Consensus Study Report

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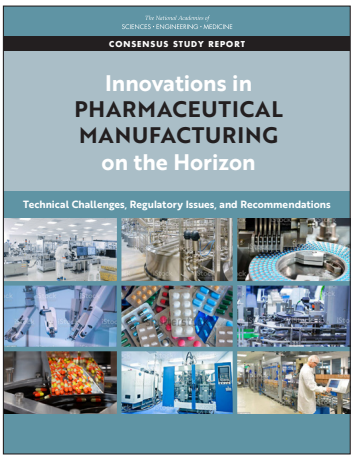
HIGHLIGHTS



Innovations in Pharmaceutical Manufacturing on the Horizon:

Technical Challenges, Regulatory Issues, and Recommendations

A primary public-health mission of the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) is to ensure patient access to safe and efficacious drugs. 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.

Many innovative technologies have been developed in recent years to advance pharmaceutical manufacturing, but not enough has been done to harness the power of science and technology fully and make vital products as available and accessible as possible. Much remains to be done 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.

This report identifies emerging technologies—such as product technologies, manufacturing processes, control and testing strategies, and platform technologies—that FDA will likely see in the next 5–10 years and that have the potential to advance pharmaceutical quality and modernize pharmaceutical manufacturing for products regulated by CDER. The report also describes technical and regulatory challenges and provides suggestions for how to overcome the regulatory challenges.

KEY MANUFACTURING INNOVATIONS ON THE HORIZON

The technologies highlighted in this report represent the most probable and extensive opportunities to advance pharmaceutical manufacturing within 5–10 years. The following innovations represent exciting opportunities to modernize pharmaceutical manufacturing, although many challenges must be overcome for them to achieve widespread adoption.

- *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.
- *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

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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.
- *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.
- *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.
- *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

THE NEED FOR REVIEW OF TECHNOLOGIES OUTSIDE THE CONTEXT OF INDIVIDUAL PRODUCTS

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. 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.

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. Although technical and regulatory challenges 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, if the business incentive is the potential to create and participate financially in a new drug-supply paradigm, disincentives begin to surface when one considers how to get the technology reviewed, approved, and accepted. Incentives need to be sufficiently aligned among all stakeholders, and the work of aligning incentives should be broadly shared and not wait for industry-centric incentives alone to evolve and prevail.

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 using proven technologies, companies regularly experience many barriers, including substantial differences in how guidelines are interpreted by regulatory authorities, what appear to be arbitrary and inflexible queries from individual reviewers and institutional health authorities, and a patchwork of commitments and quality standards to suit different markets. 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.

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. 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.

First, 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. Challenges the agency faces include the breadth of innovation in products, manufacturing processes, analytic technology, and control approaches; capacity constraints that affect consistency in evaluating innovative technologies; and dissonance between the oversight and facilitation roles.

Second, there is the external perception of risks and benefits associated with implementing innovative technologies. 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. Concerns that appear to be critical factors in business decisions to innovate include 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; the clarity or consistency in the evaluation of residual risk to product quality; and the issue of the global regulatory environment.

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. Although CDER has taken steps to strengthen its ability to accomplish that mission, the center's resources, culture, and practices are tilted so heavily toward its oversight role that it is challenging to support innovation. The following five overarching recommendations could strengthen FDA's role in fostering the use of innovative technologies to improve the quality and consistency of pharmaceutical manufacturing.

- *Strengthen expertise in innovative technology throughout CDER*. CDER should 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*. CDER should create new mechanisms and evaluate, expand, and consolidate existing pilot programs that allow

consideration of innovative technology outside individual product submissions.

- *Expand the scope and capacity of the Emerging Technology Program and the Emerging Technology Team*. The Emerging Technology Program has been recognized as an effective pilot-scale effort that would have a greater impact if capacity and scope constraints were lessened.
- *Increase external engagement to facilitate innovation and increase awareness of readiness of CDER to evaluate innovative technology*. CDER should strengthen its external engagement through a variety of efforts, such as increased engagement of regulatory scientists with public–private partnerships, nonprofits, and academic institutions in technical activities, and increase its visible leadership in the organizing, planning, and conducting of open technical meetings and less structured "listen-and-learn" sessions.
- *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. CDER should 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.

NEED FOR COLLECTIVE LEADERSHIP TO SPUR AND SUPPORT INNOVATION

Given the many parties and processes involved in delivering high-quality medicines, it is clear 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. A dramatic change in the relationship and collective leadership among entities most able to affect the outcome is needed. FDA, as a critical participant and node of influence, can and should play a direct leadership role and needs to support the ability and willingness of manufacturers to lead and drive innovative change.

COMMITTEE TO IDENTIFY INNOVATIVE TECHNOLOGIES TO ADVANCE PHARMACEUTICAL MANUFACTURING

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