in the more recent introduction of periodic continuous chromatography in downstream processing operations to enable full use of target-binding capacity of expensive chromatographic resins, such as the protein A media used to capture mAbs. Similarly, for small-molecule APIs, precedence is provided by continuous drug-product processing, which has extended traditional continuous unit operations, such as tableting and capsule-filling steps, to end-to-end drug-product formulation and filling processes (Burcham et al. 2018).

Further innovations in continuous processing for small-molecule APIs are expected to include the incorporation of flow chemistry with novel reaction mechanisms and reactor formats to enable photochemical, electrochemical, and serial biochemical catalysis; the development of hybrid batch-continuous reactors or intermittent-flow stirred tank reactors to facilitate the conduct of heterogeneous reactions in upstream processes; and membrane separations to replace distillation or crystallization operations in downstream processes (Burcham et al. 2018). Biologics manufacturing will likely see the conversion of periodic continuous-chromatography formats to fully continuous formats, such as countercurrent tangential chromatography (Shinkazh et al. 2011); the introduction of continuous precipitation and extraction operations to replace column chromatography for capture steps (Sheth et al. 2014; Li et al. 2019); the introduction of continuous viral inactivation processes based on tubular contactors rather than traditional batch-stirred tanks (Orozco et al. 2017; Gillespie et al. 2019); continuous viral filtration formats (David et al. 2019); and continuous ultrafiltration–diafiltration for preformulation of drug substances (Jabra et al. 2019; Yehl et al. 2019).

Incorporation of Recirculation and Recycle

Recirculation is the retrograde flow of material within a unit operation, and recycle involves flows of process streams from later unit operations to earlier unit operations. Both offer opportunities for API yield improvement, more efficient use of raw materials, reductions in waste generation, and improved process control by manipulating physical material feedback. There is ample precedence for accepting recirculation in a unit operation. For example, it is used in perfusion cell-culture systems with cell recirculation, batch ultrafiltration and diafiltration operations based on retentate recirculation, and mixed-suspension–mixed-product removal crystallization with mother-liquor recirculation. Innovative unit operations that use recirculation include countercurrent flows of wash buffers in continuous countercurrent tangential chromatography and in continuous precipitation operations. The recirculation of formulated, small-molecule API powder blends has also been used with additive manufacturing technology for tablet-formation operations as described in Chapter 3.

Incorporating recycle loops in a process is a bigger innovative leap than incorporating recirculation loops. An example is the recycle of heterogeneous catalysts used in flow chemistry by coupling flow reactors to continuous membrane separators (Burcham 2018). Another is the recycle of mother liquor from crystallizers to upstream reaction stages in small-molecule API production to improve yield (Patrascu and Barton 2019). In the production of biologics, the reuse of chromatography regeneration and equilibration solutions and the routing and augmenting of spent precipitants from downstream precipitation-based capture purification operations to upstream clarification operations are

examples in which recycle can substantially reduce buffer use and waste-stream volumes. The rise of more fully continuous processes will provide opportunities for the recovery and reprocessing of APIs diverted after a processing fault.

Technical Challenges

The technical challenges associated with process intensification include those associated with the introduction of innovative unit operations and are perhaps magnified by the greater scope of innovation involved. However, additional challenges are associated with integration, continuous processing, and incorporation of recirculation and recycle. The integration of unit operations leads to several efficiencies: a reduction in the total number of unit operations, each of which has finite yields and opportunities for faults, errors, and contamination events; a reduction in process footprint that results in smaller manufacturing suites; and a reduction in cost of goods. The tradeoff is that the integrated unit operation is likely to be more complex mechanically or operationally because multiple mechanisms have been combined to achieve multiple process-quality goals simultaneously in a single unit operation. That complexity is typically overcome through the implementation of suitable process-control systems and strategies that admittedly might also be more complex than the process control implemented for less intensive operations and processes. The integrated operation might also be more reliant on specialized raw materials, media, or consumables than the separate unit operations that it replaces.

Continuous operations, as discussed further in Chapters 4 and 5, require the development of safe and efficient process startup and shutdown procedures and mechanisms for tracking and diverting nonconforming material that might have been generated as a result of faults that the process-control system cannot overcome. Continuous operation will likely require parallel enabling innovations in process-control technology and strategy and in the associated in-line PAT to achieve and maintain steady-state operation and to handle transients, fluctuations, faults, and restarts; these innovations will ensure that a "state of control" is maintained during process operations. Such innovations might include new types of sensing modalities. For example, sensors that use Raman spectroscopy have already made inroads in bioreactor monitoring and might see application to downstream unit operations. It should be noted that continuous unit operations typically have much shorter timescales in which process decisions must be made than do batch operations.

Recirculation and recycle provide enhanced efficiencies and the ability to control stream composition and flow characteristics directly. However, those benefits come at the expense of the potential for accumulation of process-related and product-related impurities associated with the reverse flow of streams within or between unit operations and the potential for delayed and oscillatory responses to process disturbances and control actions because of increased system time constants that result from retrograde stream flows.

Regulatory Challenges

Several regulatory challenges arise with process intensification and are compounded versions of the challenges associated with novel unit operations. The stakes are higher because a larger portion of the overall process or the increase in processing objectives is typically involved in an intensification innovation relative to a unit operation innovation. For integrated unit operations, the compounding arises from the concatenation of the uncertainties of two or more processing objectives, such as a combined clarification and capture step for biologics. Process intensification also might reduce operational redundancies that are viewed as a process safety net. In continuous unit operations, the complexity of the integrated PAT and control systems and the short process decision-making timescales compound uncertainties. Sequential continuous unit operations that have low residence times also might eliminate the accumulation of a process intermediate and thus the intermediate quality-assurance and quality-control data that have traditionally supported drug-substance release. If a continuous downstream operation is connected directly to a continuous formulation operation, "drug substance" might cease to

exist as anything other than as a transient intermediate and might lead to the elimination of drug-substance release testing. Furthermore, in continuous operations, there is a need to focus on residence-time distributions of process units rather than on batch histories. The committee notes that both recirculation and recycle have traditionally been avoided in API production, given concerns about retaining the identity of a lot as it progresses through unit operations and the potential for the backward propagation of out-of-specification APIs or contaminants.

PROCESS INNOVATIONS THAT CREATE NEW STREAM COMPOSITIONS

New stream compositions arise from upstream operations that incorporate innovations in synthetic chemistry and in host-cell selection and engineering. They also result from the production of completely new types of drug substances and from the introduction of excipients upstream of formulation and filling operations. The new stream compositions might include differences from conventional processing in the distribution of product variants, impurities, and additives; might lead to changes in how individual downstream unit operations perform; and might require wholesale reorganizations of downstream operations.

New Routes to Production of Drug Substances

For small-molecule APIs, innovations in upstream processing are being driven by improvements in synthetic efficiency, the increasing complexity of APIs (such as oligonucleotides, large macrocycles and peptides), the desire to reduce the formation of side products and to use more environmentally friendly synthetic routes, and the need to reduce risks in handling hazardous reagents, solvents, and reactions. New synthetic routes are being based on photochemistry to form new types of bonds, access complex synthetic scaffolds, and control stereoselectivity; electrochemistry to take advantage of high chemoselectivity; and biocatalysis that uses engineered enzymes and single-pot multienzyme reaction cascades (Tom 2020). The latter case will likely extend to biologic APIs for which the engineering of post-translational modifications—such as *N*-glycan structure remodeling or elaboration for enhanced biologic activity—might be performed on partially purified material after cell culture.

For biologics, the drivers for innovation—increased volumetric productivity and simplification of and decreased burden on downstream purification operations—are similar to those for small-molecule APIs. As discussed earlier, cell engineering and bioreactor strategies have led to dramatically increased titers and specific cellular productivities of mAbs. The corresponding increased concentrations, viscosities, and physical-stability concerns will challenge the capacities, operating characteristics, and flow behaviors of traditional downstream unit operations, such as column chromatography. In addition, new cell-culture monitoring and control strategies that are based on spectroscopic probes and reporter species might reveal cell-stress levels during high-concentration cell culture and lead to culture media and feeding enhancements that result in improved product quality by narrowing the distribution of product variants formed.

Further improvements in production of biologics are likely to come from alternative hosts, including new mammalian cell lines (for example, human cell lines) that have shorter doubling times and increased genotypic and phenotypic stability (BPOG 2017b). The use of hosts that have increased stability might reduce the amount of product-related contaminants that are formed during product expression and are difficult to remove, such as glycosylation variants that are formed during mAb production or homodimers and half-molecules that are formed during bispecific antibody production with hosts designed for heterodimer expression. Eliminating those contaminants would help to increase product yields, reduce the number of challenging polishing purification steps that are required in the downstream process, and ultimately reduce important production barriers (NIIMBL 2017).

Advances in production of biologics are also anticipated to come from faster-growing, nonmammalian hosts that offer advantages over their mammalian host-cell counterparts (BPOG 2017b). Among such nonmammalian hosts, yeast is one of the most popular alternatives; multiple companies are

developing this host for protein-drug expression because required upfront investment and cost of production are lower. Although native yeast cells are problematic because they attach nonhuman glycan structures to proteins, engineered yeast-cell lines that can modify secreted protein products with more human-like glycans have been developed. Other nonmammalian expression hosts that have garnered attention include filamentous fungi, insect cells and larvae, microalgae, protozoa, silkworms, transgenic plants, and a plethora of bacterial hosts, such as *Bacillus* and *Lactococcus* genera, *Pseudomonas fluorescens*, and *Ralstonia eutropha*.

That nonmammalian hosts are typically free from contaminating mammalian adventitious virus eliminates the need for dedicated viral clearance operations that accompany mammalian hosts and thereby simplifies downstream processing. For products with post-translational modifications, pathway engineering is expected to provide enhancements to rapidly growing hosts that have limited native post-translational modification capabilities; this has been accomplished recently in yeast. *Escherichia coli*, which has a long history in biomanufacturing, has also been engineered for important post-translational modifications, including disulfide bond formation and glycosylation with human-like glycan structures; the post-translation modifications can be performed on both intracellular proteins and those secreted into the extracellular culture medium. Other innovations in host-cell engineering might be directed at eliminating problematic proteins that tend to co-purify with the target species and at identifying and mitigating inhibitory metabolites. The ready availability of a variety of gene-editing tools, coupled with nonmammalian hosts that have smaller genomes, will make host-cell engineering routine.

Another innovation expected in the production of biologics is the elimination of host cells altogether in favor of cell-free protein synthesis (CFPS) systems. In these systems, cell lysates derived from eukaryotes (such as Chinese hamster ovary [CHO] cells, wheat germ, and yeast) or bacteria (such as *E. coli*) are combined with vector DNA, amino acids, accessory proteins, nucleotides, and molecular energy sources to express recombinant proteins (Rao 2020). In CFPS-based manufacturing, the cell-culture and harvest steps have not been eliminated from the process; rather, they have been placed ahead of the product biosynthesis step to supply and refresh, as needed, the active biosynthetic reagents, which have finite half-lives. Processes that take days or weeks to design, prepare, and execute in vivo can potentially be implemented more rapidly in a cell-free system. In addition, CFPS systems that use *E. coli* can produce grams-of-protein-per-liter reaction volume; can support co-translational or post-translational modifications, such as glycosylation (Oza et al. 2015; Jaroentomeechai et al. 2018); and have reaction scales that have reached 100-L (Zawada et al. 2011). Such systems also offer the potential for less complex, better-defined process streams that are less susceptible to adventitious agents and would dramatically simplify the downstream process. They also offer the potential for producing products that would otherwise be toxic to intact host cells. Finally, CFPS systems can be freeze-dried for long-term storage at ambient temperature (Pardee et al. 2014, 2016a; Salehi et al. 2016) and then reconstituted for on-demand protein synthesis by adding water; this was recently demonstrated for protein subunit vaccines (Pardee et al. 2016b) but could be envisaged for other biologics. CFPS technology has also been adapted for portable expression of therapeutic proteins by using an integrated manufacturing platform that fits inside a suitcase (Adiga et al. 2018, 2020). In that situation, the cell-culture and biosynthetic-reagent harvest steps are operated asynchronously from the rest of the process; the cell lysates become another raw material for biosynthesis of the biologic. Accordingly, CFPS systems will give rise to new supply chains that are ideal for decentralized, cold-chain–independent production of biologics. Given the challenges of larger scale operation of this new, bifurcated approach to upstream processing, CFPS will likely debut with smaller scale production systems, perhaps even portable production systems, in which the target patient population is small, product potency is high, or remote access is required.

New Modalities with New Attributes and New Impurity Profiles

The array of new modalities is poised for rapid expansion. Antibody-related products make up one wave of expansion. An example is next-generation antibody–drug conjugates (ADCs) that are designed for site-specific warhead (cytotoxin) conjugation by incorporating one or more unnatural amino

acids into the amino acid sequence of the mAb portion to enable bioorthogonal click chemistry for warhead attachment (NIIMBL 2017). That approach would necessitate an array of process innovations, including the introduction of a novel host-cell line that can carry out the incorporation during protein synthesis, the use of an unnatural amino acid in the culture media, the conduct of a new bioorthogonal conjugation reaction that uses different solvents to link the modified mAb with the cytotoxin, and the presumed simplification of the later chromatographic or filtration-based conjugate-purification operations. The physical and chemical stability of the new conjugate will also have implications for formulation operations and process safety given the extreme toxicity of the warheads used. Future anticipated modalities that are within the Food and Drug Administration (FDA) Center for Drug Evaluation and Research oversight span oligonucleotides, cell-derived vesicles (such as mammalian exosomes and bacterial outer membrane vesicles), species that are purposely designed to be labile, and high-complexity small molecules. Such new modalities enable exploitation of new therapeutic routes and might rely on multiple catalytic or biocatalytic steps and new purification-unit operations.

Formulation During Downstream Processing

Formulation operations traditionally begin after the generation of an API with a primary aim of stabilizing and preserving its activity. However, it is possible to add excipients before formulation operations to boost API yields and manipulate stream properties during downstream processing. Innovations in this context include the use of stabilizing excipients during the chromatographic purification of recombinant protein-based and nucleic acid-based APIs and the addition of viscosity-reducing excipients to facilitate the downstream processing of high-concentration recombinant-protein streams, such as mAbs.

"Co-processed" small-molecule APIs in which a nonactive excipient, additive, or carrier component is added during the production of a drug substance—typically in particle formation, crystallization, or drying operations—can offer the possibility of improved stability of a desired solid state or tailored API physical properties (Schenck et al. 2020). Co-processing also might enable the tableting of an otherwise unprocessable API. For example, a highly hydrophobic, poorly soluble small-molecule API will typically be easier to dissolve and have much greater bioavailability in an amorphous, precipitated form vs a crystalline form because the crystalline solid is more thermodynamically stable than the corresponding amorphous solid. However, the more desirable, but less stable, amorphous form will be prone to crystalize because of energy inputs and random energetic fluctuations during processing to make the drug substance. To prevent the crystallization, an API in solution might be adsorbed into a porous carrier particle, and the loaded particle suspension dried to form a stabilized amorphous API phase within the pores of the particle. In that case, the API-loaded particles effectively make up the drug substance.

Technical Challenges

New stream compositions might have different distributions of product variants, impurities, and additives from those in conventional processing and might require changes in or wholesale reorganization of downstream unit operations. For novel synthetic approaches to small-molecule APIs, new reagents, reactor types, PAT, and operating and control strategies will likely be required, and these changes will have important implications for manufacturing processes. Similarly, novel cellular hosts used in the production of biologics might require novel growth media, feeding strategies, and monitoring and control strategies. For both novel cellular hosts and cell-free synthesis platforms, the achievable scale of production and nonhuman glycosylation are substantial impediments. Also challenging for the development of innovative expression systems based on living cells or cell-free extracts are the various impurities—for example, intracellular and secreted biomolecules, such as proteins, nucleic acids, and lipids or glycolipids—that each system introduces. The impurities are different from those arising during conventional CHO-based manufacturing and thus will need to be carefully characterized at all scales of

production and will require appropriate analytic tools for off-line and in-line monitoring. In addition, depending on the nature and quantities of the impurities, alternative hosts and expression systems will likely require customized downstream processing steps to ensure efficient removal of any system-specific contaminants. As discussed above, a variety of process innovations will likely be required for producing novel modalities, such as antibody–drug conjugates, and the stability of the new conjugate will also have implications for formulation operations and for process safety. Finally, for co-processed APIs, the unit operations required for production are more closely aligned with the equipment or capabilities of solvent-based processing operations found in a drug-substance manufacturing facility. And these operations are not compatible with most drug-product manufacturing facilities.

Regulatory Challenges

Production of APIs by using new synthetic routes or new host cells creates uncertainties in the type and distribution of contaminants and raises questions about the appropriate or tolerable levels of contaminants in setting product specifications. The same uncertainties and questions will arise with the production on new modalities.

An important regulatory issue arises in the case of co-processed APIs. If a co-processed API is defined as a drug substance, key quality attributes and the impurity profile would be determined for the co-processed API, and the stability dating period that is established for the drug product would be independent of the time of production of the co-processed API. However, defining the co-processed API as a drug-product intermediate would require that the stability date be set at the point of manufacture of the co-processed API rather than when the co-processed API is converted to a drug product. The effect of that difference in the start of stability date could lead to the drug product entering the supply chain with an earlier expiration date and thus could create a risk to supply. In addition, if no drug substance is isolated, the drug-substance stability testing expected under ICH Q1A(R2) (FDA 2003) is not possible; this will necessitate an uncertain importation of the associated stability-testing requirements into the drug-product testing regimen.

OVERCOMING REGULATORY CHALLENGES

Perhaps the main challenge associated with innovation in the manufacture of a drug substance, and with innovation more generally, is the lack of familiarity on the part of process-development scientists and engineers and on the part of regulators. The antidote to lack of familiarity is experience. In some cases, the experience might already be in house as in the adoption of techniques traditionally associated with plasma fractionation for the purification of biologic APIs that are under the purview of the FDA Center for Biologics Evaluation and Research. In the absence of in-house expertise, FDA active participation in public-private partnerships, such as NIIMBL, to alleviate risk associated with precompetitive innovation spaces might have great utility. The committee notes that the formation of consortia requires the acknowledgment by industry that the key intellectual property is vested in APIs rather than in the manufacturing process.

As noted in Chapter 1, FDA has provided a vehicle for providing preliminary feedback on technologic innovations with the establishment of the Emerging Technology Team (ETT); the effectiveness of the ETT in increasing the pace of innovation throughout the pharmaceutical industry would be enhanced by its working with consortia vs one-off interactions with individual manufacturers. Furthermore, periodic rotation of FDA reviewers and inspectors through assignments within the ETT might empower a broader cadre of regulators to be better informed and deal efficiently with innovations in drug-substance manufacture. The compilation and availability of case studies of successful introductions of innovations and even of common themes and characteristics of unsuccessful introductions would also be an extremely useful resource if confidentiality limitations can be overcome. Finally, FDA might consider providing some extramural research funding to consortia (such as NIIMBL and the Advanced Mammalian Biomanufacturing Innovation Center), other relevant Manufacturing USA

institutes (including America Makes, the Smart Manufacturing Institute and the Rapid Advancement in Process Intensification Deployment Institute), or independent, FDA-sponsored pharmaceutical-manufacturing innovation centers specifically targeted to help drive research and development efforts to alleviate risks associated with new technologies. FDA does offer extramural funding through the Broad Agency Announcement process; this mechanism could be used to advance manufacturing innovation further with additional support. Any new targeted funding initiatives would likely require new resources, which might be provided through consortium agreements or included as part of a new Prescription Drug User Fee Amendment agreement.

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3

Innovations in Manufacturing Drug Products

As noted in Chapter 2, production of the nation's drug supply involves manufacture of the drug substances—the active pharmaceutical ingredients (APIs)—and ultimately of the drug products that are delivered to patients. In this chapter, the committee focuses on the manufacture of drug products. The discussion is organized into three major sections. The first describes innovations in the manufacture of conventional drug products, the second highlights innovations in drug-product forms, and the third focuses on novel excipients that enable new drug-product formulations. In addition to highlighting the emerging technologies, the committee describes technical and regulatory challenges associated with the drug-product technologies and provides recommendations for overcoming the regulatory challenges.

INNOVATIONS IN MANUFACTURING APPROACHES FOR CONVENTIONAL DRUG PRODUCTS

The concept of continuous improvement is a philosophy of most pharmaceutical manufacturers as they strive to increase supply, gain efficiencies, and decrease costs. Innovations in the unit operations that make up the last few steps in the processing of conventional drug products are often the key to making such improvements. Such innovations are classified into three categories—additive manufacturing, lyophilization, and aseptic processing—and are described in the following sections.

Additive Manufacturing

Additive manufacturing (AM), or product formation by using 3-dimensional (3-D) printing, has been an innovation that has swept through the manufacturing sector. Indeed, one of the national manufacturing institutes launched under the Obama administration, America Makes, focuses on AM and has drawn much attention to and useful application of this technology. One of the challenges or opportunities of AM is that it takes many forms, which can be classified in various ways. For example, ASTM International has proposed categorizing AM into vat photopolymerization, material jetting, binder jetting, material extrusion, powder-bed fusion, sheet lamination, and directed energy deposition (ASTM 2012). Although there have been numerous explorations of the use of virtually all those forms for pharmaceutical-dose production at the research and development stage, only a few are sufficiently advanced to be commercially viable within 5–10 years (Jamroz et al. 2018). The three broad categories of AM forms that are most promising are powder solidification, liquid solidification, and extrusion-based systems.

The *powder solidification* route has been used to produce one approved product (NASEM 2020). In that system, a binder fluid is jetted onto a thin bed of powder blend, which includes the API, in a specific pattern that forms the tablet cross-section. That action causes the affected particles to bind, the powder left unbound is removed, and the process is repeated with multiple successive layers of powder blend until the tablet of desired size is attained. The tablet is then dried to remove the binder fluid. Further advances in this process have been announced; the powder blend is now deposited in successive thin layers in a well or blister, thus reducing the reprocessing of unbound powder but increasing the demands on good powder flow.

The *liquid solidification* route is exemplified by a technology in which a solution that contains the API is printed onto an excipient tablet and the solution dried to create the dosage form (Clarke et al. 2017). The manufacturing technology has been implemented at scale, but no product that uses it has yet been approved. Research success in the use of alternative fluid formulations—including polymer melts and suspensions of API powders (Içten et al. 2017; Radcliffe et al. 2019)—have been reported. In all cases, a solid is produced by drying to remove the solvent or by cooling to solidify the fluid formulation and thus form a stable dosage form. However, no products that use the liquid solidification route have been approved.

Extrusion-based methods, specifically those using drug-polymer filaments (Awad et al 2018), are among the most frequently reported AM methods. They can take advantage of a wide array of commercially available 3-D printing devices that can process thermoplastic polymeric filaments. To produce a dosage form, a filament that consists of a suitable polymer—a drug mixture that has the desired API composition and appropriate mechanical or rheologic properties—must be prepared. That approach requires some form of hot-melt extrusion as a preparatory step.

The common advantages of AM forms are that they are inherently continuous, allow virtually 100% monitoring of dosage forms produced, and allow rejection of faulty product at the level of an individual dose rather than a batch. Furthermore, production equipment can be scaled down to a compact size (close to bench-top size), thus enabling distributed manufacturing. With simple adjustment of the number of powder layers, the number of drops, or the amount of filament deposited, AM forms lend themselves to tailoring the dosage to the patient. AM also readily accommodates alternative 3-D shapes and thus tablet designs. The additive mode also allows introduction of multiple feed materials and thus facilitates the production of combination products and various controlled-release dosage designs.

Technical Challenges

Common technical challenges are achieving production rates that are competitive with traditional tableting or capsule-filling lines and instituting process control that is based on process analytic technology (PAT) of critical product attributes. Process control is typically restricted to control of the material deposition step rather than of critical product attributes. Another important challenge is the physics-based modeling to support development of operating regimens for classes of AM methods or design spaces for specific AM applications. Predictive modeling has advanced; for example, there are finite-element computational fluid mechanics models of drop formation (Basaran et al. 2013) and multi-physics models of extrusion deposition (Brenken et al. 2019). However, aspects that still need to be addressed include treatment of more complex formulations, such as suspensions; capture of effects of non-Newtonian fluid properties; and prediction of drop penetration into powder beds that are composed of heterogeneous blends. Beyond those common challenges, each AM form is subject to its own characteristic technical challenges, some of which are listed below.

- *Powder solidification*. Challenges include limitations of mechanical properties, such as porosity of the tablets produced; ensuring blend uniformity; recycling of powder blend that is left unbound; interaction between properties of the binder fluid and of the powder blend; and flowability of the powder blend.
- *Liquid solidification.* Challenges include the effect of a liquid's flow characteristics on the complexity and reproducibility of the drop formation process and control of the API crystal form during the solidification process.
- *Extrusion-based methods.* Challenges include production of filaments that have suitable mechanical properties, exposure of the API to two heating steps, control of the API crystal form during solidification process, and the limited number of polymer excipients that have been approved for human consumption.

Regulatory Challenges

A common regulatory challenge arises in the approval process for the technology: an integrated AM system is not approved as a technology independent of site but at each individual implementation site. In the application of AM to produce dosages that are individualized to meet the needs of specific patients, the question arises of whether the production should be treated as manufacturing or as compounding. Given the commonality of the AM methods in their exploitation of fluid-processing steps to form individual doses, it would be desirable to have comprehensive guidelines that cover the entire family of AM methods despite the variability in implementation details. Given the direct links among 3D representation, printing execution, and processing conditions, the guidelines should cover software and hardware requirements, drug-substance stability considerations during and after processing, and product-quality monitoring and control. The guidance on additive manufactured medical devices (FDA 2018) could serve as a starting point for AM guidance.

Lyophilization

Although AM innovations focus largely on solid oral dosage products of small-molecule APIs, the vast majority of large-molecule–based therapies are administered through injection or infusion. In recent years, nearly half the newly approved injectable or infusible products have required lyophilization to ensure product stability (Alexeenko and Topp 2020). As currently practiced, lyophilization is a highly inefficient batch process in which solvent is removed from a liquid formulation via sublimation of solvent, normally water, at low temperature and pressure. Given the limited global lyophilization capacity and the increasing number of products that require lyophilization, there is a substantial incentive to create and deploy new technology. In late 2017, the LyoHUB consortium issued a technology roadmap that addresses gaps in product design methods, process technology, and process equipment.[1] The manufacturing innovations that have been introduced in recent years to address those gaps consist of improvements in traditional batch-mode operations, continuous lyophilization that uses serial processing of vials, and continuous bulk lyophilization.

The most immediately implementable innovations of lyophilization are improvements in open-loop batch operations and include the development of sensors and PAT methods for monitoring product attributes, development of predictive first-principles models of heat- and mass-transfer processes, and implementation of model-based process control. Among PAT methods of particular importance for product quality are nondestructive measurements of residual moisture content that use spectroscopic methods that can be implemented on multiple scales. Important operational strategy modifications are approaches to controlled (primary) ice nucleation. Currently, primary nucleation takes place in uncontrolled fashion as a natural stochastic process that results in longer processing times and poor porosity of the dried product. Rapid depressurization is one approach for achieving such nucleation that appears to be most readily implemented. Although the improvements do not change the batch character of the lyophilization operation, they nonetheless require substantial modifications of equipment and changes in manufacturing culture and workforce skills.

Continuous lyophilization methods include conversion from the traditional tray-style batch lyophilizer designs to continuous systems in which vials are processed sequentially through nucleation and drying stages and that include enhancements, such as spinning of vials, to increase surface area for heat and mass transfer (De Meyer et al. 2015; Capozi et al. 2019). Additional improvements include acceleration of the freeze-drying process by using electromagnetic radiation from infrared heaters or by using radiofrequency dielectric heating.

Another innovation in this field is freeze drying in bulk by using such technologies as spray freeze-drying. The spray process provides a larger surface area for sublimation and allows faster heat transfer by forced convection or radiant heating. An alternative route involves the use of multiple

[1] See https://pharmahub.org/groups/lyo/lyohub_roadmapping.

successive mechanically agitated stirred vessels, each operating a specific freeze-drying phase (Touzet et al. 2018) Continuous operation enables complete containment and can produce aseptic dried particles that can then be filled into vials under aseptic conditions once the desired residual moisture content and particle-size distribution are achieved.

Application of microwave energy under vacuum conditions can also achieve rapid dehydration of a frozen product. In this process, energy transfer occurs by microwave radiation into the entire frozen mass rather than just by heat transfer from the bottom of the vial. To achieve uniform heat transfer, a configuration with multiple magnetrons is used. Microwave drying allows freeze-drying cycle times to be reduced from several days to several hours. This technology offers the considerable advantages of lower energy, capital cost, and intra-batch variability compared with conventional lyophilization. Moreover, the smaller footprint and lower cost of this drying mode could allow scale up from development to manufacturing simply by addition of parallel units.

Technical Challenges

The technical challenges of *improving batch operations* lie first in process instrumentation, especially the lack of robust and affordable in-line spectroscopic techniques for measuring product residual moisture content and vapor flow rate and distributed sensors for wireless measurement of temperature. There are also challenges in the development of dynamic models of sufficient fidelity that can quantify the effect of process variations. The most important technical challenge related to process control is to achieve ice nucleation that has consistent ice crystal structure and uniform drying rates.

The key challenge for *continuous lyophilization* is to increase heat- and mass-transfer rates so as to reduce the required residence time and thus required equipment volume for the sequential stages of primary and secondary drying. Real-time image processing of vials during and at the end of processing for quality control that is of sufficiently high resolution is important for uniformity in process monitoring. The mechanical complexity of vial handling for spinning and the effect of infrared and microware heating on product degradation also pose technical challenges.

The critical technical challenge related to *spray freeze-drying* is to provide enough residence time to achieve the desired reduction in moisture while avoiding particle agglomeration. Particle-size distribution needs to be controlled to achieve good powder flow for efficient vial filling.

Regulatory Challenges

The regulatory challenges associated with PAT, process modeling, and closed-loop control of batch operation in these technologies do not appear to be much different from those associated with their implementation in other pharmaceutical manufacturing contexts, as discussed in Chapter 4 of this report. One regulatory challenge is to find a pathway for approving a new processing technology as a platform independent of a particular product filing. Another challenge is that improving a lyophilization technology that is being used to produce an approved product—for example, with microwave vacuum drying—requires filing a major supplement or variation, including extensive product characterization data, in every country in which it is approved.

Aseptic Manufacturing

Whether or not a product is lyophilized, it needs to remain free from microbial contamination during filling of vials, syringes, or cartridges. Contamination during processing occurs from surfaces and airborne sources. Given that people are one of the primary sources of contamination, the key innovation is to eliminate the operator from the process by using fully automated processes enclosed in an isolation chamber. Accordingly, the innovative technology is a gloveless, robotic aseptic filling work cell that uses single-use disposable components. The integrated filling operation is carried out in an isolator unit in which handling is accomplished by using robotics. The isolator unit can be effectively decontaminated,

and an important source of integrity failure can be eliminated by removing the gauntlet gloves. Robust automation also enables efficient production of small batches.

Technical Challenges

The key technical challenges lie in continuous environmental monitoring to ensure aseptic conditions and in the design of robust automation technology. Robotics adds the complexity of software development, validation, and maintenance and the requirements for condition-based monitoring and maintenance. The inflexibility of robotic technology to increase volume or batch size (larger numbers of vials, syringes, or cartridges) to meet commercial demands likewise presents an implementation challenge.

Regulatory Challenges

The main regulatory challenges are associated with the extensive effort required for the initial and continuous validation process, including the established mandate of an aseptic process simulation for every combination of container, closure, fill volume, and batch size. Another regulatory barrier is the requirement for extensive environmental monitoring even though the operator is no longer part of the filling process. The degree of monitoring should be based on an assessment of the expected contamination risks.

ENABLING NEW FORMS OF DRUG PRODUCTS

As innovations in drug-product forms or compositions are being developed, the hope is that the new modalities provide increased absorption, convenience, compliance, and efficacy. Manufacturing efficiencies are also expected as new processes are developed. The drug-product innovations will most likely be common in the next 5–10 years as manufacturing processes for the new forms are refined. The three forms presented in this section—the microparticle, nanoparticle, and extracellular vesicles—are still relatively new areas of drug-product development. Such complex formulations are often referred to as "products by process" because they have quality attributes that are determined largely by their manufacturing process. The technologic and regulatory challenges that are associated with these products are described at the end of this section.

Microparticles

Microparticles are small, free-flowing entities that have particle diameters of 1–1,000 μm. They hold great promise as drug-delivery systems because of their ability to encapsulate water-insoluble and sparingly water-soluble agents with the potential to deliver an active agent in the right amount, at the right time, and to a desired location in the body in a manner that minimizes side effects. Microparticle drug-delivery systems come in many varieties, including micropellets, microgranules, microspheres, microcapsules, microsponges, and liposomal preparations. Their benefits stem from the unique and often tunable microparticle properties, including size, shape, structure, drug loading, entrapment efficiency, porosity, and release profile. Regarding size, microparticles are advantageous because they do not traverse into the interstitium and thus can act locally with prolonged effects. From a drug-loading perspective, microparticles can shield an API from environmental conditions (such as temperature, pH, oxidation, and proteolytic degradation) and can protect the body from harmful side effects of the API (such as irritation, mucosal damage, and cell toxicity). From a formulation standpoint, microparticles can be incorporated into various pharmaceutical dosage forms, such as liquids (solutions, suspensions, and parenterals), semisolids (gels, creams, and pastes), and solids (capsules, tablets, and sachets).

The mechanism of drug release from microparticles (dissolution or diffusion, osmotically driven release, and erosion) is an important design criterion and is often the direct result of innovative

manufacturing technologies or novel excipients. The most commonly used excipients in microparticle delivery systems are biopolymers of plant, animal, or microbial origin (Lengyel et al. 2019), although semisynthetic and synthetic polymers (biodegradable or nonbiodegradable) are also gaining attention (see section below on novel excipients). Production processes used to generate microparticle delivery systems include spray-drying, extrusion, coacervation, freeze-drying, emulsification, precipitation, crystallization, and microfluidics and possibly the innovative approaches discussed in the sections above. For example, novel microfluidic systems have proved advantageous for microparticle production, and various methods for engineering microparticles are emerging, such as continuous-flow–based and electrowetting-based droplet generators (Damiati et al. 2018). Another emerging approach inspired by the semiconductor industry involves continuous-flow lithography, in which a monomer solution of a photopolymerizable material (such as polyethylene-glycol-diacrylate) is pumped through a microfluidic device in the presence of light.

A promising example of a microscale bead product is development of the lyosphere. Beads formed from a liquid formulation of API and excipients are manufactured in an innovative process whose first step involves rapid freezing of drops of the formulation as they are deposited from an automated nozzle onto an ultracold metal plate (Kapoor et al. 2020). The individual frozen beads are then transferred to a freeze dryer in which they undergo the conventional multistage freeze-drying process in bulk. The key difference from conventional lyophilized material is that the result is a bead rather than a dried powder. The lyospheres produced must be analyzed for potency and titrated into the final drug-product vial to obtain the target dose (Barr et al. 2019). The possibilities of bulk dry bead storage and the ability to change the amount of lyospheres per vial provide supply chain flexibility and the flexibility to use new drug-product presentations and device opportunities. The technology has the potential to improve the thermal stability profiles of products, and it is envisioned that custom medicines could be made by using this technology.

Nanoparticles

Nanoparticles are microscopic particles less than 100 nm in diameter and include liposomes, polymers, nanocrystals, proteins, and other nanoscale molecules with applications in oncology, neurology, immunology, anti-infective materials, and cardiovascular therapeutics. Nanotechnology has opened the door to the development of nanopharmaceuticals. The new formulations are intended to overcome problems related to drug solubility or pharmacokinetics and pharmacodynamics profiles, improve the drug-release profile, or reduce toxicity or adverse side effects. The biodistribution and blood-circulation half-life of nanoparticles also can be adjusted depending on the route of administration (Alexis et al. 2008).

In nanopharmaceutical formulations, the selected drug type is encapsulated in a polymer, lipid, protein, or metal matrix. Once the matrix is determined, scale-up and quality assurance of the selected production methods are studied for commercial production. A clear understanding of clinically compliant production methods is an important regulatory concern. Many emerging nanopharmaceuticals have been proposed to improve the therapeutic outcome of the use of multiple drugs and biomolecules and to tackle unmet medical needs. However, because of the difficulties that are typically encountered in process scale-up to meet product quantity and quality requirements for clinical trials, few nanopharmaceuticals are on the market. Production at scale is a serious challenge (Souto et al. 2020a).

Various innovative production methods are used depending on the nanoparticle types. High-pressure homogenization, membrane contractor, microemulsion, multiple emulsion, and solvent emulsification diffusion are a few methods used for lipid nanoparticles. Extrusion, ionic gelation, nanoprecipitation, salting-out, and the use of supercritical fluid are a few production methods for polymer nanoparticles. Chemical and physical methods are used to produce metal nanoparticles.

One innovative technology that has enabled new ways to manufacture nanoscale drug products is microfluidics. It is extremely useful for controlled synthesis of drug-loaded nanoparticles because it provides precise fluidic modulation and enhanced mixing, is low cost, and is readily designable. A major

benefit of the enhanced mixing process involved in microfluidics is that it occurs much faster than the nucleation process of nanoparticles; this allows for production of large quantities of nanoparticles with a narrow size distribution. Research has revealed that slight alterations of the mixing strategy, microfluidic device assembly, and post-synthesis surfaces can influence the functionality and biologic effects of microfluidics-assembled nanoparticles. The functionalities and biologic effects tend to improve with the use of microfluidic devices, compared with nanoparticles produced by bulk methods (Feng et al. 2016).

Nanoparticles synthesized with biodegradable polymers are most preferred for drug-delivery systems, and lipid-shell polymer core hybrid nanoparticles are the most extensively studied nanodelivery systems. Often compared with liposomes because of their solid core structure, lipid-shell polymer nanoparticles offer biocompatibility, the ability to encapsulate different types of drugs, and high loading efficiency (Allen and Cullis 2004; Jiang et al. 2010). They can be prepared in a high-throughput manner by using microfluidic principles. The confined impingement jet mixer is a type of microfluidic device that prepares nanoparticles via flash nanoprecipitation (Johnson and Prud'homme 2003). During flash nanoprecipitation, a hydrophobic drug and an amphiphilic block copolymer (such as polyethylene glycol-*b*-polylactic acid) are co-dissolved in an organic solvent (such as tetrahydrofuran) and turbulently mixed with water through high-velocity impingement. The supersaturation of the drug–copolymer mix with the antisolvent water stimulates co-precipitation of nanoparticles within milliseconds (Han et al. 2012). Further enhancements of the microjet reactor have been made over the years, such as equipping it with a confined impinging jet, which has recently allowed innovative ciprofloxacin-loaded poly(DL-lactide-co-glycolide) nanoparticles to be produced. Nanoparticles fabricated with that method were shown to have a greater therapeutic effect with continuous and localized slow release of a highly concentrated antibiotic (Günday et al. 2020).

Overall, nanotechnology-based drug products hold tremendous promise because of their favorable size, shape, structure, and surface properties. However, maintaining their quality, safety, and efficacy over the course of the scale-up process poses a substantial challenge. Because these drug products are still relatively new and their manufacturing processes are emerging, a Quality by Design approach to gathering deep product and process understanding is needed.

Extracellular Vesicles

The release of extracellular vesicles (EVs) is a conserved cellular process that occurs in Archaea, Bacteria, and Eukarya. EVs deliver various molecular cargoes through fusion or endocytosis and modify the recipient cells' physiology. Because they are small, they can be passively delivered anywhere in the body, and their status as natural cellular products means that they are likely to cause relatively few undesirable immune reactions. Their composition and origin determine their intrinsic targeting properties, and they can cross biologic barriers and deliver their cargoes to recipient cells with virus-like efficiency; this makes them highly attractive as drug-delivery vehicles (Johnsen et al. 2014).

EVs are differentiated on the basis of their intracellular origins. One major type, microvesicles (MVs), is formed through the outward budding and fission from plasma membranes and range in size from 50 to 1,000 nm, depending on the producing cell. MVs are also referred to as microparticles, shedding vesicles, plasma membrane-derived vesicles, ectosomes, and exovesicles; however, to avoid confusion and promote standardization of nomenclature the term *microvesicle* has gained favor. From a drug-development standpoint, MVs derived from the outer membranes of bacteria—known as outer-membrane vesicles (OMVs)—have garnered substantial attention as vaccines and have attained U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval of the meningococcal group B (MenB) vaccine Bexsero, which contains 25 μg of OMVs derived from the bacterium *Neisseria meningitidis* serogroup B. Although bacterial OMVs are not as advanced for delivering drugs, several companies and many academic researchers are exploring their use as an innovative way to deliver small-molecule and large-molecule drugs.

The other major category of EVs is exosomes, which differ from MVs mainly in size and intracellular origin. Exosomes are 50–150 nm in diameter, are secreted by all mammalian cells except

mature red blood cells, and are involved in diverse physiologic and pathologic functions in the body. In contrast with MVs, exosomes are formed in the cytosol by tightly controlled inward budding into large multivesicular bodies that can then fuse with the plasma membrane and release exosomes into the extracellular space. Perhaps most relevant to drug development is the fact that exosomes can serve as vehicles to transfer membrane and cytosolic proteins, lipids, and RNA between cells and thus provide an important mode of intercellular communication. Because of their innate ability to transfer RNA (such as mRNA and miRNA) and proteins to recipient cells, exosomes have been exploited as novel drug-delivery agents for targeted treatment of various diseases.

Exosomes can be easily harvested from various cell types, and current research is focused on determining the optimal host cells from which to derive exosomes and on engineering them to host the desired therapeutic agent (Bunggulawa et al. 2018). To investigate functional characteristics of various exosomes, researchers have isolated exosomes from macrophages, metastatic cancer cells, pancreatic cancer cells, and tumor-derived cells. It is worth noting that exosomes and MVs, although distinguishable by their origin, are rarely distinguishable in practice, and this might pose characterization challenges when it comes to manufacturing these entities.

Research has shown that different types of exosomes can stimulate immune systems differently, have different safety profiles, and have a host of other different biochemical properties, such as degradation. Ultimately, the exosome type is chosen on the basis of the desired therapy and which API needs to be delivered. As noted, exosomes can be loaded with a variety of therapeutic agents to achieve a desired functionality on delivery to a patient. An API can be loaded into exosomes by a few methods, including incubation, freeze–thaw cycling, and electroporation. Each method has advantages and disadvantages with respect to safety and loading efficiency and needs to be selected for each specific application. Exosomes will help to usher in a new generation of drug delivery as research efforts in large-scale manufacturing continue.

Technical Challenges

The major challenges in producing the new particulate product forms at scale are to develop reproducible manufacturing processes and characterization methods, to ensure in vivo stability, and to manage the biophysical and chemical properties of their formulations. Advances in in-line sensors for critical quality attributes, process automation, and innovations in the engineering design of the microfluidic systems themselves are needed to speed the advancement of these pharmaceutical drug products (Agrahari and Agrahari 2018). The slow pace of traditional empirical development methods for these products also needs to be increased by using process models and integrating first principles with data-driven components where gaps in fundamental knowledge remain.

Regulatory Challenges

Major regulatory challenges include guaranteeing drug safety, efficacy, and stability during scale-up; increasing familiarity with new unit operations; and ensuring adherence to current good manufacturing practices (Leaver 2017). No defined specifications or guidelines have been published to assist drug developers in understanding what justification is required to ensure that the new unit operations provide safe and efficacious new drug forms. In addition, the critical quality attributes for these new types of drug products are not well understood, and this makes it difficult to set product specifications and design process-control strategies.

ENABLING NEW DRUG-PRODUCT FORMULATIONS: NOVEL EXCIPIENTS

The U.S. Pharmacopeia Convention (USP) defines excipients as “substances other than the active pharmaceutical ingredient…that are intentionally included in an approved drug delivery system or a finished drug product” (USP 2016). They are typically added during formulation operations after the

production of a drug substance and can often account for up to 90% of the mass of the resulting drug product. They are used to perform diverse functions, such as facilitating or enabling the production of the drug-delivery system; protecting the drug against degradation during processing, storage, or delivery; increasing the effectiveness of the drug by increasing its solubility or bioavailability; providing a means for product identification; and improving the safety, acceptability, and abuse deterrence of the drug. Unlike APIs, excipients can have complex compositions—for example, heterogeneous mixtures of related compounds, such as polysorbates—and might not have been designed or manufactured specifically for use in pharmaceuticals, such as compounds that were originally created for food and cosmetic applications.

The selection of excipients for a given drug substance depends heavily on precedent. FDA maintains a list of excipients that have been used in approved drugs, the Inactive Ingredients Database (IID),[2] that is updated quarterly. A manufacturer can make a regulatory filing for a drug product that includes one or more excipients without having to demonstrate excipient safety as long as the excipients appear in the IID and are used in amounts no greater than the listed amounts per dose for the given route of delivery. By using IID-listed excipients, manufacturers reduce the time, cost, and risk associated with regulatory filings. Manufacturers have become adept at side-stepping the introduction of new excipients by creatively using combinations of listed excipients to address formulation challenges posed by new molecular entities. For example, the number of excipients used in approved monoclonal antibody (mAb) drugs ranges from one to 13, with an average of four, including buffer species, salts, sugars and surfactants (Seymour 2020).

A manufacturer, however, might prefer to use a new excipient to solve a specific drug-product production or formulation problem that is not well addressed by IID-listed excipients.[3] The introduction of a novel excipient is a manufacturing innovation that changes stream composition and molecular-level interactions with an API compared with conventional formulations and that might be accompanied by or necessitate further innovation in manufacturing unit operations, PAT, or process control strategy. It is currently expected that new excipients would be introduced at the investigational new drug (IND) stage with safety data on each new excipient that is used with a new molecular entity. Reasons for the use of a new excipient include newly understood limitations of members of a given class of IID-listed excipients, the increased complexity of new drugs and dosage forms, and the needs of new types of manufacturing unit operations (IPQ 2020).

Our understanding of the stability and metabolism of commonly used excipients has revealed limitations within the IID. For example, polysorbate 80 is a common surfactant used in high-concentration mAb formulations. It has been shown that trace amounts of esterase enzyme impurities in an mAb drug substance can catalyze the degradation of the surfactant, including reduction of its interfacial activity (Larson et al. 2020). New, alternative surfactants have been developed by several excipient manufacturers to address the limitations of IID-listed hydrolyzable surfactants (Soane et al. 2018; Katz et al. 2019). Other limitations of current excipients include unsuitability for use in pediatric patients because of metabolic pathways that differ from adult pathways and poor performance of enteric coatings for protection of biologics.

The increasing complexity of new molecular entities is also driving the need for enabling excipients. For small-molecule drugs, the conventional rule of thumb that API molecular mass should be kept below 500 Da (Lipinski et al. 1997), and even the whole notion of a "small-molecule drug" is steadily challenged by the pursuit of large macrocyclic and oligonucleotide targets with molecular masses that can exceed 9 kDa (Selwood 2017; Tom 2020). Such high-molecular-weight, high-complexity small-

[2] See https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download.

[3] FDA defines new excipients as "any inactive ingredients that are intentionally added to therapeutic and diagnostic products, but that: (1) we believe are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery (e.g., enhance absorption or control release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration" (FDA 2005).

molecule drugs can pose substantial concerns regarding solubility, chemical stability, or physical stability that must be addressed with excipients. For example, solubility issues might be overcome with novel lipid-based excipients, polymeric amorphous stabilizers, or macrocycles that are capable of forming host–guest complexes (Havel 2018; Selwood 2017). Oligonucleotides have multiple tissue barriers, cellular targeting and uptake issues, and intracellular trafficking hurdles that a formulation must overcome, driving innovations in both excipients and drug-product forms, as described above (Juliano 2016). As discussed in Chapter 2, antibody–drug conjugates (ADCs) represent the juncture of the small-molecule and biologic drug formulation worlds and creation of an extremely high-potency class of drug species. Premature scission of the conjugate is a serious delivery concern, given the lethality of the "warhead" component of the ADC. There is a strong driver for moving beyond the repertoire of excipients currently used to stabilize mAb therapeutics to new excipients that can chemically and physically stabilize these purposely labile conjugates until they reach the targeted site, and stabilizing these new modalities might provide additional, less-invasive routes of delivery beyond the current intravenous-infusion route (Alves 2019).

New dosage forms and corresponding new routes of delivery, motivated by the desire to reduce invasiveness or to localize treatments, are also driving the development of enabling excipients. As mAb routes of administration migrate from intravenous infusion to subcutaneous and intramuscular injection to reduce patient risks and simplify administration, the mAb concentration is increased (100 mg/mL or greater) to accommodate the necessary mass dosages in a much smaller administration volume. The increased concentration results in increased formulation viscosities that can make injection difficult or impossible. New excipients, such as hydrophobic salts, have been identified that can dramatically reduce high-concentration mAb formulation viscosity (Ke et al. 2018). Other alternatives for delivery of biologics—such as oral, transdermal, nasal, and pulmonary routes—are in various stages of active preclinical development with new small-molecule, polymeric, and peptidic excipients to serve as enteric coatings, permeability enhancers, mucoadhesives, enzyme inhibitors, transport enhancers, cell penetrators, and tight-junction modulators (Anselmo et al. 2019). Beyond the route-based needs, new excipients might be required for the development of implantable delivery devices and drug-delivery device combinations (IPQ 2020).

Finally, the use of new types of equipment in the manufacture of drug products, such as hot-melt extruders (HMEs) and twin-screw granulators, presents opportunities and needs for new excipients. In an HME, an API with poor solubility or bioavailability is dispersed in an amorphous or crystalline solid state into a polymer melt and extruded in a water-free or solvent-free process to produce a solid that can be milled or pelletized to form tablets, capsules, and sustained drug-delivery depots. Beyond the high concentration of polymeric excipient used in HMEs, which itself might lead to the "new excipient" classification, new plasticizing excipients might be needed to manipulate the solid-phase solubility of the API in the polymer, and new solubilizers might be needed to manage the crystallization of amorphous API solids on release in the digestive tract (Simões et al. 2019). Twin-screw wet granulation is gaining traction as a continuous unit operation that allows wetting and nucleation phenomena to be controlled separately from consolidation and growth phenomena (El Hagrasy et al. 2013) and provides narrow material residence-time distributions (Shirazian et al. 2018). The method provides access to a wide array of particle structures with narrow property distributions. The key excipients in the granulation-step case are fillers to add bulk and binders to provide structural integrity to the consolidated solids; these excipients are augmented with powder flowability, lubrication, and disintegration agents during later tableting operations (Willecke et al. 2018). There are opportunities for new lower-viscosity binder liquids and fillers that have lower compressibility. New, continuous manufacturing formats might also provide opportunities for new excipients.

Technical Challenges

Regardless of the driver for the introduction of novel excipients by a manufacturer, the result is a new stream composition that persists through the formulation and filling operations. The safety and

efficacy of a novel excipient that is truly distinct from IID excipients will always need to be demonstrated, regardless of current or future regulatory pathways. Possible interactions between the novel excipients and the trace components in the drug-substance stream, which might fluctuate in type and amount, might directly affect the drug-product manufacturing process. For example, novel excipients might be subject to attack by unidentified trace host enzymes and lead to loss in drug-product stability or performance, or degradation byproducts might lead to the formation of aggregates or haze. Thus, an enabling novel excipient might require host-cell engineering or downstream process modifications. Incorporation of novel excipients also might require changes in the unit operations used in formulation and filling. When used in high proportions relative to the API, such as polymeric excipients used in HMEs, novel excipients might present substantial blending and drug-product uniformity challenges that require novel blending equipment. Finally, novel drug-product stream compositions might require novel sensors and control strategies for process monitoring and control during formulation and filling operations.

Regulatory Challenges

The main regulatory challenge associated with the introduction of new excipients is that they are approved with the new molecular entity; there is no mechanism for approval of new excipients in isolation. Manufacturers must assume the combined time, costs, and risks associated with demonstration of the safety of a new excipient and pharmacologic effects in addition to the demonstration of the safety and effectiveness of the drug product (FDA 2005). That challenge has long been recognized by industry and is the subject of a recent USP survey (see Box 3-1). It is clear that manufacturers might forgo the use of a novel excipient even when there are potential public health benefits. Several promising novel excipients have had no market uptake because of real and perceived regulatory barriers, and there are examples of formulations marketed elsewhere but not available for use in the United States because of novel excipient status (IPQ 2020). The challenges associated with the introduction of a new excipient in a drug product are mirrored to some extent by the challenges posed in introducing new biomaterials in medical devices.

BOX 3-1 USP Survey on Excipients

A recent USP survey of the use of novel excipients among 264 respondents who represented drug and excipient manufacturers revealed important findings:

- 55% expected to use novel excipients in the U.S. market within the next 5 years, assuming status quo in the regulatory landscape.
- 84% indicated that current excipients limited drug development mainly because of a lack of use in a selected dosage form, inability to stabilize a drug product, inability to overcome bioavailability problems, or inability to overcome solubility or permeability issues.
- 40% found it necessary to reformulate a drug product for the U.S. market, thus often causing delays ranging from one to five years, mainly because of stability, insolubility, or permeability issues.
- 28% indicated that a drug development for the U.S. market was stopped because of the limitations of current excipients, including inability to provide adequate stability, solubility, permeability, or an efficacious dosage.
- 77% experienced challenges in using novel excipients; the top five challenges were addressing regulatory, safety, cost, toxicology-data, and trust-factor concerns.

Source: Sheehan (2019).

For the novel excipient category, industry consortia and trade organizations—such as the joint Novel Excipients Working Group of the International Consortium for Innovation and Quality in Pharmaceutical Development and the International Pharmaceutical Excipients Council—are working with FDA to address the new excipient regulatory barrier (IPQ 2020). In February 2020, their efforts culminated in an FDA solicitation of comments on a proposed standalone novel excipient review pilot program designed to decouple novel excipient review from IND, new drug application (NDA), or biologics license application (BLA) reviews.[4] Under the proposed pilot program, "recognition" of a novel excipient by FDA could eliminate the need to review the excipient separately within an IND application. At the NDA or BLA stage, the safety of the finished drug product would be evaluated when "recognized" excipients are included. The intent is that approval at the NDA or BLA stage would lead to the novel excipient's inclusion in the IID and thus facilitate more widespread adoption. The rapid institution of the proposed pilot review program should encourage the introduction of novel excipients by streamlining regulatory filings for new molecular entities that involve novel excipients.

Another important regulatory barrier is the lack of international concordance in the approval process for novel excipients. There are substantial differences even in how a novel excipient is defined; an excipient treated as recognized in one jurisdiction because of its use as a food or cosmetic additive might be classified as novel in another jurisdiction. That deviation in regulatory practice has a chilling effect on innovation because a manufacturer who has global marketing intentions will formulate to the lowest common denominator.

Finally, although the IID concept is meant to enable rapid development of new drugs when established formulations are adopted for new drugs, the IID inherently encourages manufacturers to use outdated technology. The reality is that new drugs might use 20-year-old formulation technology and forgo potential performance improvements in favor of regulatory certainty and expediency. A special case arises for innovations in formulations for generics and biosimilars. Manufacturers might be locked into older formulations and compositions in an abbreviated NDA or abbreviated BLA even though new excipients might offer substantive performance enhancements (IPQ 2020). Unfortunately, old formulations of legacy drugs are essentially locked in permanently.

OVERCOMING REGULATORY CHALLENGES

As new technologies for manufacturing drug products advance in the pharmaceutical industry, early and frequent interaction with FDA is the most basic fundamental method for overcoming regulatory challenges. As noted in Chapter 1, the establishment of the Emerging Technology Team has been instrumental in opening doors for conversations with FDA so that companies investing time and effort in uncharted territories can share their plans and receive feedback. The more these conversations allow open brainstorming, discussion of "what if" scenarios, establishment of expected outcomes, and education of both sides, the smaller the chance that surprises will curtail a novel technology. For drug products, such surprises are especially problematic for two reasons: (1) at this point, the product is closer to the stage of administration to a patient, and failure is not an option inasmuch as it could have devastating effects, and (2) investment by and cost to the company has been compounded as the product has progressed through the entire drug-development pathway. Failure to consider something that FDA found to be critical could shut down a project and potentially put a small company out of business. Some suggestions for overcoming the regulatory challenges that are specific to this chapter are provided below. More general and overarching recommendations are provided in Chapter 6.

- Develop mechanisms for evaluating a technology or platform outside individual product submissions. Although not fully analogous, the principle outlined in the proposed pilot program for the toxicologic and quality evaluation of novel excipients might provide a useful illustrative example to

[4] "Novel Excipient Review Program Proposal; Request for Information and Comments," Federal Register, 84(234), 66669-66671, 5 Dec 2019.

consider more broadly for drug-product manufacturing technologies. For example, a mechanism to consider additive manufacturing platforms could guide the demonstration of their capability to deliver consistent, high-quality drug products suitable for registration reproducibly. That approach would lower the risk of implementation broadly for industry and accelerate use within an individual product submission in the future.

- Harmonize among several international regulatory agencies. Applying for approvals in multiple countries after implementing an innovative process can be expensive and time-consuming. It can often result in the presence of multiple versions of the same product on the market until all the applicable countries have approved the innovation. Developing programs similar to the European Mutual Recognition Procedure or expanding more programs like FDA's Project Orbis would be helpful to the industry and render the regulatory approval process by multiple regulatory bodies less inhibitive.
- For such new delivery formats as microparticles and nanoparticles, the industry needs regulatory guidelines so that developers and innovators have clarity on how to scale up and show equivalent characterization. There is a need for specifications or strategic guidelines for such technologies, and there is little regulatory guidance in this respect. There is no international definition of what these materials are, and this lack affects research and development funding adversely and destroys public acceptance and perception of the novel drug-product forms (Foulkes et al. 2020; Souto et al. 2020b).
- Additional regulatory changes might also facilitate the development and adoption of new excipients. For example, the granting of a period of exclusivity and concomitant development of a USP and National Formulary monograph for novel excipients might spur excipient manufacturers and drug manufacturers, respectively. The inclusion in the IID of a section that describes new excipients under development or consideration might spur earlier adoption by other manufacturers. For manufacturers of generics and biosimilars, relaxation of the requirements for similarity with the original formulation could provide important patient and manufacturability benefits. Finally, as mentioned previously, work is needed to harmonize the regulation of excipients among jurisdictions.

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4

New Control Approaches to Enable Quality Assurance and Process Capability

Innovations in pharmaceutical manufacturing will require modern process-control approaches to support quality assurance and process capability, particularly for complex processes and products. In the pharmaceutical industry, *control strategy* is defined as a "planned set of controls, derived from current product and process understanding, that assures process performance and product quality" (ICH 2009). Although that definition is broad and encompasses much more than just engineering controls, the main goal of any control strategy (engineering or administrative)[1] is to maintain a system in a state of control to minimize the chances of producing a product with poor quality characteristics (that is, to ensure quality) and to segregate, if appropriate, such materials effectively if departures from quality expectations are encountered. In this chapter, the committee discusses novel technologies and engineering applications that can be used to ensure process-outcome quality and thus increase manufacturing-process capability. New approaches for process and product sensing, data analysis and modeling, artificial intelligence (AI) and machine learning (ML) methods, and advanced process control are highlighted, and technical and regulatory challenges associated with the technologies and some recommendations for overcoming them are also provided.

SYSTEMS

Before discussing the various components of control strategy, it is important to clarify the concept of systems and to make a distinction between simple and complex systems (see Figure 4-1). *System* has been defined as "groups or combinations of interrelated, interdependent, or interacting elements forming collective entities" (Arnold and Wade 2015). Pharmaceutical-operation systems can exhibit different degrees of complexity. Complex systems tend to have higher degrees of freedom (variables), behave nonlinearly, and exhibit multiple variable interdependences. An example of a complex system is the cell-based synthesis of monoclonal antibodies using bioreactors. During their production, the system will exhibit nonlinear relationships between variables and dynamic outputs that affect each other (for example, the interrelationship between ammonia concentrations and cell density) and thus do not depend solely on process inputs. Capture of the interdependences inherent in complex systems requires much deeper process understanding; thus, the predictability of such systems might not be as high as that of simpler systems. Consequently, complex systems impose greater demands on the control strategy.

In simple systems, the final outputs of the process depend solely on measurable inputs. An example of a simple system is the process of compressing granules into tablets in which the granules have been preprocessed to provide the desired composition and structure for tablet formation. During the compression process, tablet weight and hardness depend on tablet-press inputs and granule attributes, but the process has no dynamic inputs or dynamic outputs beyond the control of humidity, which can affect plasticity. Thus, outputs, such as tablet weight and hardness, can be predicted and controlled more easily than, for example, glycosylation with mannose-type *N*-glycans in the production of monoclonal antibodies.

[1] Administrative controls are the use of training, policies, and procedures to dictate how humans work, whereas engineering controls are the controls built into systems, equipment, and facilities by using technology.

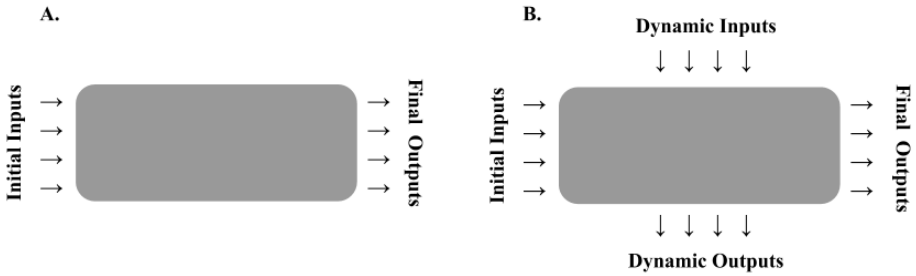

FIGURE 4-1 Depiction of a simple system (A) vs a complex system (B). Simple systems can be described as systems in which outputs depend solely on inputs and that have fewer degrees of freedom. Complex systems are described as systems that have many degrees of freedom and are nonlinear with many interdependences.

As pharmaceutical manufacturing processes become more integrated, their complexity as systems will increase; this is the case for advanced manufacturing applications, such as continuous manufacturing and intensified operations (Huang et al. 2020). The complexity of pharmaceutical processes has implications for the measurement, modeling, and control technologies used in their design and operation. The measurement of critical quality attributes and process parameters might require a broader and more sophisticated portfolio of sensor technologies. The models, although based on equations rooted in fundamental knowledge, will typically need to be supplemented with data-derived relationships, perhaps involving ML, that span the knowledge gap. The control systems might require a portfolio of hierarchical, model-based and adaptive control technologies. AI and specifically ML methods might need to play substantial roles in predicting and controlling the performance of complex pharmaceutical-manufacturing systems.

SENSORS

Sensors or analyzers are devices used to detect or measure a system characteristic or property. From a process perspective, sensing can be accomplished in three main configurations: in-line, at-line, and off-line. In-line measurements are taken directly from the process (for example, a pH measurement inside a reactor). At-line measurements are taken next to the process (for example, a tablet-weighing station near a tableting machine), typically with automatic sampling. Off-line measurements are taken outside the manufacturing suite (for example, an impurity measurement in a quality-assurance laboratory). Although all the sensors provide useful information about the manufacturing process, only in-line and some at-line sensors can be considered process analyzers because only they can provide *timely* information on the health of the process to support process-control decisions. Off-line sensors, typically laboratory analytic instruments, are commonly used to measure the final quality of a product, to ensure thorough product characterization during development, or to develop calibrations for in-line and at-line sensors.

Innovative Off-Line Analytic Methods and Sensors to Support Product Development

During the pharmaceutical-development phase, information is obtained through process studies that establish scientific understanding of the product and processes. Off-line sensors tend to provide the more detailed information about the chemical and physical characteristics of materials that helps to build that understanding. However, these analytic tools do not provide real-time results and so are deployed in off-line configurations to obtain data that require high resolution, such as data on molecular structure, glycosylation, impurities, and crystal structure. Several innovations in such analytic methods have advanced to the stage where they will support filings within the next 5 or more years.

One innovative analytic method that has been gaining attention is the liquid chromatography–mass spectrometry (LC–MS) multi-attribute method (MAM). MAM is being studied to monitor and

quantify molecular product-quality attributes and product-related or process-related impurities of post-translational modifications of biologics (Rogers et al. 2015). MAM can be used "not only during product characterization, formulation development, stability testing, and development of the manufacturing process, but also as a platform quality control method in dispositioning clinical materials for both innovative biotherapeutics and biosimilars" (Rogers et al. 2017). MAM can be used to set specifications in a more targeted manner and to perform new peak detection, which can be used as a sensitive impurity test (Schiel 2020; Starkey 2020). Although MAM is an off-line sensing approach, it is also being investigated for use in in-line sensing (Swann 2020).

Another tool that should see increasing use in the future for the evaluation of therapeutic proteins is two-dimensional nuclear magnetic resonance spectroscopy, which has the potential to be used to compare structural attributes of proteins (Schiel 2020). That potential capability is important because structural similarity is hypothesized to be indicative of functional similarity and thus could inform decisions about safety and efficacy. Additional tools noted by Schiel (2020) that could soon find their way into biopharmaceutical development and quality-assurance laboratories include

- *Electron microscopy* to evaluate the dynamics of the conformational ensembles of therapeutic monoclonal antibodies (Castellanos et al. 2018; Lei et al. 2019; Xu et al. 2019). Protein dynamics might affect mechanisms of action, side effects, adverse immune responses, viscosity, and stability.
- *Hydrogen–deuterium exchange mass spectrometry* (HDX–MS) to study protein structural dynamics to shed light on how it influences, for example, stability, interactions, or adverse immune responses (Hudgens et al. 2019). HDX–MS is sensitive to post-translational modifications.

Innovative In-Line Sensing Approaches and Sensors to Support Process Control

When designing strategies for pharmaceutical-process monitoring and control, engineers have gravitated toward simple, robust, low-maintenance sensors. The output of such sensors typically is only one process measurement per device (univariate sensors). Examples are pH meters, mass flow meters, thermocouples, scales, and humidity sensors. Although such sensors do support quality assurance, their primary role is as part of the rudimentary automation system. Specifically, the process variable measurement that the sensor provides is typically used as part of a low-level feedback control strategy centered on a single unit operation. Because they typically do not measure quality attributes, such sensors alone cannot enable active process control of product quality and cannot provide enough observability to support more advanced control strategies.

In response to the process analytic technology (PAT) initiative, the industry has taken steps to adopt sensors that monitor multiple process variables and, most important, quality attributes (outcomes). Some of the most promising process sensors are based on vibrational spectroscopy (Romero-Torres et al. 2009). They offer multiple benefits, such as in situ measurements, no need for sample preparation, and rapid scanning. However, they do require tailored calibrations, which are normally constructed by using multivariate statistical approaches.[2] Thus, companies need to expand (and even redefine) their analytic-chemistry (and supporting) competences with chemometric skills that are not part of traditional academic curricula. Such novel and sophisticated sensors are also more expensive and less rugged than the classic sensors. Thus, the adoption of these spectroscopy-based sensors for process monitoring has been slower than might be expected. Nevertheless, the major companies have invested in the development of measurement and control strategies that use spectroscopic sensing devices and have actively shared their experiences throughout the industry (Futran 2020). In the next 5 years, the Food and Drug Administration (FDA) will need to continue developing workforce competences in spectroscopic methods and their deployment constraints. Although the technologies are not new to the pharmaceutical industry, they are not yet standard (Futran 2020).

[2] See http://ftp.uspbpep.com/v29240/usp29nf24s0_c1119.html#usp29nf24s0_c1119.

Other novel process sensing approaches that are receiving attention are based on electric capacitance volume-tomography measurement of mass flow of particulate streams (Li et al. 2015) and dielectric spectroscopy for viable-cell density, cell size, intracellular conductivity, and membrane capacitance (Opel et al. 2010). The in-line measurement of mass flow in continuous solid oral-dosage lines offers the benefits of enabling direct monitoring of intermediate process streams to establish the state of control and of enabling decoupling of control structures.

An approach to increase the observability obtainable with individual sensors is to combine information from multiple sensors to monitor the state of a process or infer unmeasured (or unmeasurable) process variables. Combining information from multiple sensors is typically achieved by using models, which can be data-driven, hybrid, or mechanistic. A soft sensor is one such application; it consists of a model that draws on multiple sensor measurements as inputs to predict an unmeasurable process variable. In the next 5–10 years, the committee expects pharmaceutical companies to use more model-based monitoring that integrates the information from multiple sensors (established and advanced) and to use models to infer process state and process outcome, including quality. Depending on the scope of a model and whether sensor information is taken at a specific time or over a time window, several approaches—soft sensors, model-based data-reconciliation methods, or state estimation—are available (Moreno et al. 2019).

Technical Challenges

The challenges in adopting novel sensing approaches are closely tied to the maturity of the sensing technology and the level of customization and rigor needed for its intended use. As discussed above, advanced and multipurpose sensing technologies typically require tailored multivariate chemometric models for monitoring or quantifying chemicals or properties in complex mixtures. The custom models need to be developed, validated (including design of new validation protocols), maintained, and updated by experts who understand the science behind the sensing mechanism, the complex-mixture properties (and dynamics), and the fundamentals behind the multivariate algorithm used. Given that the competences needed are not part of any academic curricula but rather a specialization, it is challenging to recruit a critical mass of talent to develop and support these applications.

Regulatory Challenges

A perceived regulatory challenge in adopting novel sensors, particularly those usually characterized as PAT, is the notion that the intended use of any advanced sensor is always real-time-release testing. That notion has created confusion in the pharmaceutical industry and potentially led to missing an opportunity inasmuch as new sensing technology is commonly scrutinized with the same rigor as methods used for quality control and product release. For example, using Raman spectroscopy as part of a glucose-feedback controller should not be seen differently from using a classic pH meter as part of a pH-control strategy. The confusion might be caused by the practice in the pharmaceutical industry of using regulatory language when describing technology (for example, equating Design of Experiments with Quality by Design, a spectrometer with PAT, or near infrared spectroscopy with real-time-release testing). The use of new technologies to improve process capability (not necessarily to replace final testing) can be focused on improving process reliability (for example, saving batches, improving process predictability, and reducing the cost of quality) and on increasing performance. Better performance and capability can then allow for increasing plant throughput capacity (increasing productivity and minimizing product shortages) and making a case for reduced testing (after high capabilities are demonstrated). Real-time-release testing can also be implemented in cases in which it is possible to measure or estimate a quality attribute with high fidelity (low risk) by using information obtained before completion of the manufacturing process.

Another regulatory challenge (or *perceived* regulatory challenge) in the use of spectroscopy-based methods that require tailored models is that any change in a model as part of lifecycle-management activities requires a prior approval supplement. *Development and Submission of Near Infrared Analytical Procedures Guidance for the Industry*[3] indicates that post-approval changes will be risk-based. Also, the International Council for Harmonisation (ICH) has recognized the need for more guidance and clarity related to these new measurement approaches and has issued a final concept paper (ICH Q14).[4] The purpose of ICH Q14 is "harmonising the scientific approaches of Analytical Procedure Development, and providing the principles relating to the description of Analytical Procedure Development process. Applying this guideline will improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures." The work plan for the new ICH guideline has May 2022 as the date for adoption.

DATA ANALYTICS AND SYSTEM MODELING

In this report, the term *data analytics* is used to describe the process of gaining knowledge from data related to the manufacturing process. Typically, that knowledge is captured via statistical, AI-based or mathematical models. As discussed in ICH (2012), models can be used to increase scientific understanding, estimate state variables of a process, predict process behavior, and drive control strategies. Models can be created by data-mining, by using first principles, or by combining data-driven and mechanistic models (hybrid models) (Romero-Torres et al. 2018). In contrast with the more mechanistically based models that are required for product and process design, models that are used to support real-time manufacturing decisions are generally hybrid models that include the use of reduced-order forms of mechanistic models. Models can be used at any stage of the process lifecycle, and the level of oversight should be "commensurate with the level of risk (*to the patient*) associated with the use of the specific model" (ICH 2012). Table 4-1 explains the three categories in which models can fall regarding submissions.

In this section, the committee discusses the combination of data analytics and various types of models to improve quality assurance and process control and capability. In some cases, the combination could potentially lead to a reduction in or elimination of some tests.

TABLE 4-1 ICH Model Categories

Model Category	Intended Use	Examples
Low-impact model	Typically used to support product or process development	MLR model to evaluate DOE data for formulation optimization
Medium-impact model	Can be useful in ensuring product quality but is not the sole predictor of product quality	Most design-space models and models used for process control, such as PLS model of a Raman-based application to control glucose and lactate concentrations in a bioreactor
High-impact model	Can be used as a predictor or surrogate of product quality	A chemometric model for product assay, a surrogate model for dissolution, and real-time-release testing models

Abbreviations: MLR, multilinear regression; DOE, design of experiments; and PLS, partial least squares.
Source: ICH (2012).

[3] See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-submission-near-infrared-analytical-procedures. See Types of Changes and Reporting Categories, p. 17.

[4] See https://database.ich.org/sites/default/files/Q2R2-Q14_EWG_Business_Plan.pdf.

Models for System Design and Process Understanding

Models used for design are typically mechanistically based, for example, consisting of sets of ordinary or partial differential equations. The developer of the model understands the fundamental principles appropriate for describing the system and assembles the equations into a system that can be solved numerically. An example is a computational fluid-dynamics (CFD) model that can be used to simulate mixing of an active pharmaceutical ingredient (API) and provide much more spatially detailed information than conventional sensors. CFD models can often be used for primary mixing validation (Prior 2020). Furthermore, that type of simulation can predict behavior and allow computational exploration of different scenarios during the development phase. Such simulations, however, are often too computationally time-consuming to provide answers in real time and might not be able to capture all the underlying complex phenomena or to account for stochastic behavior in a system. For those reasons, data-driven or hybrid models that incorporate data and mechanistic understanding of a process are important alternatives.

In the next 5 years, the committee expects to see the increased use of a combination of first-principles models, data-driven models (such as deep neural networks), and hybrid models. Such combinations could improve process development while reducing the number of experiments needed to establish better process conditions (von Stosch and Willis 2016; Kaschif 2019; Narayanan et al. 2019).

Advanced Analytics for Process Monitoring and Continued Verification

A key application of advanced analytics is in continued process verification (CPV) and in process monitoring. CPV is the ongoing program of verifying the state of the process during routine production (FDA 2011). It encompasses data on relevant process trends and quality attributes of incoming materials or components, in-process material, and finished products. The data-analytics techniques commonly used for CPV are univariate statistical process control methods, which are now well established. However, there is increased use of multivariate statistical process control (MSPC) methods that use more sophisticated techniques, such as principal component analysis and partial least squares, to characterize the ideal multivariate fingerprint of a validated state. That fingerprint can then be used to measure how far newly manufactured batches are from the validated state (or how close). According to ICH (2012), MSPC models that are used for CPV with a traditional method for release testing would probably be classified as medium-impact models.

Models for Advanced Process Control

Models are at the heart of advanced process control (APC) strategies, and applications include model predictive control (MPC) (Lee 2011), fault detection and diagnosis (Venkatasubramanian et al. 2003), condition-based monitoring (Ganesh et al. 2020), and real-time process optimization (Huang et al. 2020). Those capabilities, which are becoming part of the Industry 4.0 paradigm (Deloitte 2015; Romero-Torres et al. 2017), move process knowledge and understanding to true real-time process optimization and operations management. In APC, analytics and computational modeling can be incorporated to recognize that an event has happened. Depending on the time scale and magnitude of an event, different actions need to be taken, including the following:

- Exercise immediate feedback-control action.
- Identify and diagnose a process fault that requires timely intervention.
- Identify a performance degradation that requires scheduled maintenance action.
- Identify a discrepancy between model prediction and process performance that requires real-time optimization to update process set points.

The BioPhorum Operations Group describes a digital-plant maturity model with five levels,[5] and real-time process optimization and operations management are characteristic of the highest level in the maturity model, which is referred to as the adaptive plant. By using advanced and soft sensors and data-driven modeling, some companies have realized integrated real-time optimization of operations, such as wet granulation and fluid-bed drying (Huang 2020).

The Digital Twin

Digital twins could have many applications in pharmaceutical manufacturing, such as process flowsheet simulation, real-time process corrections, and reduction in timelines for technology transfer (Futran 2020; Huang 2020). If a physical asset is replicated as a digital twin, real-time corrections can be tested to evaluate potential implications before changes are applied to the "real" system. Similarly, a change in the technology-transfer process can be examined by using a digital twin to analyze how it could affect the process before it is made in the "real" system or process.

The initial version of the mathematical model that underpins the digital twin might not capture the stochastic behavior of the system because it uses mean or most likely model parameter values. However, the digital twin can be used with Monte Carlo or established Bayesian inference methods to capture the effects of uncertainty in the model parameters and system outputs. Specifically, the combination of the mathematical model with real-time process data available from sensors at a particular time or over a time window can be used to assess the effect of parameter uncertainty on predicted system performance and quantitative risk associated with system outputs. Note that the level of remaining uncertainty depends on multiple factors, including the number of variables that affect the solution that can be collected from sensors (process degrees of freedom) and the ability to collect important variables through sensing (process observability). One potential innovation that will change process development in the next 5–10 years is the use of digital twins that are developed with hybrid modeling approaches, including AI methods.

Potential of Artificial Intelligence

AI refers broadly to computer simulation of intelligent behavior, which includes model training or learning from experiences quantified through data. As the use of automation increases, for example, in the digital-plant maturity model, the application of AI to APC increases. ML is a subset of AI that uses large amounts of data and statistical methods of fitting data to facilitate classification (such as the type of fault that occurred) or regression (such as the amount of error between a first-principles model and reality). Statistical methods that are used in ML (such as principal component analysis) can vary widely in their complexity and interpretability. As computational power has increased, more-complex fitting methods have been implemented for better matching of large amounts of data (Greengard 2016). Deep neural networks, for example, use many layers of neurons and connections to represent highly nonlinear correlations and can provide accurate predictions when appropriately trained. In 2015, a Microsoft research team demonstrated that a deep neural network could outperform human classification of images (He et al. 2015). With successes like those, neural networks continue to increase in complexity and accuracy.

General advances in AI and ML can be found in voice recognition, targeted advertising, and self-driving cars; all are driven by vast data collection and advances in algorithms. Although the committee did not identify many direct uses of ML in its investigations, innovators clearly are recognizing its potential, and the amount of data that are and will be collected through sensors will enable increased use of these techniques in the coming years. The identification of trends in large pharmaceutical process datasets and the generation of the data-driven component of hybrid models, as described earlier in this chapter, are natural targets for the application of ML methods. In those cases, assuming that the datasets

[5] See https://www.biophorum.com/download/digital-plant-maturity-model-v-2/.

used to train the models adequately cover the operating range of the system variables and encompass all the variables that must be measured for the system to be observable, ML methods can produce models of sufficient accuracy to enable increased automation and progress toward an adaptive plant. Those advances can lead to more autonomous robotics that contribute to a reduction in human intervention, as was described for aseptic filling in Chapter 3. The use of ML can also lead to more innovation by uncovering previously unknown correlations in the data.

Multilevel Control Structures

The sensors, process analytics, and modeling techniques described in the previous sections constitute the core components that are required for the implementation of fully integrated manufacturing systems. In batch operations traditionally used in pharmaceutical manufacturing, each unit operation might be equipped with its own process-control system that consists of its controlled variables, manipulated variables, sensors that are used to measure the controlled variables, and specific control logic for adjusting the manipulated variables. As the industry progresses from traditional batch operation to integrated process trains, as is the case in continuous manufacturing, the dynamics of the successive unit operations need to be closely linked. Moreover, to replace the quality-assurance checks, critical process parameters and critical quality attributes (CQAs) have to be monitored and controlled in real time by incorporating them into the control-system design. If a performance-based control approach is used (ICH Q12), the control logic to maintain a CQA within a target might span more than one unit operation (for example, ratio control of multiple powder feeders to maintain the API concentration measured at the outlet of the powder blender). However, those two control levels—control of basic equipment operation and CQAs—do not suffice to ensure that the entire production line is maintained in a state of control. A third level of coordination is needed among the unit operations. Thus, a plantwide control strategy that might include both feedback and feedforward elements or might involve more sophisticated model-predictive control systems discussed in the previous sections is needed (Su et al. 2019).

Such hierarchical control-system design offers multiple additional possibilities. It can accommodate implementation of modular systems (see Chapter 5) in which each module has its native local control system, and a plantwide control level is configured on the basis of the specific arrangement of the modules. The design can accommodate hybrid production lines in which some of the unit operations are operated in batch mode and others in continuous mode. A hybrid production system might be appropriate if a continuous unit operation is too difficult to control, is subject to performance degradation, or has a long residence time. To benefit from process integration, however, the batch steps must also have control systems in place for critical process variables and CQAs. Moreover, to achieve acceptable plant dynamics, the batch steps will need to be downsized and have automated loading and unloading to achieve overall continuous material flow on a system scale. To balance batch size and cycle times, the batch stages might need to be operated in parallel. However, to control complexity, the number of transitions from batch to continuous or from continuous to batch in the overall process train might need to be restricted. Finally, in this hierarchical control structure, specific processing stages that involve robotic operations can readily be accommodated: the robotic stage is only an electromechanical unit that is locally controlled and can operate in batch or continuous mode as part of a hybrid production or continuous process train.

Technical Challenges

The innovations described above entail many technical challenges. The main challenges in adopting models for system design and process understanding are due to system complexity, knowledge and data availability, and workforce competence. For simpler systems, it is easier to identify the physical and chemical phenomena that govern their behavior; for complex systems, this level of mechanistic representation is difficult to assemble.

In adopting advanced analytics for CPV, there are several challenges. First, the use of analytics requires information systems through which process information (in-line, at-line, and off-line) is aggregated automatically and reliably, but such centralized data repositories require investment and some specialized training. Second, products made in campaigns might not reflect random behavior because of systematic changes in equipment, staff, and raw materials, and this is especially true for products that are manufactured with low frequency (many products are made with frequencies of fewer than 25 batches/year). Third, alarms or investigation actions are usually based not on statistical control limits but rather on action limits and registered specifications, and systematic variation is usually not investigated unless process performance falls outside action limits or registered specifications. Fourth, in many companies, there is no formal governance or business process for continuous improvement based on CPV activities. Fifth, if effective knowledge-management programs are lacking, the right information is often not available to the right people at the right time.

Increased application specifically of AI and ML tools poses several challenges. Some of the most accurate ML models, such as deep neural networks that use many complex layers, can become difficult to interpret. Although the structure of a neural network is well defined, the weights that are associated with the connections in the network and the bias are determined during model training in an iterative fashion by using numerical algorithms. During training, the model predicts output on the basis of training-data input, the error between the model's prediction and the training-data output is assessed, and the model weights and bias are modified by the algorithm logic to decrease the error in the model's prediction. Three major technical challenges arise from these types of models:

- As the scope of the ML model and dataset are expanded to increase model prediction accuracy, the model also increases in complexity and decreases in interpretability. Although a less interpretable model might capture correlations better, the ability of a human to use that information to attribute causation will decrease. For example, deep neural networks can easily contain tens of thousands of learned parameters that are associated with abstract correlations in the data. Associating the model structure and learned weights with physical reality to understand why a prediction was made remains an open field of research.[6]
- By design, ML approaches, including neural networks, are intended to change as they are given new data. Although accumulation of new data typically increases accuracy, the continuous nature of the evolution of the model makes it difficult to assess why a given input can result in a different prediction from one version of the model to another. To facilitate interpretation, model training can be performed in discrete events that create new model versions. However, that approach inherently introduces delays in model improvement and adds software engineering complexity.
- In the training of complex models, especially nonlinear ones, the risk of overfitting a model can be substantial. An overfitted model might not capture actual system behavior and might thus lead to faulty predictions. Research is continuing in this field.

The committee emphasizes that data analytics and modeling are at the heart of APC and that FDA will need to prepare for advances in them. There are, however, challenges that the pharmaceutical-manufacturing industry will need to address for successful implementation of these technologies. First, few experts in data analytics and system modeling are also knowledgeable in pharmaceutical manufacturing. Data analytics and system modeling constitute a specialty in themselves that requires advanced knowledge of statistics and mathematics. Experts in this field are in high demand outside the pharmaceutical industry, so efforts need to be made to grow expertise and to retain it. To achieve reliable results robustly, it is important that data analysts or modelers can work closely with domain experts during the model-identification phase, that they can communicate effectively with FDA regulators, and that the FDA staff have the background to engage in the discussion.

[6] See https://www.darpa.mil/program/explainable-artificial-intelligence.

A second major challenge is to build an effective infrastructure for knowledge management. ICH Q10 addresses the need for knowledge management as an enabling capability for product quality, control, and continual improvement, but there are many subtleties and complications in doing so effectively (ICH 2009). Collecting sufficient curated and contextualized data, which are needed to create ML models, takes time and expertise, which are scarce.

A third major challenge, which is related to the second, is the issue of observability. Not all important variables that enable system predictability are measured or measurable. As discussed in the section on digital twins, the incorporation of more variables can decrease uncertainty but is not always possible. When it is not, some variables might be inferred from variables that are measured directly by using models.

A fourth challenge is the availability of representative data. Many products are manufactured with low frequencies (for example, three to five batches per year). That translates into a lack of representative data that can be used to characterize the long-term behavior of a system and to design robust model-maintenance programs.

Finally, the technical challenges in the implementation of APC reside mainly in the establishment of reliable data flow from sensors and process equipment and the development of robust models for control. However, important issues are associated with design of the control-system logic. Specifically, there are challenges in the design of flexibly configurable process-control systems for modular processes. The hierarchical architecture can readily accommodate alternative configurations of module-level and plantwide control elements, but the design of platforms that enable flexible configuration of those control elements as modules are being reconfigured for different products requires further development. Ensuring system integrity will also be a key requirement. Similarly, the robust operation of highly intensified unit operations or sequences of operations can be achieved only through active process control inasmuch as intensification by its very nature exploits higher degrees of interaction between process variables. Such intensified operations thus might require customized control-system designs, including the use of more advanced methods, such as adaptive and nonlinear model predictive control.

Regulatory Challenges

Several important regulatory challenges are associated with the technologies described above. The regulatory challenges for increased automation and AI align closely with their technical challenges. The lack of interpretability in some of the most accurate models and the continuous nature of the evolution of the models might lead to difficulty in regulatory applications. Nonetheless, the committee concludes that many applications of increased automation and AI pose low impact, as defined in Table 1, and provide value to process improvements. Therefore, such advances should be acceptable to regulators. At the same time, higher-impact uses of increased automation and AI can be complemented with first principles to lower the risk posed by the applications and meet regulatory expectations.

In the case of APC, many advanced control strategies require a high degree of at-scale process understanding to allow for system modeling in the presence of common disturbances. That degree of at-scale process understanding is not usually available at the time of filing, especially for such complex processes as bioreactions. Thus, for companies to be able to adopt more advanced control mechanisms, such as MPC and hierarchical control system designs, they probably will have to require regulatory post-approval changes. ICH Q12 is expected to facilitate such changes and encourage the continuous adoption of innovation.[7]

The committee notes that the hybrid production mode of operation potentially raises a regulatory issue associated with the definition of the batch. As noted earlier, in such hybrid lines, batches are generated and processed in one or more internal processing units that then feed continuous units, but the final process output stream is continuous. Flexibility in the interpretation of what constitutes a lot or batch

[7] See https://www.fda.gov/files/drugs/published/Q12-Technical-and-Regulatory-Considerations-for-Pharmaceutical-Product-Lifecycle-Management-Core-Guideline-Guidance-for-Industry.pdf.

in the context of continuous manufacturing has been allowed, and the committee finds that similar flexibility should be allowed in the interpretation of a batch with hybrid production systems that would be independent of the operational batches that are internal to the hybrid process.

OVERCOMING REGULATORY CHALLENGES

FDA has been active in creating an ecosystem that will enable the adoption of more sophisticated control mechanisms. Its efforts include issuing the PAT guidance and other advanced guidelines and creating the Emerging Technology Team. The committee applauds those efforts but finds that the agency can help to foster innovation further and provides suggestions below.

- *Terminology alignment and clarification.* There is a great opportunity for terminology alignment and clarification. Differences in definitions throughout the industry have caused substantial confusion. From a regulatory perspective, it might be beneficial for the agency to work with the industry to distinguish regulatory language from descriptions of scientific or engineering principles and practices. Doing so will be key in helping the pharmaceutical industry to share best practices and adopt a more fit-for-purpose approach in evaluating the adoption of novel sensors and control strategies for various applications. An updated PAT guideline might also be beneficial; it should incorporate standard control-theory terms, such as process observability, fault detection, fault classification, and process-condition monitoring. An example of confusing terminology is the use of the term *control* when referring to specifications.
- *Expectation-setting and management.* One of the main reasons that the pharmaceutical industry has been slower to adopt more advanced control strategies is unrealistic expectations. As discussed, the most-cited value proposition for new control approaches is usually real-time-release testing or at least reduction in the time for post-manufacture quality assessment. Reduction or elimination of quality testing, especially for complex systems, should be the result of good engineering design and reserved for processes that have high process capability, observability, and predictability. Nevertheless, processes with low capabilities and predictabilities can benefit tremendously from better control mechanisms to increase the process reliability that directly affects "supply-ability." Depending on the manufacturing frequency, cost of goods, process complexity, and available infrastructure, a company can make business decisions about what level of observability and control should be built into its processes. A recommendation is to communicate innovation value proposition in the context of the pharmaceutical supply chain, financials, and operations.
- *People, process, and technology.* Another important concept that surfaced during the committee workshops (NASEM 2020a,b) and has been extensively discussed by change-management leaders, such as McKinsey[8] and Boston Consulting,[9] is "people, process, and technology." Although the concept is not new and is related to expectation-setting and management, the committee finds that it should have greater presence in FDA's discussions of new control approaches and innovations. The implementation of technology alone will not lead to improved process capabilities, supply-chain reliability, and agility. Technology adoption should go through business processes, such as stage gating, and should be mapped through the lens of change management. If that is done, it will become evident that key branches of the typical pharmaceutical organization are not part of the innovation conversations or even adoption of business workflows.
- *Impact of manufacturing-equipment health.* Condition-based monitoring of manufacturing equipment and processes enables timely identification of performance degradation and reduction in unplanned downtimes and thus improves process capability and provides higher assurance of product

[8] See https://www.mckinsey.com/business-functions/mckinsey-digital/our-insights/the-next-generation-operating-model-for-the-digital-world.

[9] See https://image-src.bcg.com/Images/BCG-Take-Control-of-Your-Digital-Future-May-2018_tcm30-191195.pdf.

quality. The committee recommends that the agency become familiar with condition-based monitoring approaches and provide incentives for their use.

- *Inspector competences.* The increased reliance on advanced control strategies—including fault detection and mitigation strategies and condition-based monitoring—requires that inspection staff have the expertise to understand the technologies and best practices in their application. FDA needs to have the additional resources to hire and continue training and retention of these essential human resources.
- *Modularization replication*. The trend toward modularization of process systems, plug-and-play unit operations, and even miniaturized portable production systems provides opportunities to incorporate sensing and control technologies. The trend is described in detail in the next chapter. Given the many modular concepts, system definition and standardization might be more challenging than control integration. Here, the influence of regulators can have a beneficial effect on driving standards for modularization that have integrated sensing and control technologies. Such standards could substantially reduce timelines for the startup of pharmaceutical manufacturing in new facilities and in retrofits of conventional facilities.
- *Digitized work instructions.* As more observability and new alarms are implemented to alert personnel about possible process and equipment upsets, there will be a need to rely on digitized work instructions that can walk personnel through a set of decision and action workflows (logic) that might be too complicated to be captured in paper format (or on a single visual workflow). The committee expects these expert-system digitized instructions to become more common, and FDA should become aware of the trend.
- *Guidance.* To reduce the perceived uncertainty in FDA acceptance of innovations in sensing, modeling, ML applications, and advanced control, it would be desirable for FDA to issue focused guidance on their cGMP implementation and expectations for their management, analogous with the recent near-infrared analytic-procedures guidance (FDA 2015). Such guidance could draw on recent initial industry efforts led by the Pharmaceutical Discovery, Development and Manufacturing Forum of the American Institute of Chemical Engineers (PD2M-AIChE), which has resulted in implementation guidelines that draw on recent industry experiences with soft-sensor method validation, APC, and ML methods (Huang et al. 2020).

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5

Innovations in Integrated, Flexible, and Distributed Manufacturing Networks

In the next 5–10 years, the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) is likely to see substantial innovations in integrated, flexible, and distributed manufacturing. Those advances are in many ways the culmination of the innovations that have been discussed in the preceding chapters and provide a fully integrated approach to the manufacture of drug substances and drug products and enable new, distributed manufacturing systems. In this chapter, the committee discusses projected innovations and technical and regulatory hurdles that might stand in the way of implementation of end-to-end manufacturing systems, modular approaches to streamline development and production, and deployment and use of highly portable manufacturing units. Those integrated systems are largely interrelated, so technical and regulatory challenges related to them and committee recommendations for addressing them are discussed together at the conclusion of the chapter.

END-TO-END SYSTEMS

System Description

End-to-end manufacturing involves the effective integration of all the necessary components in manufacturing systems from raw materials through final drug products. In end-to-end manufacturing, raw materials flow through a continuous series or small incremental series of unit operations with intermediate transfers in a closed system, which ideally includes final drug-product release. It differs substantially from typical pharmaceutical manufacturing in which unit operations are largely independent and material in one operation can be held pending in-process testing before the next one. Where standard manufacturing processes separate raw-material inputs, drug substance, and drug product, end-to-end systems seek a single, inclusive, integrated production process that can lead to important departures from the status quo. For example, legacy processes often consider the drug substance as a raw material, but end-to-end innovations in material and process assessment and handling and in process control and reliability will increasingly integrate the production of drug substance and drug product. Furthermore, the ability to trace mass balance through the material flow streams is critical for end-to-end processes and is foundational for monitoring stability in these systems; thus, application of innovative in-line measurements to enable fast feedback is fundamental to their control.

The emergence of commercial end-to-end systems started with a hybrid of small-batch and continuous flows and has occurred primarily in small-molecule manufacturing. An example is a commercially available granulation system that uses continuous powder and binder feeds to a continuous twin-screw mixer–granulator and then transitions to a segmented fluid-bed dryer in which each segment operates essentially as a batch before materials are blended together for downstream continuous processing (Vercruysse et al. 2013). Although such hybrid approaches offer important process advantages, the transition points (continuous to batch and vice versa) can make it difficult to manage the stability of the process flow. FDA is increasingly likely to see the evolution of hybrid systems that focus on minimizing uncertainties related to batch–continuous transition points by using mass-balance sensing and control. Furthermore, small-batch processing might be increasingly implemented as a means of

providing fast feedback, especially where end-point control offers an inherent advantage for process stability. Overall, end-to-end integration will simplify handling and reduce the overall cycle time for production, and it is increasingly likely to be seen in regulatory filings.

In large-molecule manufacturing, end-to-end integration of bioreactors with downstream processing is still in its early days, and continuing innovation in end-to-end systems in bioprocessing applications is expected (Smart 2013). Because of the length of upstream processes in the production of many biologics, much of the growth in end-to-end processing has centered on downstream purification and formulation and fill–finish activities. In the future, integration of upstream fed-batch processes with downstream continuous processes might enable a truly end-to-end processing capability for production of biologics and appears increasingly likely to be presented to FDA within 5–10 years.

Integral to and critical for an effective end-to-end system is the matched adaptation of in-process testing to enable quality assessment and process control. In-line sensing is the ideal approach; it requires no mass removal and avoids handling delays and analytic process queues associated with conventional testing. Associated data analytics, including multivariate analysis, are expected to be an important enabler within the next several years, and it is anticipated that increased integration of plantwide data analytics throughout manufacturing processes will greatly facilitate process validation, quality assessment, and root-cause analysis of product-quality issues. Increased use of data analytics might further advance end-to-end processes through better fault prediction, detection, and recovery. As was described in Chapter 4, sensing and statistical modeling enable process stability, which is essential for effective end-to-end systems.

Drivers of Development

The development of end-to-end approaches is being driven primarily by economic factors because the systems are designed for efficiency and can scale to meet market demand and reduce inventory. The end-to-end approach leads to efficiencies in the use of resources relative to output and reduced cycle times in development, production, and distribution. The approach is contrary to that in today's pharmaceutical industry, in which production is based on available capital equipment and is geared to large batches so as to reduce needed regulatory compliance testing. The resulting substantial work-in-progress[1] and product inventories contribute to the characterization of the pharmaceutical industry as having undesirably low inventory turnover—a key manufacturing performance metric defined as the ratio of product sales to materials in inventory in a given period (Spector 2018). End-to-end processes and agile supply strategies can rectify that problem by decreasing both raw materials and work-in-progress inventories.

Although there clearly are opportunities to "right-size" production scales, in a way that is consistent with continuous and small-batch processing, adoption of scaled-down end-to-end systems has been impeded by the existence of legacy capital equipment and processes. Specifically, when companies try to create end-to-end facilities by including existing batch equipment, which is typically designed for large-batch production, they lose some of the benefits of an end-to-end approach. Several speakers during the committee workshops commented that use of right-sized, continuous end-to-end systems will most likely come with products that can be made, distributed, and administered in no other way (NASEM 2020a,b). That said, there is a growing sense of acceptance for end-to-end thinking, driven partly by reinterpretation of a regulatory batch in the context of FDA's guidance for continuous manufacturing with process analytic technology (PAT). In biologic processing for which much longer batch-cycle times are required in bioreactors, there is a trend toward right-sizing through the use of small single-use process vessels, especially in the early growth stage of a product's market introduction (Jensen 2016).

[1] "Work-in-progress" inventory refers to unfinished goods in the production process.

Applications

To be successful, innovations in end-to-end systems need to meet several criteria beyond technologic invention (Griffin et al. 2012). Successful innovations address important problems, are based on deep technical understanding, are implemented effectively, and gain market acceptance. Market acceptance can be a substantial challenge for regulated products for which the solutions in question might be outside the bounds of current regulatory thinking, at least as perceived by industry. Successful pharmaceutical innovation requires a drug product that solves an important problem for a cohort of patients, has an actionable means of drug delivery and treatment, and has a price structure that can cover development and manufacturing costs while being competitive in controlling factors in the marketplace, including health-care insurance and reimbursement. In the post-blockbuster-drug era and with the greater emergence of personalized medicine, the drivers described appear to favor the application of end-to-end approaches, and the aging of large-batch infrastructure likely will provide further incentives to use end-to-end manufacturing systems.

End-to-end systems are enabling some highly innovative and relevant approaches to drug manufacturing described later in this chapter, including modular and distributed manufacturing. Elements common to those systems include continuous flow and implementation of advanced assay methods, data analytics, and process controls that can reduce or eliminate conventional in-process testing.

MODULAR SYSTEMS

System Description

Modular systems are composed of interconnected unit-operation "modules" that are often in a fully closed end-to-end system. The component modules can be arranged and adapted to enable a single facility to manufacture a large array of drugs and biologics (Rogers et al. 2020). The approach is in marked contrast with standard facility designs and manufacturing operations that tend to be "fit for purpose" to produce large batches of a single product or class of products and are not as easily adapted to changing requirements in manufacturing breadth and scale.

Modular approaches are emerging primarily in small-molecule manufacturing. Small-molecule production facilities can be designed in such a way that each module occupies a predictable space and has defined inputs from and outputs to other modules. Processes can then be developed and adapted by using existing modules within the facility with greatly reduced need for design of unique hardware and processes. Because new processes are based largely on existing modules, facilities can be more easily reconfigured, and new manufacturing campaigns started more rapidly. Such newfound agility supports production scales that enable precision and personalized medicine, reconfigurable facilities that are responsive to surge requirements, and even distributed manufacturing concepts.

In large-molecule manufacturing, production is often based on unit-operation modules. The reuse of modules (such as chromatography and tangential flow-filtration units) is well accepted, and process development is often geared toward use of broadly applicable technologies. Single-use systems have greatly increased the ability to turn over unit operations rapidly in an agile facility format, and there is an increasing push toward fully closed systems and continuous-manufacturing approaches facilitated by modular operations. The use of fully closed systems of modules has important implications for in-process testing and design of control systems in complex biologics manufacturing campaigns.

Drivers of Development

The introduction of modularity into manufacturing systems has been driven by the desire to reduce drug costs, address drug-shortages, and provide increased manufacturing flexibility for multiproduct-facility concepts. Modular systems might reduce or eliminate the separation of drug-substance and final drug-product manufacture. In addition to reducing the manufacturing-facility capital

costs and the timeline to facility availability, the use of standardized unit operations throughout a product portfolio can reduce equipment lead time and process development time and can improve process predictability and quality. Such adaptable systems might enable deployment at the point of care in some cases and potentially meet the needs of personalized-medicine approaches more cost-effectively. The use of standardized modules might also simplify technology transfer of processes by enabling addition of manufacturing trains or sites and a more streamlined process to demonstrate site equivalence. Regulatory familiarity with specific modular approaches has the potential to streamline regulatory approval, as discussed below.

Applications

In both small- and large-molecule production systems, modular approaches potentially can enable rapid changes in manufacturing processes to accommodate a wide array of products and increase production by duplicating identical module trains. Such approaches, when combined with continuous-production methods, can decrease the manufacturing footprint to far less than that of a typical pharmaceutical-manufacturing facility. In addition to the potential to increase efficiency and throughput in traditional facilities, a set of potential uses emerges wherein the modular facility has a small footprint (for example, shipping-container size) and is capable of fully end-to-end production. That capability could be used to serve remote locations and underserved parts of the world or as part of a disaster response to provide an array of critical drugs until normal supply chains can be re-established. The ability to produce a wide array of products could have important national-security implications by enabling an "on-demand" nationally distributed production capability for critical drugs in short supply and enabling increased domestic capabilities for drug manufacture.

The ability to reconfigure module-based processes rapidly could enable a more efficient means of addressing rare diseases and precision and personalized medicine (Siiskonen et al. 2020). In such cases when only a few doses are needed, modular manufacturing units might emerge as a routine modality up to and including highly portable modular systems, as described in the following section. It is important to note that the use of modular systems, even within a facility compliant with current good manufacturing practices (cGMP) and especially for the unique applications described here has substantial quality and regulatory implications, which are discussed in detail below.

HIGHLY PORTABLE SYSTEMS

System Description

Highly portable systems are composed of interconnected unit-operation modules, often in a fully closed end-to-end system, that are packaged in the smallest footprint possible to enable portability. Being extremely small is what sets highly portable systems apart from the modular systems described above. They have designs that typically compress all operations into a single box that can fit on the back of a truck (in the near term) or in a suitcase (in the midterm). A key facet of small, portable systems is their enabling chemical reactions that occur as reactants flow through relatively small tubes and chambers; this is in stark contrast with the large vats that are used to carry out most large-scale drug production. These miniaturized versions, like the larger modular systems, maintain a degree of process flexibility by swapping in different module components. That flexibility theoretically enables them to be reconfigured so that a single system can be used to produce multiple drugs or biologics with turnover time reduced to only a few hours. The portability and relative simplicity of these small-scale systems creates unique opportunities for automated production that requires little human oversight. There is a potential for decentralized and even point-of-care production that can be deployed on time scales that are not currently possible and to regions of the world that lack sufficient drug-manufacturing capabilities.

Highly portable systems are emerging in both small- and large-molecule manufacturing. Portable systems for small-molecule production are based on continuous-flow synthesis, a strategy that exploits microfluidics, that is, involves pumping reagents through a series of microchamber modules that are interconnected by thin, flexible tubes. The result is an uninterrupted assembly line of chemical reactions and processes required to synthesize and then purify a drug. Although they are small, such systems can handle reaction conditions of up to 250°C and pressures reaching 17 atmospheres. Incorporation of various in-line sensors enables process monitoring and analytic testing of the product, and the resulting data can be used in process-control strategies to maintain optimal conditions within different microchambers by altering reaction conditions and reagent loading. The systems are still largely in development in academic laboratories and industry but are demonstrating substantial promise in breadth of capabilities and product quality. For example, continuous end-to-end synthesis has been achieved in a refrigerator-size (about 1.25-m^3) unit that yielded sufficient quantities of diphenhydramine hydrochloride, lidocaine hydrochloride, diazepam, and fluoxetine hydrochloride per day to supply hundreds to thousands of oral or topical liquid doses that conformed to *U.S. Pharmacopeia* standards (Adamo et al. 2016). More recently, smaller systems (about 0.5 m^3) that can manufacture final oral solid doses as tablets from drug substances have been reported (Azad et al. 2018; Zhang et al. 2018). The portable, flexible, and modular nature of these emerging systems have wide applicability for drug manufacturing, as discussed in greater detail below.

In large-molecule manufacturing, portable production can also be achieved by using small-footprint manufacturing systems that comprise modular unit operations that include a biosynthesis module for producing the biologic, a purification module for separating the protein drug from the producing host cell and host-cell proteins by using chromatography, and a formulation module for suspending the purified protein drug in a buffer that preserves it until it is administered to a patient. Although the overall operating principles are similar to those described above for portable manufacturing of small molecules, the biosynthesis module constitutes a key differentiator and is one of the most challenging components to develop. In systems that have been described to date, this module has consisted of either living yeast cells (for example, *Pichia pastoris)* that can be engineered to secrete large amounts human-like proteins or cell-free extracts from reconstituted lyophilized Chinese hamster ovary (CHO) cells, which are shelf-stable for up to 2 years and thus have advantages over systems based on even fast-growing cells like yeast (Adiga et al. 2018; Crowell et al. 2018). Future systems are likely to explore alternative expression hosts or cell-free extracts as discussed below. It is important to note that portable systems described to date are remarkably small, fitting on a benchtop or in a suitcase, and can produce various clinical-quality recombinant therapeutic proteins in a liquid dosage form by using integrated production, purification, and formulation in a single control architecture.

Drivers of Development

The drivers of the development of highly portable manufacturing systems are largely independent of the financial drivers typical of pharmaceutical manufacturing. The drivers center on provision of drugs or biologics to populations that would otherwise be unable to acquire them because of cost, logistics, or specificity of the drug. Many of the drivers would be expected to originate in government agencies or philanthropic groups and to include the manufacture of critical drugs in austere environments and in response to humanitarian crises. More in line with typical financial drivers are the needs for emerging precision and personalized medicine, which might require dose-tailored, patient-specific, or rare-disease–specific batches of a drug. In addition, because many drugs could be produced on demand at the point of care, highly portable systems could eliminate the need for centralized manufacturing and long-term storage and thereby address many of the supply-chain challenges in the United States and around the world, especially in regions that lack large-scale drug-manufacturing and storage facilities. Small-batch portable manufacturing could also bring down production costs and improve patient access to drugs whenever and wherever they are needed.

Applications

The potential applications of highly portable manufacturing systems are aligned with the drivers of their development and include the following:

- The manufacture of small amounts of drugs that are prohibitively expensive to produce in large-scale plants, such as "orphan drugs" that are needed by few patients or precision and personalized medicines that are tailored to the genetic or molecular profiles of specific patient populations.
- Response to drug shortages or surges in demand for specific drugs with speed and logistical flexibility.
- The supply of medicines to austere environments, such as developing countries or battlefields in remote locations.
- The supply of much-needed drugs to people affected by disease outbreaks, natural or man-made disasters, or wars.

Many of the applications are shared with larger, deployable modular systems, but the highly portable systems can enable rapidly deployable and highly specific applications that stem from the ability to deliver medicine at point-of-care settings, including a patient's bedside, a doctor's office, a local pharmacy, a battlefield, a disaster area, underserved parts of the world, and remote locations. As with modular systems, highly portable systems introduce a host of quality and regulatory implications and challenges, which are discussed in detail below.

KEY TECHNICAL CHALLENGES FOR INNOVATIONS

Most key technical challenges in integrated, flexible, and distributed manufacturing networks are broadly applicable to end-to-end, modular, and highly portable systems. There are three main types of challenges: (1) process challenges are specific technologic challenges in manufacturing that could have substantial effects on the future adoption of the technologies, (2) assay challenges concern the specific methods that enable these manufacturing concepts, and (3) control challenges are critical for all the manufacturing approaches, but most critical for highly portable systems.

Process Challenges

Precursor and Supply Chain

A critical consideration for all the manufacturing processes, but especially those in systems intended for deployment outside a standard cGMP facility environment, is the supply chain of raw materials, including drug-substance precursors, media and buffer components, assay reagents, lyophilized cells, and DNA plasmids. The development of a manageable and robust logistical supply chain and the ability to track, test, and ensure the quality of the supplies can present a highly complex set of problems, especially in deployable systems. Although logistical concerns are outside the scope of this report, critical issues regarding quality aspects of the supply chain remain. Typical inbound material in a cGMP facility will undergo a specific set of tests that include validated methods to prove the identity and purity of the material. Additional measures might be needed to ensure the stability of the precursor if it is labile and the environmental conditions to which it is exposed as it progresses through the stages of the supply chain are not well controlled. As these novel manufacturing approaches become further separated from a typical cGMP environment, challenges regarding supply-chain quality assessment will increase, and innovative methods might be required to ensure the quality and acceptability of inbound raw materials and supplies to enable the use of these systems.

Expression Systems for Biologics

As noted earlier, implementation of end-to-end systems in biologics production is less mature than in small-molecule production largely because of the complexity and longer duration of upstream biologics production that can cause a mismatch between upstream production and downstream purification throughputs (IAVI 2020). Continuous upstream processes are in development but are not widely used in a fully end-to-end manufacturing approach. The most common cell line for biologics production that is relevant to CDER is the mammalian CHO line. CHO cells have become the preferred host for making complex protein products, such as monoclonal antibodies because they are known to express production-relevant quantities of fully functional proteins into the culture supernatant, and this simplifies downstream purification. CHO-produced proteins are expressed with human-like post-translational modifications, in particular disulfide bond formation and glycosylation patterns, and thus are generally well tolerated by humans. Because CHO cells require long production times and have high material costs, much activity is focused on the development of alternative hosts and expression systems that might be more adaptable to end-to-end biologics production (IAVI 2020). See Chapter 2 for a more detailed discussion.

Low Production Volumes

As discussed above, one primary driver for the efficiencies in modular and deployable systems is the ability to manufacture small lots of drugs targeted specifically to small populations and potentially even to individuals. During normal production, drug-substance and drug-product doses are retained both for quality assessment and for ongoing stability programs. Although the number of doses retained is relatively minor in comparison with normal full-scale production lots, as lot size decreases, these standard approaches could result in a situation in which the amount of retained material exceeds the material intended for patient use. The full implementation of the small production runs enabled by modular and deployable systems depends on development of innovative approaches to assessment of product quality and stability that match the lot size and intended product use. The technical approaches to process control and in-line testing described primarily in Chapter 4 might be effective in decreasing the amount of material needed for quality assessment to address this challenge.

Highly Complex Molecules

The use of end-to-end and modular systems has the theoretical benefit of being able to be reconfigured to produce many drugs. Drugs that have simple structures might be amenable to production with a standardized set of production modules. Similarly, the ability of a set of modules to produce one member of a class of drug increases the probability that other drugs in the class will be producible. Increased drug complexity might increase the need for unique modules or require drug-substance precursors that are more difficult to source. That need or requirement presents a big challenge when the systems are deployed to more austere environments. Development of manufacturing processes that rely less on complex precursors or unique processes is therefore a key technical challenge for the full realization of these systems, particularly highly portable systems.

Assay Challenges

The use of integrated, flexible, and distributed manufacturing systems will depend largely on the ability to maintain quality and prove that it is acceptable and equivalent to that of existing processes. The complexity and quality risk associated with an innovative manufacturing process might depend on the degree to which it differs from accepted or licensed processes. When an end-to-end process aligns closely with established processes, adaptation of existing assay methods to end-to-end systems might be relatively straightforward. As the process is increasingly innovative with respect to unit operations and

continuous processing, opportunities to leverage standard assays might decrease, and innovative methods and use of models might be needed to monitor product quality throughout the process. An extreme example is a highly portable system in which all in-process testing, process control, and release testing are necessarily embedded within the system and requires extreme robustness and validation.

Challenges can also occur in the manufacture of increasingly novel drugs. Systems might be designed to manufacture drugs that have been approved and have critical quality attributes and metrics that are well known and accepted. In such a case, it should be possible to adapt assays to measure the known attributes and thus simplify quality assessment. As a product is increasingly specialized—for example, as required for precision medicine—the ability to use standardized assays decreases, and specific quality attributes might require innovative assessment approaches. The full realization of the agility of end-to-end and modular manufacturing processes is based not only on the increased capabilities of the manufacturing processes but on the ability to assess product quality during and after production in a way that matches the efficiencies of traditional manufacturing.

Chapter 4 describes the use of novel in-line sensing approaches to monitor many process variables to assess quality attributes. In-line sensors allow in situ measurements, eliminate sampling preparation, and enable real-time monitoring. The challenge in implementation of the current sensors is that they are more expensive and less rugged than traditional sensors and require labor-intensive and sophisticated calibration. All those factors are at odds with more agile and flexible manufacturing approaches defined in this chapter. The expansion of large-scale data analytics, including machine learning, to support process validation throughout the entire manufacturing process has the potential to reduce final product testing in the next 5–10 years and is seen as a key enabler of the systems described in this chapter.

Control Challenges

Process Controls for End-to-End Systems

One of the technical challenges associated with module-based and end-to-end systems is the potential complexity of process controls. Models designed for standard process controls theoretically can be applied to end-to-end systems, including flowsheet models that describe the integration and interaction of processes within the manufacturing system. It is important to note that end-to-end systems are not necessarily synonymous with fully continuous processing. In fact, hybrid approaches that use both batch and continuous processes can have important control advantages, although it is important to reduce complexity by minimizing the number of transitions between batch and continuous processes. The advantages stem from the fact that control instabilities that might be difficult to manage in a fully continuous process can be corrected at batch processing steps. A full discussion of control strategies in hybrid end-to-end processes was presented in Chapter 4.

Software and Hardware Development and Integration

Addressing control challenges in integrated, flexible, and distributed manufacturing processes will require innovations in software and hardware. According to the workshop on advanced manufacturing technologies held at the International Conference on Accelerating Biopharmaceutical Development in 2019 (Lee and Mantle 2020), improved automation and robotics could be a factor in realizing the vision of rapid and flexible manufacturing of biopharmaceuticals. During that workshop, robotics was touted as a key enabling technology to improve compliance with quality and safety standards. As discussed in Chapter 4, the adaptive plant in the digital-plant maturity model supports multiple manufacturing modes, such as modular and continuous; however, there is substantial reliance on automation and information-technology support.

The digital twin is another enabling technology for integrated, flexible, and distributed manufacturing processes. Using digital-twin technology increases flexibility of manufacturing by allowing virtual modifications of manufacturing configurations and testing of all processes before the

optimal configuration is determined. Combining the digital twin with real-time data and data-processing allows tracking of health indicators and detection and diagnosis of faults. That approach leads to greater resiliency in end-to-end systems. Digital-twin technology, however, relies on large-scale data collection and data integrity. Chapter 4 provides more information on how digital-twin technology can address control challenges in integrated systems.

Designing control strategies for highly adaptable and reconfigurable modular systems is complex. The modularity of the manufacturing process lends itself to modular software design, implementation, and testing, and that is consistent with modern software engineering that relies on modular design to facilitate implementation and testing.[2] Standardization of software and hardware interfaces allows greater interoperability without the need to redesign or reimplement solutions. Futran (2020) stated that modular design of software and hardware and standardization of their interfaces enable transition to a high-throughput line, if needed, and provide an approach to lowering costs by enabling lower production when high throughput is unnecessary. Although extensible software solutions are more expensive in the original implementation and testing of a single product, the incremental cost of adding new products can be reduced, and the overall quality is improved (Bockle et al. 2004).

The testing of well-designed modular software is widespread in many industries. Risk-based methods and testing at various levels of integration of the software and hardware can be used.[3] The committee recommends that regulators become knowledgeable about these methods so that they can assess the level of rigor that should be and is used for various systems.

Safety and Security

The high degree of automation that is required especially as systems progress from modular to portable will require not only highly innovative control approaches but unprecedented levels of safety and security built into the hardware and software. Control technologies that can trigger actions in real time and without human intervention require robust failure detection and fault tolerance. As manufacturing moves toward the adaptive plant, automation progresses from predominantly manual processing to predictive behavior to adaptive behavior in which controls adapt on the basis of detected states. Such advancement requires increased reliance on sensors and modeling. The PAT initiative encourages the use of that type of technology to increase innovation through the phases of development, manufacturing, and quality assurance of pharmaceuticals within the scope of current regulations. Nonetheless, there is a need to identify where current regulations need to be updated to handle the level of automation that is being explored with integrated, flexible, and distributed manufacturing networks.

Data, multivariate data acquisition, and analytic tools are crucial in the design, analysis, and control of manufacturing processes. Speakers at the committee's workshops discussed the potential to incorporate data lakes (centralized data repositories) to advance data analytics (NASEM 2020a,b). Unlike traditional data-warehousing approaches, data lakes allow capture of data from multiple sources and storing of data that are not yet completely understood. The data-lake approach makes it possible to advance analytics without the need to rerun processes to capture and store data that were not previously understood or known to be useful. It also makes it possible to find new behavior in the manufacturing process, such as correlations of conditions with faults, that might not have been expected. The reliance on data, however, requires advanced security measures to ensure that the data have not been compromised. At the committee's first workshop, the ability both to trust the data and to act on them were identified as barriers to leveraging of process data (NASEM 2020a). Stored data can lose their credibility in many ways, such as hardware faults and malicious behavior. Hardware faults can include sensor faults, in which data collected are invalid or a data-storage device becomes corrupted. The Pharma 4.0 Special Interest Group aims to address those issues.[4]

[2] See http://aosd.net/importance-of-modularity-in-programming/.
[3] See https://www.atlassian.com/continuous-delivery/software-testing/types-of-software-testing.
[4] See https://ispe.org/initiatives/pharma-4.0#.

KEY REGULATORY CHALLENGES TO INNOVATIONS

Regulatory approval focuses primarily on the product, but the associated innovative approaches to manufacturing also must be approved. Although standard end-to-end approaches might not face substantial challenge or disincentive, the regulatory challenges to modular systems that reuse modules and systems that are deployed in mobile cGMP environments are far greater. The most innovative manufacturing systems are portable ones that operate outside typical cGMP controls with minimal operator oversight and full on-board drug-release capability. Those systems encounter several obvious regulatory challenges, but they are becoming mature and robust enough to push the regulatory envelope within 5–10 years. The challenges described below include overarching challenges and more specific ones related to the definition of a manufacturing facility and approaches to quality management.

Challenges in the Regulatory Approach

The regulatory framework is based on approval of individual products, so there is no way to evaluate a manufacturing approach outside that framework, and this presents substantial problems in transitioning manufacturing processes to innovative systems. It is particularly evident when viewed from a product-specific perspective. Retroactively developing processes to enable marketed drugs to transition to new systems would likely be financially untenable. In the current regulatory system, if a pharmaceutical company wanted to manufacture a set of critical drugs, for example, in a highly portable system, each drug would need to be approved separately for manufacturing in that system. That burden creates a situation in which modular and portable systems—which are designed for broad applicability and agile changeover—are difficult to implement to their full potential. That regulatory hurdle exists for approved products, which would require further regulatory approval to enable manufacture in a new system, and for new products that are not yet approved. The product-centric approach to regulatory approval, although justified and necessary, can present important impediments to the maximal use of end-to-end, modular, and highly portable systems because neither the process, a component module, nor the portable system has a mechanism by which it can be approved outside the product approval process.

Challenges in Defining a Manufacturing Facility

The FDA approach to licensing manufacturing facilities is well understood by industry and follows cGMP guidelines that provide predictable requirements (for example, for process-performance qualification runs and preapproval inspections) for products that are in the approval process. The use of modular systems, for example, to duplicate a process in a separate facility would typically require that facility also to be licensed, so there is no defined mechanism by which the modular approach offers a regulatory advantage. Facility definition becomes more difficult if a facility is contained within a transportable POD that can be relocated, and more difficult still is the highly portable system in which the "facility" is a suitcase. Potential use of the systems internationally adds yet another layer of complexity. To enable implementation, an innovative and flexible regulatory approach will need to take into account unique quality-management approaches and facility definitions. Some examples of questions about this type of system are provided below; the list is not exhaustive, nor does it reflect the full complexity of implementation and regulatory acceptance of these systems.

- How are facilities that do not have a physical address regulated?
- Can processes within identical modular facilities be duplicated efficiently to support surge manufacturing?
- How will in-process and release testing be handled without a standard onsite quality-control and quality-assurance unit?

- How will data be managed in this new manufacturing-facility construct? How will data be collected and shared? How well connected do the facilities need to be? How will data be protected?
- How does an event in one area of a distributed manufacturing network affect the rest of the network? How are control systems integrated?

The committee concludes that the full implementation of these systems will not occur without easing the regulatory burden and a proactive approach by FDA to enable their use.

Challenges Related to Quality Management

Closely related to defining a manufacturing facility are potential differences in the standard expected cGMP infrastructure and quality systems. The differences are most apparent in the case of a highly portable system; there are questions as to whether the system is equipment or is itself a manufacturing facility. However, all modular and end-to-end processes deviate to some degree from standard cGMP processes. Any of the differences can present a substantial regulatory hurdle to be overcome, but when a given system has multiple differences, the regulatory challenges can pose an insurmountable challenge for timely and cost-effective drug approvals and manufacture. Several examples are provided in Table 5-1. If there is a requirement to address each difference in a manner that proves at least equivalence to accepted processes, that requirement could present a substantial financial and time burden. The committee finds that adoption of increasingly innovative manufacturing technologies will require equally innovative regulatory approaches.

OVERCOMING REGULATORY CHALLENGES

Guidance

One mechanism that facilitates adoption of novel approaches is the publication of FDA guidance documents. They provide a framework for an approach to implementation and are authoritative descriptions of FDA's expectations. The innovative approaches described in this chapter constitute a gradation of innovation from end-to-end manufacturing in the context of cGMP facilities to reconfigurable manufacturing modules that enable repeatable processes and agile changeover to highly portable systems that at first glance are antithetical to accepted cGMP approaches. Thus, there will likely need to be a graded approach to guidance documents as each approach matures and is implemented. FDA draft guidance—such as "Advancement of Emerging Technology to Modernize the Pharmaceutical Manufacturing Base" and "Quality Considerations for Continuous Manufacturing"—and the still-in-development ICH Q13 "Continuous Manufacturing of Drug Substances and Drug Products" can serve as examples. Those documents illustrate the type of industry guidance needed to provide a framework of process definitions and quality-related strategies to help to advance innovative approaches through regulatory acceptance in the United States and internationally.

For end-to-end manufacturing, the primary regulatory guidance will need to describe approaches to quality for systems that do not have typical in-process and release testing and that might have specialized, highly advanced control systems that are based on innovative in-line testing methods. The typical differentiation between drug substance and final drug product might also present regulatory challenges in end-to-end systems, in which process intermediates are not as easily defined. The ultimate realization of a fully automated end-to-end process is the ability to rely on control using well-defined process parameters to enable immediate product release.

TABLE 5-1 Examples of Questions Related to Product Quality for Innovative Manufacturing Formats

Topic	Example Questions
Manufacturing environment	• Are cGMP-compliant environmental conditions relevant in fully closed end-to-end systems? • How can cGMP environmental compliance be maintained, or even sampled, in highly portable systems? • Are there unique operator qualifications, especially in highly automated systems?
System portability	• Will a deployable process (for example, one that can be moved to another location within a manufacturing POD or truck) require full installation and operational qualification of all systems at each redeployment? • Will facility inspections be required after each redeployment? • How will process repeatability be assessed when the system's address changes or when identical systems are used for the same production process?
Oversight of quality assurance and quality control	• How will in-process testing be viewed in fully end-to-end systems? • How are drug substance and product-quality assessments handled in a fully end-to-end process, especially a fully closed process? Is the lack of a drug-substance stability program an issue? • Can product release be based on analysis of quality throughout the process? • How will release of parenteral dosage forms be managed in highly portable systems? • Will full supportive product data or a subset (such as stability or bioequivalence data) be required for replicated portable modules? What would be the data requirements for a network of identical systems?
Low production volumes	• How will lots be defined if only a few doses are produced at a time? How will lots be defined in fully end-to-end or continuous systems? • How will analytic standards be defined in systems that produce low volumes of special products and dosage forms, for example, in personalized medicine? • Are there acceptable approaches to enable nondestructive release testing for low-volume production runs? • What is the acceptable approach to stability in low-volume production runs?

The next level of complexity comes with the introduction of reconfigurable modules. The full implementation of a modular system is expected to involve module-based unit operations in a number of manufacturing processes and for various product lines. Modular approaches will be most effective and create the greatest efficiencies when manufacturers can be assured that there is a regulatory advantage to using particular modules—that is, a decreased scrutiny of the module-based manufacturing process. That regulatory accommodation is predicated on a degree of consistency within the modules that can be defined in guidance documents and that still enable the desired system configurability and agility.

The most ambitious approach is to divorce production from a classical cGMP environment and support structure. Although that is clearly applicable to more standard cGMP systems contained in a portable cleanroom, the concept is best exemplified in fully portable systems that make only a few doses.

The utility of those systems will likely depend on their ability to produce a moderately sized set of desired drugs. At the moment, that would mean that each drug would need to be approved for manufacture in that specialized system. Apart from the monumental task of maintaining and proving product quality in the systems, the financial and regulatory burden of enabling each manufacturable drug makes implementation difficult to envision. In addition, proving the reliability of what would almost necessarily be a fully automated control system presents its own regulatory challenges and costs. There is a need for a highly innovative regulatory approach that could enable manufacture and release of a drug on the basis of nonstandard in-line quality checks and release tests, probably with few onboard process controls. Almost by definition, that would require substantial relief from standard regulatory requirements and a rethinking of approaches to measure product quality. Guidance on adoption of innovative quality-assessment approaches could facilitate implementation by removing some degree of regulatory risk.

Regulatory Science and Agency Involvement in Phased Approaches

Although guidance documents described above could greatly facilitate implementation of novel manufacturing technologies, it is clear that direct FDA involvement with implementation could provide important advantages and accelerate the use of innovative systems. For example, FDA has been involved with companies that have developed continuous processes and modular approaches. That interaction between companies and regulators has proved to be powerful and has in some cases facilitated adoption of technologies. The highly innovative technologies and approaches envisioned in this chapter will likely not advance, or at best will not advance quickly, in the absence of a major shift in drivers or incentives or without direct participation by FDA in their development and maturation.

The FDA Emerging Technology Team is an important mechanism for the agency to understand what is on the horizon; however, advances in regulatory science could be greatly accelerated by an increased emphasis on hands-on research and testing by FDA. For example, development of a useful approach to regulation of modules could be accelerated if FDA scientists actually used the modules, aided in their development, and formulated guidance rather than waiting for a regulatory filing and only then providing expectations. Innovative regulatory approaches to decrease or eliminate subsets of cGMP controls could benefit from hands-on analysis of early systems by FDA, with evaluation and early guidance for developers independently of product-specific filing. FDA could also assist in outlining phased approaches to implementation of advanced manufacturing systems. For example, the first implementation of a highly portable system could occur in a cGMP facility that has the appropriate facility and quality support structures. FDA could then work closely with developers to outline an acceptable path to maintain product quality control and assurance outside the normal cGMP environment and provide a set of acceptable success criteria for continuing development and a path toward implementation. The fundamental recommendation is that FDA needs to be an active participant in removing barriers to innovative approaches. In some cases, given the drivers described in this chapter, the costs to private industry might be too high, despite the benefits that could eventually be realized by their implementation.

A related mechanism that FDA could leverage to accomplish hands-on research on and testing of new technology is the creation of specific testing laboratories that are designed to facilitate collaboration between the developers of novel manufacturing systems, the end users of the systems, and FDA. Such collaboration could produce use cases, systems to implement the use cases, and FDA regulation best practices or modifications to accelerate the process of technology transfer. That approach could lead to a pragmatic reduction in regulatory barriers or perceived barriers. The start-up cost of the partnership would be high, but all parties would benefit from it. End users of the manufacturing systems (the pharmaceutical companies) would have a large incentive because they would be influencing system development and receiving direct feedback from FDA that will help them bring their products to market. The approach has proved effective in the co-design of high-performance computing systems for the Department of Energy (DOE); small proxies for large-application software are used to allow hardware vendors and application developers to make many iterations before the product is delivered, and this makes final acceptance of the

whole product much more efficient.[5] It allows all parties to become more agile and flexible through the entire process of deploying innovative technology. In the context of this report, pharmaceutical companies can provide use cases that represent the core characteristics of their overall processes, similar to proxy applications, and the developers of the technology can apply their solutions to the specific use cases. FDA can use the approach to foresee innovations, understand how current regulations apply to them, and use its knowledge of the technology to evolve regulations to meet the needs of future technologies.

For the distant future of manufacturing innovation, the committee recommends strong collaboration with developers of novel manufacturing systems, end users of manufacturing systems, and academia. The committee recognizes that, as systems become more continuous and rely on sensors, data analytics, and automation, the breadth of expertise in the workforce greatly expands. Working with academia and with public-private partnerships, such as NIIMBL, to develop multidisciplinary programs that are forward-looking can help to address future workforce shortfalls, address long-term research issues, and create a pipeline for future innovation. The committee recommends evaluating the Predictive Science Academic Alliance Program[6] in DOE as an example. That program supports multi-institution centers to address key research areas and provides opportunities for students to work directly with DOE laboratory personnel.

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[5] Proxy software is a simpler version of the full software. Small proxy applications allow application developers to incorporate new technologies and evaluate the complexity and the benefits of the technology in their applications quickly. Similarly, the hardware vendors can use proxy applications to improve understanding of the use cases and requirements of their technologies.

[6] See https://psaap.llnl.gov.

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6

Advancing Innovation: Observations, Challenges, Opportunities, and Recommendations

The committee received input from a number of experts and stakeholders, many of whom have been advocates, champions, and practitioners of innovative technologies and who have direct experience in the business, scientific, technical, and regulatory factors that affect the rate of progress in the field. A concern commonly expressed was that the agility, robustness, and overall industrial maturity of pharmaceutical manufacturing need attention and investment to guard against the many potential vulnerabilities that could threaten access to products essential to public health. In addition, there is a strong consensus that advanced manufacturing technologies can and must play a central role in moving toward a successful future for the global supply chain.

What became evident to the committee in conducting its analysis is that many stakeholders have a role to play and can influence the outcome of this endeavor. The members of the public who benefit greatly from pharmaceutical products are the ultimate stakeholders and depend heavily on industry and regulators to enable and protect the future availability of high-quality medicines. However, reflecting on the various parties and the overall system responsible for delivering this important value to the public, the committee concludes that no single organization or entity—however well-financed, large, powerful, or influential—has either the capability or a mandate to lead the broader community to this future state on its own.

Historically, the pace of improvement arguably has suffered at the whole-system level because of fundamental structural barriers and because of the roles and incentives of the various key participants in the pharmaceutical-manufacturing ecosystem. In particular, the predominant drivers of value for the industry and the public are the pharmaceutical products themselves—not the technologies deployed to manufacture them. That reality has important implications both for industrial developers and manufacturers of products and for regulatory authorities reviewing and overseeing them. Thus, neither pharmaceutical companies nor regulatory agencies are able to take a fully strategic, system-focused approach to the implementation of advanced manufacturing technology. Even if each organization acts responsibly and effectively within the expectations, motivations, and incentives of its own mandate, there is no concerted driving force or "invisible hand" that is guiding the system toward an overall desirable end point. A substantive change in the relationship and collective leadership among entities most able to achieve the outcome will be required. The committee concludes that the Food and Drug Administration (FDA), as a critical participant and node of influence, can and should play a direct leadership role. FDA also needs to support the ability and willingness of manufacturers to lead and drive innovative change.

It is noteworthy that in the case of the COVID-19 pandemic, the incentives of industry, regulators, and society were strongly aligned. FDA was seen from the committee's perspective as playing a co-leadership role in enabling the rapid advancement of vaccines and therapeutics, including innovative manufacturing technologies. That case provides a clear example of the power of FDA leadership and suggests an important opportunity if it were effectively applied more generally to pharmaceutical manufacturing.

In this chapter, the committee first provides some examples of key innovations likely to be implemented in the next 5–10 years that will be particularly important for both manufacturers and regulators. The discussion is not intended to be a comprehensive summary of innovations covered in Chapters 2–5. Rather, it highlights the importance and opportunity of pharmaceutical-manufacturing

innovation and underscores the associated challenges in achieving the desired future state. The committee then discusses the implications of technology review that is confined to product applications, incentives, and disincentives that have affected innovation in pharmaceutical manufacturing and the role that FDA could play in advancing innovation. The chapter concludes with the committee's overarching recommendations. The committee emphasizes that its task was to focus on the role of FDA in preparing for and facilitating innovation to reach this future state. Accordingly, this report does not make recommendations to other stakeholders in the pharmaceutical ecosystem, but the committee acknowledges the critical need for them to undertake actions in support of shared goals.

KEY MANUFACURING INNOVATIONS

In this report, the committee has described many innovations for manufacturing drug substances and drug products, to advance new control approaches, and to develop integrated, flexible, and distributed manufacturing networks. The committee is impressed by the wealth of innovative technology in development and the great opportunity for such innovation to benefit all stakeholders, provided that appropriate incentives can be aligned between business and regulatory priorities. This concluding chapter of the report highlights a subset of the innovations discussed more fully in Chapters 2–5. The technologies discussed here are ones that offer the most probable and extensive opportunities to advance pharmaceutical manufacturing within 5–10 years. It should be noted that the committee has deliberately represented many of these innovations by classes rather than individual technologies; it is likely that a diversity of novel technology within a class will be implemented on similar timelines.

New Routes to Produce Drug Substances

As discussed in Chapter 2, innovations in manufacturing technology used to synthesize active pharmaceutical ingredients (APIs) or drug substances are advancing toward implementation. For small- and large-molecule pharmaceuticals, photochemistry, electrochemistry, biocatalysis, cell-free protein synthesis, and cell-based biosynthesis that uses alternative hosts are all gaining traction and likely to be implemented in the next decade. Those technologies are motivated by a combination of process- and product-related needs, including improvements in process efficiency, speed, cost, throughput, safety and environmental sustainability. They also can improve the assurance of product quality by reducing the risk of side-product formation or other undesired variants. These novel synthetic approaches are also driven by product innovations, including higher-complexity small molecules, engineered biomolecules that are difficult to produce in traditional cell-based processes, and such emerging modalities as oligonucleotide and RNA-based therapies.

The implementation of a broad suite of new methods of drug synthesis should not require a fundamental shift in the regulatory system associated with their manufacture. However, the breadth and scope of the products and processes that are contemplated will likely place substantial additional demands on FDA with respect to the volume and complexity of product review. Novel processes and new impurities will likely involve much learning on the part of both industry and regulators: uncertainties will abound, unexpected control issues will arise, and challenges in setting manufacturing ranges and specifications will need to be addressed and overcome.

Co-Processed Active Pharmaceutical Ingredients

As discussed in Chapter 2, innovations in API manufacture might include substantive changes in the traditional boundary between API and drug-product formulation operations. Addition of nonactive excipients or carriers during production of drug substances offers the potential to improve yields and manipulate attributes of a process stream to achieve a desired outcome. Co-processed APIs might be advantageous, for example, in particle formation, crystallization, or drying operations to improve stability of a desired solid state or to tailor physical properties of the APIs.

The regulatory challenge presented by a co-processed API is related to regulatory definitions and has important implications for how the expiry date is determined for such products. Defining a co-processed API as a drug-product intermediate—rather than a drug substance—could have the effect of setting the start of the stability dating period further upstream before a drug product itself is manufactured. That action could lead to the drug product entering the supply chain with an earlier expiry date and thus reduce overall supply-chain agility and robustness.

Process Intensification

As discussed in Chapter 2, process intensification can be achieved through technology-driven changes in manufacturing process flow, thereby increasing performance and efficiency. Expected innovations include the integration or reduction of multiple traditional unit operations (including solution preparation), the replacement of batch processes with continuous formats, and the incorporation of recirculation and recycle approaches. Those innovations are likely to afford a number of improvements that are also foundational in the development of modular systems and flexible, distributed manufacturing networks (discussed in Chapter 5; see also below). Specifically, substantial reductions in the number of unit operations, equipment size, solution volumes, in-process hold requirements, raw-material use, and waste generation can be achieved. More efficient, higher-yielding processes enable smaller manufacturing footprints and reduced capital and operating costs. For pharmaceutical manufacturers, those improvements will help to overcome some of the most difficult impediments in supply-chain investment and decision-making and make it more feasible to create redundant and surge capacity and thus improve overall capability and security of pharmaceutical supply.

To realize the potential benefits of process intensification, it will be critical to ensure that process control and assurance of product quality are not compromised. Rather than conducting oversight of a discrete set of unit operations, each with its own discrete set of performance and quality expectations, a more holistic demand is placed on an integrated, intensified system. Multiple mechanisms of achieving product-quality objectives might be used simultaneously rather than sequentially. Process intermediates and associated quality-control and quality-assurance data might be eliminated, and this would increase dependence on the sophistication and capability of process-control systems. The use of recirculation and recycle approaches might heighten the potential for process- and product-related impurities to accumulate or for backward propagation of out-of-specification materials, which would further challenge traditional batch definition and control paradigms.

Additive Manufacturing

As discussed in Chapter 3, additive manufacturing or product formation by three-dimensional (3-D) printing is a radical alternative for manufacture of pharmaceutical products in comparison with conventional tablet production. The most promising technologies include powder solidification, liquid solidification, and extrusion-based methods, all of which use precise layering of materials in a successive, specific pattern to arrive at the final dosage form. Those technologies also have the capability of tailoring desired characteristics of a drug product, for example, geometry, porosity, and API composition (including combinations of APIs and excipients) that can be custom-fitted for a specific indication or for individual patient requirements. And additive manufacturing enables monitoring and acceptance or rejection of a product at the individual-dose level and can be scaled down to compact size, potentially supporting highly distributed manufacturing.

To achieve broad implementation of 3-D printed pharmaceuticals, industry and regulators will need to address a number of challenges, including technical challenges that pertain to each method and the essential connection between the additive manufacturing process and the critical attributes of a product. Novel excipients might also be required. Proactive regulatory engagement and guidance will be important for guiding the broad category of additive manufacturing (regardless of variations in

technology) and specifically the topic of individualized dose production and whether this should be treated as drug compounding or manufacturing.

Advanced Process Control and Automation

As discussed in Chapter 4, important advances are being made in sensor technology, data analytics, and system modeling, and manufacturers will increasingly rely on these innovations to design, understand, and control complex processes. The combined characteristics of various off-line, at-line, and in-line sensors will create an unprecedented ability to measure process variables and product attributes. To use the enormous quantity and resolving power of such data effectively, sophisticated analytics, models, and artificial intelligence will be required to support advanced process-control strategies, continued process verification, and ultimately real-time process optimization and more automated operation and management of manufacturing.

The innovations will be critical for the future of pharmaceutical manufacturing. As innovative product modalities and technologies to manufacture drug substances (Chapter 2) and drug products (Chapter 3) emerge, there is an increased need to ensure process capability and product quality that must be addressed by advanced control strategies. The expected benefits of innovations in integrated, flexible, and distributed manufacturing networks (Chapter 5) will be extremely difficult to achieve through traditional quality-management systems that were built around large, centralized facilities and supply-chain networks. The ability to achieve consistency of operations and quality in smaller, more modularized operations will depend heavily on integrated advanced process control and automation.

The challenges for regulators and industry pertain to the complexity and sophistication of the technology itself and to the paradigm-changing integration of these capabilities into development and manufacturing. Because control strategy is so foundational, much care, expertise, and experience will be required to ensure that these innovations can deliver on the promise of improving quality assurance and process capability.

Modular Systems

As discussed in Chapter 5, modular systems that leverage innovations in drug-substance and drug-product manufacturing and technologic advances in process control and automation present an opportunity to reshape the very nature of manufacturing facilities and the global supply chain. Unit operations that have greatly reduced footprints can be more readily modularized and lead to a flexible and rapidly reconfigurable capability that can support manufacture of a large array of drugs and biologics. In some cases, fully end-to end manufacture—from input raw materials to finished drug product—might be accomplished with one or a few closely associated modules. In addition, modular systems can be easily replicated and deployed quickly, either in the context of an existing facility or in other locations.

The integrated, flexible, and distributed manufacturing networks that modular systems will make possible constitute a paradigm shift in the industry—away from traditional large, bespoke, centralized facilities that were based on predictable, stable pharmaceutical portfolios and a strong drive to leverage economies of scale. Rapid response to patient and health-care system needs that range from niche and personalized therapies to varying patient needs across geographic and demographic boundaries will be enabled by widespread implementation of modular systems.

To achieve the dimensions of potential supply-chain agility and efficiency afforded by modular systems, innovation in how manufacturing processes, facilities, and networks are designed, defined, validated, operated, and monitored will be required. Indeed, using conventional approaches to many of those aspects would undermine the fundamental attributes that drive the innovations, so adaptations of conventional regulatory models will be needed. A variety of questions about traditional quality-management approaches will have to be addressed, including the degree of redundant qualification and validation that will be necessary for each deployment or redeployment of identical modules and processes

and how in-process, release, and stability-testing paradigms and control systems will be integrated and managed among distributed networks.

THE EFFECT OF PRODUCT REVIEW AND APPROVAL AS THE BASIS OF ACCEPTANCE AND IMPLEMENTATION OF MANUFACTURING TECHNOLOGY

An important factor in the pace of manufacturing innovation is the reality that formal regulatory review of technology occurs specifically in the context of individual products. Technology is evaluated with respect to its suitability to deliver a high-quality product consistently and is not approved outright on its own. Although that paradigm might be appropriate for the pharmaceutical regulatory regime, it places a large burden on any manufacturer that seeks to bring forward a novel technology in support of product approval for the first time. Even if regulators have had exposure to and generally support a particular manufacturing innovation, only when a product that uses it has been fully subjected to detailed review and approval can an initial understanding of its genuine regulatory status be achieved. It is entirely incumbent on the manufacturer to satisfy all requirements that regulators need to approve the product, which might include unanticipated activities, costs, and time that could affect the financial viability of the product. In such a context, introducing innovative manufacturing can be a risky proposition. As will be discussed below, unless there is sufficient incentive for a manufacturer to bear the burden of potential cost and risk on behalf of a particular product, it often makes business sense to use more conventional technology for the product. Thus, the overall potential of a manufacturing innovation to influence many products or the global supply chain is not easily built into the value proposition for a single product. That is especially true of older, more established products, such as generics, for which the costs of introducing more modern, efficient technologies are difficult to justify for products that have smaller profit margins. In addition, even when a first such approval is achieved, it will take much time and effort—through the review and approval of other products—for a particular manufacturing technology to be broadly and successfully adopted.

THE NEED FOR INCENTIVES TO ADVANCE TECHNOLOGY INNOVATION

A strong and consistent view expressed during this study pertains to the effect of incentives and disincentives on innovation. Although the technical and regulatory challenges described in this report pose hurdles, none likely presents a greater barrier than insufficient, conflicting, or countervailing incentives. Such forces are relevant—often in different ways—to manufacturers and regulators. A summary of incentive-related challenges and illustrative examples is provided below.

The most obvious strong incentive for manufacturing innovation occurs when a pharmaceutical product fundamentally depends on the technology in such a way that the therapeutic benefit cannot otherwise be delivered to patients. For example, the development of antibody–drug conjugates for oncology indications created great complexities and challenges in manufacturing and analytics, but the clinical benefits of the products and potential financial returns were sufficient motivation for manufacturers to develop the necessary technology. The incentives of industry and regulators aligned well, and they agreed that a process must be developed to make the products available to patients.

In a more challenging case, a manufacturing innovation itself is being advanced as a central feature of a potentially disruptive business model. Small-scale, automated, integrated, and portable drug-manufacturing systems serve as an illustrative example. As these technologies increasingly demonstrate feasibility, they raise the prospect of a transformation of traditional manufacturing and supply chains, and business enterprises can be launched to pursue commercialization of such opportunities (see, for example, Love 2020). Here, the underlying value proposition is not the "what"' (a particular pharmaceutical product) but rather the "how" (highly flexible, distributed manufacturing and supply). The business incentive is driven by the potential to create and participate financially in this new drug-supply paradigm. However, for the new technology to be reviewed, approved, and accepted, it needs to be attached to a product. The logical choice is typically *not* an innovative pharmaceutical product for which speed to

patients could be undermined by a slower, more complex, expensive, and riskier development program. The better choice would appear to be advancing the technology with a well-established or generic product because that would entail less risk, but the effort and cost of gaining approvals for such products manufactured with novel technology might not be sufficient to generate a positive return on investment. Such an innovative enterprise might need exceptionally strong financial backing, faith in the viability and long-term impact of both the technology and business model to succeed, and the wherewithal to improve and adapt as needed. Those challenges are not trivial and will prove too great for some aspiring enterprises to overcome; some will simply fail, be sold, or sell the technology to other businesses. Even if the technologic and transformational potential exists, the business realities in the manufacturing ecosystem of innovators, suppliers, and end-users are not set up for a transformational *pace* of change. Implementation stalls because the incentives to finance, drive, or accelerate the transformation are insufficient. A final complication is that the fundamental direct role of the regulator occurs at the product-review stage in which attention is appropriately focused on ensuring the suitability of the novel manufacturing system to deliver a high-quality product reliably and is indifferent to business models or manufacturing costs.

Manufacturers of pharmaceutical products have extensive experience with the constraints and burdens of existing manufacturing technologies. They have had to learn to adapt and live with any adverse attributes and have invested to mitigate issues with supply reliability and business exposure. Those companies are generally aware of and interested in the opportunities afforded by manufacturing innovations to overcome and move past the burdens of legacy processes and facilities. However, under what circumstances are there sufficient incentives to invest? If the objective is to introduce new technology as a replacement for older technology in the same supply-chain model, favorable circumstances occur typically when additional, expanded capacity is needed or existing capacity has reached the end of its useful life. Even when such conditions exist, the implementation of innovative technologies must be carefully considered in relation to the portfolio of products for which they would be intended and the reality that each product must be successfully transitioned to the new technology. In the case of generics manufacturers, multiple products must often be transitioned simultaneously. Attendant risks and costs associated with undertaking such an implementation could include the need to increase the redundancy of capacity, to expand inventory stockpiles to ensure continuity of supply, and to address new and unexpected vulnerabilities of manufacturing processes and critical quality attributes discovered during implementation. Those risks and costs are substantial for large pharmaceutical manufacturers and can be insurmountable for smaller manufacturers or contract manufacturing organizations (CMOs).

For manufacturers of commercial products, such risks and costs, coupled with the uncertainties of managing global regulatory acceptance of post-licensure changes, are strong disincentives to pursue innovative manufacturing technology aggressively. For developers of innovative products, it is conceivable that novel technologies can be introduced early in clinical development and track with new product candidates as they mature in the pipeline toward commercialization. That approach has been undertaken by some manufacturers (NASEM 2020a,b), but the timing, success, and breadth of implementation in such cases are inextricably linked to the clinical advancement of the product candidates and therefore fraught with uncertainty: if a product fails in clinical trials, the manufacturing innovation similarly does not advance. For manufacturers of generic and biosimilar products that were designed and produced by originators many years ago, the challenge of modernizing technology is particularly acute if doing so would increase risk and cost. Given the enormous preponderance of such drugs in the global pharmaceutical landscape, the implications for the overall supply-chain robustness and product quality of having too few incentives are concerning. In the absence of a substantial effort to rebalance incentives, circumstances do not suggest a rapid shift toward adoption of cutting-edge technologies.

The above discussion focuses primarily on incentives from the industry point of view, and this is due to a general perspective that the responsibility for proposing and justifying innovative technologies rests entirely on manufacturers. As the examples above illustrate, the realities of evaluation and approval of pharmaceutical products and associated manufacturing technologies seriously limit the value proposition—and therefore capability—for industry to advance and implement the broad spectrum of

potentially available improvements necessary to achieve the future state of a mature, agile, and flexible manufacturing sector in which drug shortages are minimized. Although the need to shift the balance in favor of innovation has been vigorously articulated by FDA leadership, visible actions to propagate that view through the full regulatory network are less evident. Ultimately, it will be essential for incentives to be sufficiently aligned among all stakeholders—otherwise, innovation will continue to advance slowly and haphazardly. The committee concludes that the work of aligning incentives needs to be broadly shared and cannot afford to wait for industry-centric drivers alone to evolve and prevail. A more active, strategic, system-focused effort will be required.

THE NEED FOR GLOBAL CONVERGENCE AND HARMONIZATION

A strong and recurrent theme encountered during this study is the challenge posed by differences in regulatory expectations and requirements of international health authorities. Pharmaceutical companies often aspire to register and commercialize their products in multiple geographic regions or globally, and the cost, effort, and complexity of the endeavor can be daunting or even insurmountable for small manufacturers. To meet chemistry, manufacturing, and control requirements, an extensive dossier must be prepared that provides assurance that the manufacturer can reliably supply a high-quality product that meets accepted quality standards. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Quality Guidelines[1] represent an enormous effort to achieve greater worldwide harmonization of regulatory requirements. Indeed, the principles outlined in the various guidelines constitute a common, aligned framework that has generally supported more uniform quality standards and improved the efficiency of pharmaceutical regulation and the caliber of medicines approved and distributed around the globe. However, even in the case of well-established product categories that are manufactured by using proven technologies, companies regularly experience substantial differences in how guidelines are interpreted by regulatory authorities.

Navigating a path to timely approvals in multiple geographic areas inevitably is an immense accomplishment subject to many twists and turns. The industry experience is that queries, interests, and concerns of individual reviewers and institutional health authorities are still variable and seemingly often arbitrary and inflexible. In the best case, the process can be resource- and time-intensive; manufacturers are often trying to achieve business-critical approvals without creating a patchwork of commitments and quality standards to suit different markets. Such a situation should be avoided whenever possible because it creates logistical challenges and results in a more-complex and less-flexible supply chain if products are made and released to meet the requirements of specific countries. In those cases, manufacturers typically will default to the most conservative and rigorous standard applied by any regulatory authority worldwide even if other authorities would apply different risk algorithms for any given quality or control attribute.

The burden of seeking approvals for multiple geographic areas is great, and including novel manufacturing methods in the approval process increases the effort and cost and carries a greater risk of delays or an inability to register products in some countries. Any progress that can be made to enhance or accelerate regulatory harmonization and consistency will clearly reduce current disincentives for global implementation of innovative manufacturing technology. It should also be noted that the ICH mission does not involve an overt mandate to support and enable manufacturing innovation; such organizations as FDA and the European Medicines Agency should help global health authorities to appreciate the connection between advanced technologies and the resource-efficient supply of safe, effective, high-quality medicines.

POST-APPROVAL CHANGES: ESSENTIAL FOR ACCELERATING INNOVATION

Another important global regulatory opportunity to support manufacturing innovation pertains to post-approval changes. To create wide-scale change, advanced technology must be applicable to approved

[1] See https://www.ich.org/page/quality-guidelines.

products—those being manufactured and supplied to patients. The full complement of commercial pharmaceutical products (including generics)—many of which were developed and registered years or even decades ago—should have legitimate, viable access to post-licensure improvements. Otherwise, the actual implementation and impact of innovation will lag profoundly behind the state of technology with little overall effect on the stability and security of the global supply chain. Conversely, if innovations in manufacturing technology can be expected to apply only to *future* products, the ability to realize value and return on investment will be constrained by the risks and potentially long timelines associated with research and development. Moreover, there are strong pressures to accelerate development to bring the most promising products to patients faster, and this pressure inevitably leads to a situation in which, even for newly launched products, implementation of cutting-edge technology must be deferred until after initial product launch. Those considerations emphasize that the regulatory path to post-approval changes will be critical in enabling and accelerating manufacturing innovation.

As discussed in the context of incentives and global harmonization, industry's ability and willingness to pursue post-approval changes have been constrained by several factors. In response, global regulators have recognized the challenges and have sought to develop guidance documents to provide a framework for post-approval changes, of which the most recent and notable is ICH *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*.[2] The guidance is explicitly directed toward the commercial phase of the product life cycle and represents a major effort to address issues that have hindered the full realization of the vision of a more flexible and agile pharmaceutical manufacturing sector that has been advocated for the last 2 decades. The harmonized regulatory tools, enablers, and guiding principles described in ICH *Q12* include categorization of post-approval chemistry, manufacturing, and control changes; definition of established conditions; post-approval change-management protocol; and product life-cycle management. They are intended to support innovation and continuous improvement by enabling industry to implement desired post-approval manufacturing changes more efficiently and effectively. With the combination of an effective pharmaceutical quality system, a strong and complementary relationship between regulator assessment and inspection, and detailed guidance for analytic changes made in marketed products, a solid toolkit appears to be in place.

The ultimate success of ICH *Q12* will, however, depend not only on the specific merits and comprehensiveness of the guidance itself. It will require an intensive, sustained effort on the part of the industry and regulators to agree on how the guidance will be used in practice. With consistent support and a genuine sense of partnership, experimentation, and continuous adaptation and improvement of the process, the initiative has a chance to make a lasting difference. However, the committee emphasizes that there are important challenges for this guidance to support and affect the full spectrum of pharmaceutical manufacturing enterprises, including not only product originators but also generics manufacturers and CMOs.

CHALLENGES WITHIN THE SPHERE OF FDA INFLUENCE IN SUPPORTING AND ENABLING INNOVATION

FDA is a public-health agency that oversees the quality and efficacy of marketed drugs to ensure patient safety. Its oversight role also includes ensuring patient access to safe therapies, and this means that the agency has a critical role in supporting and enabling manufacturing innovation that can improve product quality *and* lessen the risk of drug shortages. The importance of that role in supporting innovation is acknowledged and emphasized as mission-critical by FDA leaders in the Center for Drug Evaluation and Research (CDER) in public presentations and various reports.[3] CDER has also taken an important step in supporting innovation through the establishment of the Emerging Technology Program in 2014.[4]

[2] See https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf.
[3] See https://www.fda.gov/media/93524/download and https://www.fda.gov/media/95444/download.
[4] See https://www.fda.gov/media/95444/download.

Yet the totality of stakeholder experience that has informed this committee indicates that the role of CDER in enabling innovation is underdeveloped, and this underdevelopment jeopardizes the center's ability to meet its full public-health mission. The themes described in this section were identified as challenges within the sphere of CDER's authority or influence that affect the implementation of innovative technology by manufacturers. It is worth re-emphasizing that the committee is fully aware that CDER cannot advance innovation without efforts by other stakeholders in the pharmaceutical manufacturing ecosystem. Success depends on the concomitant actions of other critical stakeholders, especially the industry and policy-makers. However, the committee's task was to recommend actions that FDA should undertake to prepare for and accelerate adoption of innovative technology in pharmaceutical manufacturing.

Expertise, Capacity, and Culture in the Center for Drug Evaluation and Research

The capability of CDER to evaluate risk to patient safety associated with novel manufacturing technology is linked to technical expertise, capacity, and a culture that actively incentivizes the center's role in alleviating the risk associated with the implementation of innovation. Several challenges to that capability are described below.

- *Breadth of innovative technology*. The breadth of innovation in products, manufacturing processes, analytic technology, and control approaches presents staffing and training challenges to ensure that CDER has the expertise necessary for evaluating new technologies. Widely acknowledged shortages of skilled workers in the pharmaceutical industry contribute to the challenge and create competition between the agency and the industry for recruitment and retention of talented staff who have the needed expertise.[5]
- *Capacity constraints that affect consistency in evaluating innovative technology***.** The CDER Emerging Technology Team (ETT) is designed to be a knowledge interface between sponsors of innovative technology and reviewers and inspectors in their evaluation and oversight roles.[6] The views expressed in the committee's workshops indicate that although the ETT is valued in its external-interface role, the stakeholder experience has been that internal dissemination of expertise throughout the agency is inconsistent. That suggests that the capacity of the ETT to sustain external engagement with industry, cultivate the internal expertise necessary to inform that interaction, and support the transfer of the expertise to reviewers and inspectors is constrained. The inconsistencies lead to industry's hesitation to implement innovative technologies because of the expectation that reviewers and inspectors will need to be educated through iterative information requests throughout the life cycle of the product.
- *Dissonance between oversight and facilitation roles.* CDER's role in ensuring that industry practices do not lead to unacceptable risk to patients is appropriately and deeply embedded in the culture and practices of the center. However, that posture presents challenges for CDER to support and enable innovation because the regulator and the regulated industry are primed to approach all interactions with formality and caution and thus constrain the shared learning opportunities. The perspective of the stakeholders that informed this committee is that although FDA leadership has encouraged the use of novel technologies to strengthen the robustness of the manufacturing processes for pharmaceuticals, a disconnect between the podium and the practice of front-line regulators erodes the industry's confidence that an investment in innovative technology will not derail planned regulatory review timelines. The user fees paid by industry provided through the Prescription Drug User Fee Act (PDUFA) provide the agency with substantial funding, and PDUFA requires reviewers to conform to aggressive review timelines to meet performance benchmarks.[7] The iterations of information requests and reviewer education associated with the first use of an innovative technology create a highly stressful environment in light of PDUFA

[5] See http://phrma-docs.phrma.org/files/dmfile/TEConomy-PhRMA-STEM-Report-Final.pdf, pp. 16-17.
[6] See https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program.
[7] See https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-fiscal-years-2018-2022.

deadlines for both industry and regulator. Prior reviewer experience with or exposure to new technologies offers important advantages during the review cycle, but mechanisms for that opportunity are highly constrained.

External Perception of Risks and Benefits Associated with Implementing Innovative Technologies

It is evident to the committee that industry decisions to implement innovative technologies do not depend solely on the maturity and readiness of a specific technology itself. Key considerations in implementing innovations are the risk of disrupting timelines to market, the possibility of extensive and expensive efforts to gain regulatory approval, and the potential for substantial post-approval commitments. Although the industry's perception of risk is influenced by many factors, it appears that the uncertainties associated with regulatory review timelines and overall resource burdens are substantial disincentives to innovate. The agency's visible posture toward innovation therefore highly influences industry decisions to go to market or to implement innovative manufacturing technology. Although CDER uses guidance documents to represent its posture toward innovation, the timeline and process for developing and formalizing guidance hamper the effectiveness of this mechanism to signal readiness on a timescale that would support innovative companies.

Industry's concerns about the readiness of CDER suggest that the following perceived risks are critical factors in business decisions related to innovation in manufacturing processes.

- *Protracted or unsuccessful reviews***.** The approval process for regulatory filings requires the product sponsor to anticipate the data that reviewers might require to demonstrate the identity, safety, purity, and potency of a drug through a consistent manufacturing process. That approach poses a dilemma for sponsors who are introducing novel technologies because either an excess or an insufficiency of data to support the application could place the sponsor (and the agency) at risk of a protracted regulatory review process that could undermine the ability to achieve timely approval. Novel applications that incorporate new types of data or data integration might demand a greater level of communication and comprehension than is manageable by either the sponsor or the reviewer.
- *Clarity and consistency in the evaluation of residual risk to product quality*. Innovation in process or analytic technology might introduce new uncertainties for product quality that cannot be fully eliminated, especially in the case of complex drug products. It is unclear to stakeholders how the regulators will weigh risk and benefit for innovations that greatly enable flexibility and agility (for example, highly intensified, small-footprint modular systems) and thus address public-health needs but that might present a theoretical quality concern with no clear and cost-effective path to resolution. Industry's perception is that inconsistencies in this risk–benefit calculus for residual risk will propagate through all stages of review and inspection of the product life cycle.
- *Global regulatory environment*. As discussed above, the resource-intensive effort to satisfy regulators in multiple geographic areas is a disincentive to implement innovation because it is uncertain whether the benefit outweighs the burden. Industry's perception that CDER is committed to leading the development of international guidance would heavily influence the balance of this risk–benefit evaluation in favor of innovation.

COMMITTEE RECOMMENDATIONS

CDER's capabilities and capacity to evaluate innovative technology should be perceived by industry as more certain if the pace of deployment is to increase. This report has identified technologies that are likely to come before CDER in the next 5–10 years. In general, innovations that enable new products to market (for example, patient-centric dosage formulations) have greater business incentives to balance industry concerns with the uncertainties in the regulatory review processes. Decisions to deploy manufacturing innovation to improve supply-chain agility will be more sensitive to the perceived readiness of regulators because access to new markets is not a business driver for this type of innovation.

On the basis of that distinction, industry will likely deploy innovations that bring new products to market more quickly than ones that improve manufacturing and supply-chain agility, assuming equivalent technical maturity and no change in external drivers. The status quo is unlikely to support CDER's objective of reducing drug shortages associated with manufacturing failures related to existing products, including generic drugs. It should be noted that the committee thoughtfully considered the specific challenges that face the generic-drug manufacturers with respect to innovation. The challenges are substantially different from those facing the original product developer because the cost–benefit analysis rarely justifies changing established manufacturing processes for generic drugs except if the original product was manufactured by using an innovative process that must be adopted to produce the equivalent generic product. The committee concludes that the incentives needed to change the calculus for generic-drug manufacturers belong primarily in the policy sphere, not the regulatory sphere. Although FDA should continue to be an influential voice advising policy-makers who are considering ways to lessen the cost pressures and increase the business drivers in favor of innovation to improve quality and increase our domestic supply of generic medicines, the committee does not feel that new recommendations to the agency directed specifically to innovation for generics manufacturing are warranted.

As noted above, CDER's public-health mission to ensure patient access to safe and efficacious therapies drives the strategic need to facilitate innovation in manufacturing pharmaceuticals. The committee commends CDER for its willingness to examine mechanisms to strengthen the important role that the center plays in changing the status quo, which is too often a paralyzing stasis because of industry's perception of risk. The overall observation of the committee is that the center's resources, culture, and practices are tilted so heavily toward its oversight role that it is challenging to support innovation. For CDER to be more effective in supporting innovation, it should address four areas in concert:

- *Expertise and capacity of regulators* at all stages of product life cycles so that they can apply risk-based evaluation to innovative technologies.
- *Mechanisms* to decouple consideration of innovative technologies from applications for specific products under review.
- *Stakeholder perception of readiness* so that stakeholders are assured that innovative technologies will not result in unpredictable resource demands and long review timelines.
- *Engagement of CDER staff as regulatory scientists* so that precompetitive shared knowledge and principles of practice can be established and inform implementation of innovative technologies.

It should be noted that the first item above refers to internal CDER capabilities, whereas the others refer to positioning the center for more active roles in fostering innovation both internally and externally. Unless CDER acts to strengthen its stance in all four areas, industry will continue its risk avoidance with respect to innovation unless innovation is necessary to bring a new product to market. The recommendations that follow support the development of expertise, expanded capacity, and opportunities to strengthen FDA's role in incentivizing the use of the innovative technologies to improve the quality and consistency of pharmaceutical manufacturing.

Strengthen Expertise in Innovative Technology Throughout CDER

The committee concludes that expertise in novel manufacturing technology needs to be cultivated not only within the ETT but throughout the center to ensure consistency in review and inspection. The committee recommends that CDER examine internal practices to increase technical fluency among its scientists through such actions as the following:

- ***Evaluate priorities in hiring and retention practices*** to determine whether there is appropriate emphasis on acquiring, retaining, and rewarding future-leaning expertise and whether

additional flexibility in compensation structures might be necessary to compete for talent and to motivate and support people who demonstrate thoughtful and effective leadership in fostering innovation.

- ***Ensure that staff-development plans support continuous education in innovative technologies*** through such mechanisms as dedicated time in performance plans for targeted training and attendance at technical conferences on innovative technologies, periodic rotation of reviewers and inspectors through assignments in the ETT, and mentorships that pair innovation-oriented staff with field inspectors.

Advance Innovative Mechanisms for Evaluating Technology Outside Product Approvals

A consistent theme expressed to the committee is that CDER's ability to foster innovation is fundamentally constrained by the center's formal evaluation of technology only as it applies to specific products. It is clear to the committee that any substantial acceleration in implementation of innovative technology requires the center to engage earlier and more broadly in considering the suitability of the novel enabling technologies. Therefore, the committee recommends that CDER ***create new mechanisms and evaluate, expand, and consolidate existing pilot programs that allow consideration of innovative technology outside individual product submissions*** to accelerate implementation, lessen risk, and increase regulatory familiarity in ways that are transparent to the pharmaceutical ecosystem. To manage demand, CDER could set priorities for suggestions to consider innovative technologies from industry consortia over those from individual organizations. Consideration of evaluation also could depend on the broad applicability of a technology and the willingness of sponsors to share lessons and outcomes. Although the committee is aware of limitations on the center's authority for formally reviewing technology outside the context of individual products, the importance of finding a path forward for other types of evaluation is a critical strategic need that should be addressed by the agency. For example, the center should consider more fluid and targeted guidance and participation in other publication mechanisms, such as case studies and white papers. It would be highly valuable to disseminate more timely and smaller units of information on the center's perspective regarding the maturity and challenges of enabling technologies and likely applications and to allow public comment in an interactive and collaborative environment. Those approaches could be particularly valuable for emerging technologies for which few opportunities for product review have been presented to the agency and for which it might be premature to contemplate meaningful guidance. CDER's role in stimulating and supporting the International Symposia on Continuous Manufacturing of Pharmaceuticals and associated whitepapers is a good example to build on and might be extended to many of the emerging technologies discussed in this report.

Expand the Scope and Capacity of the Emerging Technology Program

During this study, stakeholders expressed appreciation for the Emerging Technology Program as an effective pilot-scale effort that is recognized as a valuable bidirectional mechanism by which FDA and industry can explore the issues related to innovative manufacturing technology and how they might affect technical development, manufacturing, control, and regulatory expectations. However, there was a consensus that the program would have greater impact if capacity and scope constraints were lessened. The committee recommends expanding the influence of the ETT through the following actions:

- ***Dedicate independent funding of the ETT*** to decrease dependence on other CDER organizations and PDUFA-associated constraints and to enable greater external engagement and balance between CDER's internal priorities and external priorities for implementation of innovations.
- ***Increase the number of dedicated full-time employees in the ETT*** to ensure relevant expertise and capacity to evaluate innovative technologies for small-molecule and complex biotechnology product submissions and to ensure effective and consistent dissemination of expertise from the ETT to reviewers and inspectors.

- ***Broaden the criteria for entry into the Emerging Technology Program*** to include innovation that is neutral to product quality but enables agility, flexibility, and efficiency in the manufacturing process, the supply chain, or control strategy to encourage deployment of innovations in both new products and post-approval modifications.
- ***Increase transparency of the capacity of the ETT and program outcomes*** to inform expectations of program utility, highlight common themes, and inform case studies for implementing innovative technologies in regulatory submissions.

Increase External Engagement to Facilitate Innovation and Increase Awareness of Readiness of CDER to Evaluate Novel Technologies

The committee concludes that increased external engagement speeds shared learning between regulatory and industry scientists and lessens uncertainty in the assessment of risk from the perspective of both parties. The committee recommends that CDER strengthen its external engagement through the following efforts:

- ***Increase engagement of regulatory scientists with public–private partnerships, nonprofits, and academic institutions*** in technical activities, such as workshops, case-study and road-mapping exercises, and industrywide initiatives that help to develop a shared sense of purpose, lexicon, and activities to drive innovation and alleviate the risks associated with introducing innovation in manufacturing technologies.
- ***Increase visible leadership in organizing, planning, and conducting open technical meetings and less structured "listen-and-learn" sessions***—hosted by CDER or in partnership with outside organizations—to facilitate a consensus on principles of practice for implementing innovative manufacturing technologies and to encourage sharing of applications by industry groups to the Emerging Technology Program.
- ***Leverage agency investment, extramural-research funding mechanisms, and partnerships with nonprofit consortia and academia*** to define research and development priorities, create affordable workforce-development training courses, and facilitate short-term sabbaticals for reviewers and inspectors. Industry consortia—such as the International Consortium for Innovation and Quality in Pharmaceutical Development, the National Institute for Innovation in Manufacturing Biopharmaceuticals (which is sponsored by the Department of Commerce) and the Advanced Mammalian Biomanufacturing Industrial Consortia (which are sponsored by the National Science Foundation)—can serve as mechanisms to share knowledge. Greater leverage of academic partnerships through the FDA-sponsored Centers of Excellence in Regulatory Science or encouragement of the formation of consortia modeled on the Advanced Simulation and Computing Predictive Science Academic Alliance Program, which is sponsored by the Department of Energy, could offer additional opportunities to engage directly in precompetitive research to advance CDER's research and personnel-development priorities.

Expand Leadership Role in Global Regulatory Harmonization

The heterogeneity of regulatory requirements in various regions is a critical factor in guiding industry's willingness to implement innovative technologies and in CDER's strategic objective to foster innovation. As mentioned above, the committee concludes that guidelines, such as ICH *Q12*, in development are highly effective in reducing real and perceived barriers to post-approval modifications but require sustained leadership by the United States to align global practices. Furthermore, substantial effort is needed to ensure that ICH guidelines are interpreted consistently within CDER. Therefore, the committee recommends that ***CDER increase dedicated resources and incentives to support greater emphasis on consistency in implementation of existing ICH guidelines and to enable leadership in ICH working groups*** to accelerate harmonization. To complement ICH-focused efforts, CDER should

consider and pursue more direct interaction with key regulatory agencies through information exchange, training, and mechanisms to support mutual recognition programs for inspections. Where possible, FDA should emphasize advancement of innovative manufacturing technology as an explicit purpose and benefit of harmonization activities.

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Appendix A

Biographic Information on the Committee to Identify Innovative Technologies to Advance Pharmaceutical Manufacturing

Gintaras V. Reklaitis (NAE) (*Chair*) is Gedge Distinguished Professor of Chemical Engineering and professor of industrial and physical pharmacy (by courtesy) at Purdue University. His research involves the application of computing and systems technology to support the design and operation of processing systems, emphasizing the investigation of Industry 4.0 approaches to support batch and semicontinuous manufacturing operations and methods for plantwide and enterprisewide planning and optimization. His recent work has been in continuous manufacturing of pharmaceutical solid oral-dosage forms and the use of drop-on-demand technology for individualized dosage production. He has served on the Board of Directors of the American Institute of Chemical Engineers, the Council for Chemical Research, and the CACHE Corporation and continues to serve on the editorial boards of several journals. He has published 300 papers and book chapters and edited or written nine books. Dr. Reklaitis became a member of the National Academy of Engineering in 2007. He has served on multiple National Academies committees, including as chair of the Planning Committee for Continuous Manufacturing for the Modernization of Pharmaceutical Production. Dr. Reklaitis received his PhD in chemical engineering from Stanford University.

Timothy Charlebois is vice president of technology and innovation strategy for BioTherapeutics Pharmaceutical Sciences at Pfizer. He is responsible for developing, integrating, and maintaining a strategy for process, product, and analytic technologies in support of the biotherapeutics and vaccines portfolio at Pfizer. He is also responsible for supporting biologics in-licensing and out-licensing due-diligence activities. He has 20 years of experience in mammalian and microbial process development, including expression vector design, cell-line selection and screening, GMP cell banking and characterization, genetic stability and viral safety testing, cell-culture and purification process design and validation, and biochemical and microbial assay development and quality control. He has extensive experience with the preparation and submission of regulatory dossiers pertaining to the manufacture and control of biopharmaceutical products. Dr. Charlebois received his PhD in biology from the University of Virginia.

Matthew DeLisa is William L. Lewis Professor in the Smith School of Chemical and Biomolecular Engineering at Cornell University. His research focuses on the molecular machines of protein biosynthesis as a target for understanding and reprogramming cellular function and as a toolbox for the creation of therapeutically and industrially relevant molecules. His unique approach involves probing and exploiting the function and specificity of cellular-protein machinery by integrating protein engineering—the science of redesigning natural biomolecular scaffolds—with microbial genetics, biochemistry, and molecular biology. The goal of his work is a deep understanding of the complexities of intracellular protein machinery that can be used to inform the engineering of cellular processes for the purpose of discovery, design, and production of a diverse array of useful products and processes. His contributions to science and engineering include the invention of numerous commercially important technologies for facilitating the discovery, design, and manufacture of human drugs and seminal discoveries in cellular-protein folding and protein translocation. Dr. DeLisa received his PhD in chemical engineering from the University of Maryland.

Christopher Earnhart is the chief technology officer for the Enabling Biotechnologies (EB) office in the Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense (CBRN). He is responsible for assessing and implementing technologies and infrastructure capabilities to accelerate the development of CBRN medical countermeasures (MCM) and enable a rapid-response MCM capability for the Department of Defense. Earlier, he was the joint product lead for the Platforms for the Rapid Integrated Solutions for Medical Countermeasures (PRISM) office and provided programmatic and technical leadership to implement platform-based discovery, design, manufacturing, and testing technologies to streamline MCM development and reduce risk. Dr. Earnhart was a key member of the Department of Defense's Advanced Development and Manufacturing (DoD-ADM) Capabilities team that oversaw the planning, construction, and commissioning of the DoD-ADM biomanufacturing facility. Dr. Earnhart earned his PhD from the College of William and Mary Virginia Institute of Marine Science as a National Science Foundation fellow studying comparative immunology. He completed postdoctoral training in bacterial pathogenesis and vaccine research at the Medical College of Virginia, Virginia Commonwealth University as an American Heart Association fellow, where he studied virulence factors and developed vaccines for Lyme disease and other spirochetal diseases.

Stephen W. Hadley is a senior program officer for vaccine development at the Bill and Melinda Gates Foundation. His role at the foundation is to provide support for problem-solving treatments that require process development, manufacturing, and analytic testing of recombinant proteins and monoclonal antibodies. He is also involved in assessing new bioprocessing technologies that enable low-cost production of biologics. Before arriving at the foundation, Dr. Hadley was vice president of quality for Chemistry, Manufacturing, and Control (CMC) Biologics, a biologics contract development and manufacturing organization, and was responsible for oversight of quality assurance, quality control, and analytic and formulation development activities for the company. During his tenure at CMC Biologics, the organization executed several facility-expansion projects and good manufacturing practice compliance initiatives to prepare for successful European Medicines Agency and US Food and Drug Administration preapproval inspections. Dr. Hadley received his PhD in organic chemistry and natural products chemistry from the University of Washington.

Arlene Joyner is a branch chief at the Biomedical Advanced Research and Development Authority (BARDA) of the U.S. Department of Health and Human Services and the deputy director of the Pharmaceutical Countermeasure Infrastructure Division that leads several mission-critical program activities focusing on public–private partnerships. Within BARDA, she is also the program manager for Fill Finish Manufacturing and Contract Development and Manufacturing Organization networks that oversee essential BARDA Core Service programs. Ms. Joyner is the continuous manufacturing program lead and the technical monitor for all contractor staff that specialize in small molecules, large molecules, and vaccines, technology transfers, manufacturing and product development, analytic methods, IP issues, and supply chain and logistics. Before joining BARDA, she spent 6 years at Merck & Co., conducting quality auditing and supervising vaccine-manufacturing operations. She also worked at Baxter in the vaccines division for 16 years, where her responsibilities included upstream manufacturing/fermentation, downstream/purification manufacturing, column chromatography, buffer preparation, supply chain, and program-management operations. Ms. Joyner received her MS in chemical engineering from Villanova University.

Katherine Lewis is division leader in the application, simulation, and quality program at Lawrence Livermore National Laboratory (LLNL). In this role, she leads about 160 computer scientists primarily in supporting the Weapons and Complex Integration Directorate. She also leads an LLNL project to investigate artificial-intelligence and machine-learning techniques for solutions in physics simulations. A large part of this project is related to integrating physics knowledge into models and understanding uncertainties in model predictions. Her expertise is in physics simulations with a focus on setup and workflows, involvement of the user community, and machine learning. She began her career at LLNL in

June 1998 in the field of massively parallel mesh generation. Ms. Lewis received her BS in mathematics, with a minor in computer science, from the University of San Francisco.

Paul Mort is a professor in the Department of Materials Engineering Center for Particulate Products and Processes at Purdue University. Dr. Mort recently joined the Materials Engineering faculty in support of Purdue's Center for Particulate Products and Processes. He is globally recognized as an expert in particulate processing and powder technology. He has a demonstrated history of product innovation and driving process efficiency in the consumer-goods industry, including 24 years with Procter & Gamble specializing in granular detergents. Dr. Mort is an editor for the journal *Powder Technology* and consultant with the International Fine Particle Research Institute, working to develop a pipeline of prospective articles for the journal. He is active in linking particle technology with adjacent technical communities, including pharmaceutical processing and process control. Dr. Mort received his PhD from Rutgers University.

Todd Przybycien is a professor in the Howard P. Isermann Department of Chemical and Biological Engineering at Rensselaer Polytechnic Institute. He works on industrial downstream bioprocessing and on drug-delivery and medical-device development. Those activities are linked via fundamental interests in biophysics and in colloid and interface science. His approach is to use spectroscopic, optical, physical, simulation, and informatics tools to connect microscopic, molecular-level behavior to macroscopic, process-level engineering decision variables. His current research topics include downstream processing development of next-generation macromolecular affinity chromatography media based on PEGylated ligands; chromatographic performance as a function of systematic and stochastic uncertainty in mobile phase delivery; continuous precipitation-based processes for protein purification; protein-drug delivery to overcome interfacial denaturation in the delivery of proteins from poly(lactide-co-glycolide) microspheres via protein PEGylation; enhancing spreading, mucolysis, and antimicrobial activity in pulmonary drug delivery with surfactants; and protein adsorption topics impact of microscale and nanoscale surface features on protein adsorption behavior. Dr. Przybycien received his PhD in chemical engineering from the California Institute of Technology.

Kelley Rogers is the technical program manager for the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) in the National Institute of Standards and Technology (NIST) Office of Advanced Manufacturing. She is responsible for technical quality and coordination with NIIMBL, a NIST-sponsored Manufacturing USA institute whose mission is to accelerate biopharmaceutical manufacturing innovation in the United States. She is on detail from NIST's Material Measurement Laboratory, where she serves as the technical program director for biosciences and health. In previous positions, Dr. Rogers worked as a principal investigator identifying novel targets for antimicrobial drugs in the pharmaceutical industry. She was a postdoctoral fellow and staff fellow in the National Institute of Digestive, Diabetes, and Kidney Diseases of the National Institutes of Health. Her research background is in bacterial protein synthesis and gene expression. Dr. Rogers received a PhD in molecular biophysics and biochemistry from Yale University.

Saly Romero-Torres is senior director of digital quality systems at Pantheon by Thermo Fisher Scientific. Previously, she was senior manager of advanced data analytics at Biogen, where she led a team of mathematicians, statisticians, and advanced process-control engineers. She has over 15 years of experience in process analytic technologies and advanced manufacturing of biopharmaceuticals with a focus in the use of advanced sensors, advanced process control, data analytics, machine learning, and operational excellence tools. Her personal mission is advancing pharmaceutical manufacturing processes to enhance plant operations and, more important, improving patients' access to critical therapies. Dr. Romero-Torres received her PhD in analytic chemistry from Purdue University and is also a North Carolina State Biomanufacturing Training and Education Center fellow.

Gregory Stephanopoulos (NAE) is the W.H. Dow Professor of Chemical Engineering and Biotechnology in the Department of Chemical Engineering at Massachusetts Institute of Technology. His laboratory applies metabolic engineering and synthetic biology to understand and synthesize isoprenoids at industrially relevant levels. His group focuses on the upstream pathway responsible for supplying the building blocks for all isoprenoids, primarily through the microbial 2-methyl-(D)-erythritol-4-phosphate pathway. The work is performed through such methods as multivariate modular engineering of pathways to find the optimal expression levels of pathway genes and through the use of novel arrangements of co-cultured organisms. Those strategies, among others, have enabled his laboratory to create platforms for high-level production of isoprenoids. His group also focuses on the production of individual isoprenoids, especially on heterologous production of the anticancer drug Taxol, and has successfully produced gram-scale titers of the first cyclized precursor and performed enzymatic studies to reveal previously unknown bottlenecks and methods of alleviating them. Dr. Stephanopoulos is a co-author or editor of five books, more than 360 papers, and 50 patents. He is the editor-in-chief of *Metabolic Engineering* and *Current Opinion in Biotechnology* and serves on the editorial boards of seven scientific journals and the advisory boards of five chemical-engineering departments. For his research and educational contributions, Dr. Stephanopoulos has been recognized with numerous awards. In 2003, he was inducted into the National Academy of Engineering Dr. Stephanopoulos received his PhD in chemical engineering from the University of Minnesota.

Seongkyu Yoon is professor in the Francis College of Engineering of the University of Massachusetts (UMass), Lowell. Currently, Dr. Yoon is working as a co-director of Massachusetts Biomanufacturing Center, is the UMass site director of the National Science Foundation Industry–University Cooperative Research Centers Program and the Advanced Mammalian Biomanufacturing Innovation Center, and the UMass technical lead for Manufacturing USA in Biomanufacturing. His research interests include process-system engineering, systems biotechnology, bioprocess innovation, regulatory sciences, and biomanufacturing innovation. He is leading a systems-biology research group while conducting research in systems biotechnology, life-science informatics, and regulatory sciences with goals of developing an innovative biomanufacturing platform of protein–cell-gene biotherapeutics. Dr. Yoon received his PhD in chemical engineering from McMaster University, Canada, and his MBA from Babson College.

Appendix B

Disclosure of Unavoidable Conflicts of Interest

The conflict-of-interest policy of the National Academies of Sciences, Engineering, and Medicine (https://www.nationalacademies.org/about/institutional-policies-and-procedures/conflict-of-interest-policies-and-procedures) prohibits the appointment of an individual to a committee like the one that authored this Consensus Study Report if the individual has a conflict of interest that is relevant to the task to be performed. An exception to this prohibition is permitted only if the National Academies determine that the conflict is unavoidable and the conflict is promptly and publicly disclosed.

When the committee that authored this report was established a determination of whether there was a conflict of interest was made for each committee member given the individual's circumstances and the task being undertaken by the committee. A determination that an individual has a conflict of interest is not an assessment of that individual's actual behavior or character or ability to act objectively despite the conflicting interest.

Dr. Timothy Charlebois was determined to have a conflict of interest because he is the Vice President of Technology and Innovation Strategy for BioTherapeutics Pharmaceutical Sciences at Pfizer.

Dr. Todd Przybycien was determined to have a conflict of interest because he currently consults for Pfizer.

Dr. Matthew DeLisa was determined to have a conflict of interest because of his financial interest in four spinoff companies from his university laboratory (Glycobia, Versatope, Ajuta Therapeutics, and SwiftScale Biologics) and his patents relevant to the manufacturing of protein drugs.

Saly Romero-Torres was determined to have a conflict of interest because she initially was the Senior Manager of Advanced Data Analytics at Biogen and is now a Senior Director of Digital Quality Systems at Thermo Fisher Scientific.

In each case, the National Academies determined that the experience and expertise of the individuals were needed for the committee to accomplish the task for which it was established. The National Academies could not find other available individuals who had the equivalent experience and expertise and did not have a conflict of interest. Therefore, the National Academies concluded that the conflicts were unavoidable and publicly disclosed them on its website (www.nationalacademies.org).

Appendix C

Workshop and Webinar Agendas

WORKSHOP 1: FEBRUARY 27-28, 2020

Workshop on Innovations in Pharmaceutical Manufacturing

Hosted by Committee to Identify Innovative Technologies to Advance Pharmaceutical Manufacturing

AGENDA

THURSDAY, FEBRUARY 27, 2020

The overall goal of this workshop is to identify and discuss potential innovative technologies that could realistically be implemented in the next 5-10 years.

8:30 **Welcome**
Gintaras Reklaitis
Purdue University

8:40 **Workshop Introduction**
Janet Woodcock
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Session 1: Drug Product

Moderators: Gintaras Reklaitis, Purdue University; Matthew DeLisa, Cornell University

9:00 **PCMM and Beyond—Next Gen Innovation for Solid Oral Dosage Forms**
Dan Blackwood
Pfizer

9:25 **Disruptive Innovation for Next Generation Biomanufacturing**
Govind Rao
University of Maryland, Baltimore County

9:50 **Enabling Technologies for Manufacturing Thermostable and Cost-Effective Biopharmaceuticals**
Akhilesh Bhambhani
Merck

10:15 **Challenges for Advanced Drug Delivery**
Richard Korsmeyer
Consultant

10:40 ***Break/Mingle***

10:55 **Innovative Drug Products in the Pipeline**
David Lechuga-Ballesteros
AstraZeneca

11:20 Discussion Panel with Morning Speakers and Audience

12:20 ***Lunch Break***

Session 2: Control and Analytics

Moderators: Saly Romero-Torres, Biogen; Seongkyu Yoon, University of Massachusetts

1:15 **Modeling, Data Analytics, and Machine Learning for Process Development and Verification**
Richard Braatz
Massachusetts Institute of Technology

1:40 **Innovative Analytical Technologies and Biopharmaceutical Reference Materials**
John Schiel
National Institute of Standards and Technology

2:05 **A Look to the Future: Multi-Attribute Methods and Controls**
Tiffany Thiel
Amgen

2:30 **Harnessing the Power of Analytical Sensors in Pharmaceutical Manufacturing: Past, Present, and Future Goals**
Karin Balss
Janssen

2:55 ***Break/Mingle***

3:15 **Emerging Opportunities and Challenges in Biologics Manufacturing Digital Process Data Analytics**
Jack Prior
Sanofi

3:40 **Value-Focused Analytics and Digital Technology Roadmap for Advancing Biomanufacturing**
Jun Huang
Pfizer

4:05 Discussion with Afternoon Speakers and Audience

5:00 ***Adjourn***

Appendix C

FRIDAY, FEBRUARY 28, 2020

8:30 **Welcome to Day 2**
Gintaras Reklaitis
Purdue University

Session 3: Drug Substance Production

Moderators: Timothy Charlebois, Pfizer; Todd Przybycien, Rensselaer Polytechnic Institute

8:40 **Compact Factory for Drugs on Demand: Technology, Implementation, and Impact**
Salvatore Mascia
Continuus

9:05 **Innovations in Development of Synthetic Small Molecule Drug Substance**
Jean Tom
Bristol-Myers Squibb

9:30 **The Biopharmaceutical Industry's Emerging Continuous and Integrated Platform for Recombinant Protein**
Jon Coffman
AstraZeneca

9:55 **Hierarchy of High Impact Improvements in Bio Manufacturing**
Günter Jagschies
GE Healthcare (Retired), remote

10:20 **Discussion Panel with Morning Speakers and Audience**
Additional Panelists: Gregg Nyberg, Merck; Jorg Thommes, Gates; Andy Bommarius, Georgia Tech

11:20 ***Break/Mingle***

Session 4: What's Missing?

The goal of this session is to identify innovations that might not have been discussed in earlier sessions. That is, this session provides the opportunity for "free" discussion.

11:45 Discussion Session with Speakers and Audience

12:45 **Closing Remarks**
Gintaras Reklaitis
Purdue University

1:00 ***Adjourn Workshop***

WORKSHOP 2: JUNE 2-3, 2020

VIRTUAL WORKSHOP ON TECHNICAL AND REGULATORY BARRIERS TO INNOVATIONS IN PHARMACEUTICAL MANUFACTURING

HOSTED BY COMMITTEE TO IDENTIFY INNOVATIVE TECHNOLOGIES TO ADVANCE PHARMACEUTICAL MANUFACTURING

AGENDA

June 2, 2020

9:00 **Welcome and Workshop Introduction**
Gintaras Reklaitis
Purdue University

9:05 **Perspective from the Office of Pharmaceutical Quality on Barriers to Innovation**
Michael Kopcha
Director, Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Session 1: Delivering on Manufacturing Innovation: Challenges and Opportunities

Committee Moderator: Matthew DeLisa, Cornell University

Secondary Moderator: Timothy Charlebois, Pfizer

9:25 **Regulatory Challenges to Pharmaceutical Innovation**
Roger Nosal
Pfizer

9:50 **Innovative Strategies to Control Product Quality Attributes and Reduce Commercialization Timelines**
Patrick Swann
Amgen

10:15 ***Break***

10:25 **The Need for Regulatory Flexibility to Support Flexible Manufacturing**
Christine Moore
Merck

10:50 **A Role for Public-Private Partnerships in Advancing Biopharmaceutical Manufacturing Innovation**
Kelvin Lee
University of Delaware

11:15 **Discussion Panel with Morning Speakers and Audience**

Moderator will ask questions submitted by committee or audience members.

12:00 ***Lunch Break***

Session 2: Blurring the Boundaries: Integration, Intensification, and Control

Committee Moderator: Stephen Hadley, Bill and Melinda Gates Foundation

Secondary Moderator: Todd Przybycien, Rensselaer Polytechnic Institute

12:30 **Opening the Door to the Future – Why Continuous Manufacturing was the Key**
Paul Collins
Lilly

12:55 **Considerations for the Design and Construction of Next Generation Biologics Manufacturing Facilities**
Jim Thomas
Just – Evotec Biologics

1:20 **Janssen's Journey Towards Improved, More Agile Manufacturing through Deployment of Sensor and Model Based Advanced Process Control: Barriers and Opportunities**
Mauricio Futran
Janssen

1:45 **"Right-sized" Efficient Multi-Product Manufacturing**
Kerry Love
Sunflower Therapeutics

2:10 ***Break***

2:25 **The Alchemy of Process Control: Regulatory Flexibility and Supply Robustness**
Kim Wolfram
Biogen

2:50 **Control Strategy as a Critical Aspect of Manufacturing Innovation: Opportunities and Challenges on the Path to Implementation**
Jason Starkey
Pfizer

3:15 **Discussion Panel with Afternoon Speakers and Audience**

Moderator will ask questions submitted by committee or audience members.

4:00 **Adjourn**

June 3, 2020

9:00 **Welcome to Day 2**
Gintaras Reklaitis
Purdue University

Session 3: Innovative Processing Technologies

Committee Moderator: Kelley Rogers, National Institute of Standards and Technology

Secondary Moderator: Timothy Charlebois, Pfizer

9:05 **Addressing Technical and Regulatory Challenges in the Development of Innovative Drug Delivery Technologies to Increase Access in Global Health Settings**
Susan Hershenson and Ping Zhao
Bill and Melinda Gates Foundation

9:30 **Modern Aseptic Processing – What Are You Validating and Why?**
Brent Lieffers
Singota Solutions

9:55 **Novel Formulations to Improve Biologics Stability**
Patricia Seymour
BDO

10:20 ***Break***

10:30 **Innovative Formulations and Delivery Technologies: Practical Aspects from Development to FDA Approvals**
Mansoor Khan
Texas A&M

10:55 **3D Printing Pharmaceutical Dosage Forms at Commercial Scale: Aprecia's Journey**
Jae Yoo
Aprecia

11:20 **Innovations in Freeze Drying**
Steve Nail
Baxter

11:45 **Discussion Panel with Morning Speakers and Audience**

Moderator will ask questions submitted by committee or audience members.

12:30 ***Lunch Break***

Session 4: Disruptive Technologies and Convergent Innovations

Committee Moderator: Todd Przybycien, Rensselaer Polytechnic Institute

Secondary Moderator: Christopher Earnhart, JPEO-CBRND

1:00 **Perspectives from an Investor in Start-Up Life Science Industrials that Provide Fundamental Technologies and Services to Biopharma**
Gustavo Mahler
Dynamk Capital

1:25 **Novel Approaches to Manufacturing to Enable Rapid Response**
Amy Jenkins
Defense Advanced Research Projects Agency

1:50 **Perspectives from an Institutional Innovation Firm on Pioneering Life Science Platforms and Their Challenges**
Noubar Afeyan
Flagship Pioneering

2:15 **Discussion Panel with Afternoon Speakers and Audience**

Moderator will ask questions submitted by committee or audience members.

3:00 **Closing Remarks**
Gintaras Reklaitis
Purdue University

3:15 ***Adjourn Workshop***

WEBINAR 1: JUNE 29, 2020

COMMITTEE TO IDENTIFY INNOVATIVE TECHNOLOGIES TO ADVANCE PHARMACEUTICAL MANUFACTURING

WEBINAR WITH CENTER FOR DRUG EVALUATION AND RESEARCH, US FOOD AND DRUG ADMINISTRATION

JUNE 29, 2020

AGENDA

10:30 **Purpose of Open Session**
G.V. Rex Reklaitis
Chair, Committee to Identify Innovative Technologies to Advance Pharmaceutical Manufacturing
Burton and Kathryn Gedge Distinguished Professor, Purdue University

10:35 **Conversation with Study Sponsor on Regulatory Requirements, Scope of Responsibility, and Preparedness for Innovative Technologies**
Sau (Larry) Lee
Director, Emerging Technology Team Chair
OTR, OPQ, FDA

Katherine Tyner
Associate Director for Science (acting)
CDER, OPQ, FDA

11:50 **Opportunity for Public Comment**

12:00 ***END OF OPEN SESSION***

WEBINAR 2: AUGUST 11, 2020

COMMITTEE TO IDENTIFY INNOVATIVE TECHNOLOGIES TO ADVANCE PHARMACEUTICAL MANUFACTURING

WEBINAR WITH THE ASSOCIATION FOR ACCESSIBLE MEDICINES

AUGUST 11, 2020

AGENDA

11:00 **Purpose of Open Session**
G.V. Rex Reklaitis
Chair, Committee to Identify Innovative Technologies to Advance Pharmaceutical Manufacturing
Burton and Kathryn Gedge Distinguished Professor, Purdue University

11:05 **Conversation with the Association for Accessible Medicines on Innovations in the Manufacture of Generics Drugs and Barriers to Innovations**
David Gaugh
Senior Vice President, Sciences & Regulatory Affairs
Association for Accessible Medicines

Lisa Parks
Vice President, Sciences & Regulatory Affairs
Association for Accessible Medicines

12:20 **Opportunity for Public Comment**

12:30 ***END OF OPEN SESSION***

Appendix D

Innovations in Pharmaceutical Manufacturing Proceeding of a Workshop—in Brief

See https://www.nap.edu/catalog/25814/innovations-in-pharmaceutical-manufacturing-proceedings-of-a-workshop-in-brief

Appendix E

Barriers to Innovations in Pharmaceutical Manufacturing Proceeding of a Workshop—in Brief

See https://www.nap.edu/catalog/25907/barriers-to-innovations-in-pharmaceutical-manufacturing-proceedings-of-a-workshop