The National Academies of SCIENCES ENGINEERING MEDICINE

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

Motivations for Study

- Need to achieve an agile, flexible manufacturing sector that can produce high-quality drugs reliably without extensive regulatory oversight. *Current pandemic emphasizes the need for change*.
- To create such a system, need to enable innovations in pharmaceutical manufacturing.

Statement of Task

- Identify emerging technologies that have the potential to advance pharmaceutical quality and modernize manufacturing for CDER-regulated products.
- Describe technical and regulatory issues associated with innovations.
- Recommend how to overcome regulatory issues to facilitate adoption of novel technologies.

Committee

Gintaras Reklaitis (NAE) (Chair), Purdue University
Timothy Charlebois, Pfizer
Matthew DeLisa, Cornell University
Christopher Earnhart, U.S. Army, Department of Defense
Stephen W. Hadley, Bill & Melinda Gates Foundation
Arlene Joyner, U.S. Department of Health and Human Services
Katherine Lewis, Lawrence Livermore National Laboratory
Paul Mort, Purdue University
Todd Przbycien, Rensselaer Polytechnic Institute
Kelley Rogers, National Institute of Standards and Technology
Saly Romero-Torres, Thermo Fisher Scientific
Gregory Stephanopoulos (NAE), Massachusetts Institute of Technology
Seongkyu Yoon, University of Massachusetts Lowell

National Academies Staff: Ellen Mantus, Marilee Shelton-Davenport, Kesiah Clement

The National Academies of SCIENCES ENGINEERING MEDICINE

Committee's Approach to Task

- Identified innovations that FDA is likely to see, not what innovations should be pursued.
- Focused on the role of FDA in preparing for and facilitating innovation, not other stakeholders in the pharmaceutical ecosystem.
- *Emphasized the need for all to play a role in achieving the goal of a flexible, agile pharmaceutical sector.*

Manufacturing Innovations on the Horizon

Technology Categorization

- Drug Substance
- Drug Product
- Automation & Control Technologies
- Innovative Manufacturing Networks

Key Manufacturing Innovations on the Horizon

- New routes to synthesize drug substances.
- Co-processed active pharmaceutical ingredients.
- Process intensification to create more efficient, higher-yielding processes and enable smaller manufacturing footprints.

Key Manufacturing Innovations on the Horizon

- Additive manufacturing technologies that can tailor and customize characteristics of a drug product.
- Advanced process control and automation ultimately to support real-time process optimization and automated operation and management of manufacturing.
- Modular systems to offer the possibility of creating integrated, flexible, and distributed manufacturing networks.

Challenges Imposed by Regulatory Process

- Product & Technology review process
- Alignment of Incentives for Manufacturing Innovation
- Global Harmonization
- Post-approval Change
- FDA internal limitations

Product Review and Implementation of Manufacturing Technology

- The existing regulatory process in which technology review only occurs in the context of an individual product places a large burden on any manufacturer to use innovative technology.
- *Unless there is sufficient incentive for a manufacturer to bear the possibility of unanticipated activities, costs, and time on behalf of a particular product, the manufacturer will likely use a conventional technology.*

Need for Alignment of Incentives

- Strong and consistent views have been expressed regarding the effect of incentives and disincentives on innovation.
- *Although technical and regulatory challenges described in this report pose hurdles, none likely presents a greater barrier than insufficient, conflicting, or countervailing incentives.*

Need for Alignment of Incentives

- 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.
- *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.*

Need for Global Convergence and Harmonization

- Differences in regulatory expectations and requirements of international health authorities pose considerable challenges, and the burden of seeking approvals for multiple geographic areas is great.
- *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

- The regulatory requirements concerning changes in the manufacturing process after product approval are an impediment to advancing innovative technologies.
- ICH has developed guidance (Q12) that is directed explicitly to the commercial phase of the product life cycle.
- 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 at FDA

- The committee appreciates the important steps and commitments that FDA and specifically CDER have taken to foster innovations.
- *However, the views expressed in the workshops 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.*

Expertise, Capacity, and Culture at FDA

- Breadth of innovation in products, manufacturing processes, analytic technology, and control approaches present staffing and training challenges.
- Capacity constraints appear to affect consistency in evaluating innovative technologies.
- There appears to be dissonance between the oversight and facilitation roles.

External Perception of Risks and Benefits

- Data requirements for regulatory filings to demonstrate the identity, safety, purity, and potency of a drug manufactured with innovative technology.
- No clarity or consistency in the evaluation of residual risk to product quality.
- The issue of the global regulatory environment.

Committee Recommendations

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.

Committee Recommendations

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.

Committee Recommendations

Expand the scope and capacity of the Emerging Technology Program and the Emerging Technology Team. Recommended actions: (1) dedicate independent funding to the ETT, (2) expand the dedicated ETT staff, (3) broaden the criteria for entry into the program, and (4) increase transparency of the capacity of the ETT and program outcomes.

Committee Recommendations

Increase external engagement to facilitate innovation and increase awareness of readiness of CDER to evaluate innovative technology. Recommended efforts: increase engagement, increase visible leadership, and leverage agency investments, extramural-research funding mechanisms, and partnerships.

Committee Recommendations

Expand the leadership role in global regulatory harmonization efforts. 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.

Concluding Statements

- *The agility, robustness, and overall maturity of the pharmaceutical-manufacturing sector need attention and investment.*
- *And there is a strong consensus that advanced manufacturing technologies can and must play a central role in creating a future agile, flexible industry that can produce high-quality drugs reliably.*

Concluding Statements

Although no single organization or entity has the capability or the mandate to lead the broader community to this desired future state…

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.