U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF PHARMACEUTICAL QUALITY

2021 ANNUAL REPORT

Assuring quality medicines are available to the American public

February 2022
www.fda.gov

"Three pillars of a secure and robust drug supply chain are **quality,** diversification, and redundancy."

—White House 100-Day Report

OPQ's Mission

The Office of Pharmaceutical Quality's (OPQ) mission is to assure quality medicines are available to the American public. Quality is achieved by assuring every dose of product is safe and effective and free of contamination and defects. As part of FDA's Center for Drug Evaluation and Research (CDER), OPQ works closely with other FDA offices to assure only quality drug products are available in the U.S. so patients and consumers have confidence in their next dose of medicine.

OPQ supports CDER's mission to ensure human drugs are readily available to patients and safe and effective for their intended use, while meeting established quality standards. This mission informs a long-held vision to sustain a pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight. As the world continues to navigate the effects of the continuing COVID-19 public health emergency, pharmaceutical quality is perhaps more important than ever before. In June 2021, the importance of access to high-quality medicines was a focus of a White House 100-Day Report

on resilient supply chains.[1] In this report, the White House recommended strategies to improve supply chain transparency and incentivize resilience. The report recommends, among other things, establishing novel pharmaceutical production technologies and creating a rating system to evaluate the robustness of a pharmaceutical manufacturing site's quality management. OPQ is working to realize these recommendations with three key initiatives: the Emerging Technology Program, the Framework for Regulatory Advanced Manufacturing Evaluation, and Quality Management Maturity Ratings.

Emerging Technology Program

CDER's Emerging Technology Program (ETP) allows industry to meet with FDA experts to discuss and resolve potential technical and regulatory issues related to new technologies prior to filing a regulatory submission.[2] A major milestone for this program in 2021 was the 100th FDA-sponsored ETP meeting. Another major milestone in the ETP is the graduation of technologies. A technology graduates from ETP when it can proceed fully through the standard application assessment process without engagement of the ETP. Graduation is an important step as it signals FDA's confidence in industry's ability to successfully develop and submit applications using the technology and FDA's readiness to evaluate the technology. In 2021, the ETP graduated its first technology, continuous direct compression, a process that consists of dispensing, mixing, and compressing materials to form tablets using equipment that is connected, with no breaks in the process. CDER is now creating the next generation of the ETP (ETP 2.0) to meet expanding workload challenges related to increasing ETP proposals, enhance communication with those looking to adopt new technologies, and train more FDA staff to evaluate graduating technologies.

158

FDA-sponsored ETP meetings since the launch of the program

1

Graduated technology from the ETP: Continuous Direct Compression

"Advanced manufacturing offers many advantages over traditional pharmaceutical manufacturing, including that, once implemented, it can be used far more cost-effectively than traditional manufacturing."

—White House 100-Day Report

1 Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth: https://www.whitehouse.gov/wp-content/uploads/2021/06/100-day-supply-chain-review-report.pdf

2 https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program

3 https://www.nationalacademies.org/event/10-28-2021/innovations-in-pharmaceutical-manufacturing-on-the-horizon-a-virtual-dissemination-workshop

4 https://www.fda.gov/news-events/fda-voices/fdas-advanced-manufacturing-initiatives-helping-provide-quality-human-drugs-patients

"FDA should lead the development of a framework to measure and provide transparency regarding a facility's **quality management maturity** with engagement from industry, academia, and other stakeholders."

—White House 100-Day Report

Framework for Regulatory Advanced Manufacturing Evaluation

Engagement with CDER's ETP can be vital to successfully implementing and launching a new technology; at the same time, the overall regulatory framework needs to support advanced manufacturing. OPQ funded the National Academies of Science, Engineering and Medicine to gather public input on innovative technologies in pharmaceutical manufacturing foreseen in the next 5-10 years. A series of workshops ending in 2021 brought together industry, academic, and government experts to discuss the future of pharmaceutical manufacturing and issue a consensus report.[3] Knowing the technologies that may play a major role in the future will allow FDA to prepare a Framework for Regulatory Advanced Manufacturing Evaluation (FRAME). An internal Center for Advancement of Manufacturing Pharmaceuticals and Biopharmaceuticals was established between the Center for Biologics Evaluation and Research (CBER) and CDER in 2021 to further align FDA thinking and policy related to advanced manufacturing and the regulatory framework.[4]

Quality Management Maturity Ratings

A root cause of many drug shortages is the absence of incentives for manufacturers to strive for more than simply meeting Current Good Manufacturing Practice (CGMP) regulations and to develop mature quality management systems.[5] Mature quality management uses a performance and patient-focused system to identify areas of improvement and implement effective changes. FDA has proposed the development of a rating system that will help incentivize drug manufacturers to achieve quality management maturity (QMM) at their facilities. OPQ led the formation of an Agency-wide, cross-functional team to develop a QMM rating program and launched two pilot programs to support the development of a strategy to objectively rate the QMM of manufacturing sites. A domestic pilot of finished dosage form manufacturers ended in 2021[6] and a second pilot of international active pharmaceutical ingredient manufacturers[7] will remain active until early 2022. A QMM rating system will inform regulators and purchasers about the performance and robustness of drug manufacturing facilities and give patients confidence in the availability of their products.

5 https://www.fda.gov/media/131130/download

6 https://www.federalregister.gov/documents/2020/10/16/2020-22976/quality-management-maturity-for-finished-dosage-forms-pilot-program-for-domestic-drug-product

7 https://www.federalregister.gov/d/2020-22977

OPQ's Core Functions

Collaboration is critical to OPQ's core functions of inspection, assessment, surveillance, research, and policy. As shared at the 2021 Pharmaceutical Quality Symposium,[8] OPQ supports the assessment of every type of human drug application including investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs), including those approved under the abbreviated pathway (biosimilars). Despite the ongoing COVID-19 public health emergency, OPQ supported FDA in meeting and even exceeding performance goals in 2021.[9]

Inspection

Facility inspections are an essential tool for regulating quality. In particular, pre-approval inspections[10] are needed around 20% of the time to assure that a manufacturing facility named in an application is capable of manufacturing in conformance to CGMP requirements and that the data submitted in the application are accurate and complete. OPQ leads pre-license inspections for biotechnology products and participates

1,300+
OPQ Staff

9
OPQ Sub-Offices

2
Locations:
White Oak, MD
St. Louis, MO

8 See recordings of the symposium here: https://www.fda.gov/drugs/news-events-human-drugs/pharmaceutical-quality-symposium-2021-innovations-changing-world-10262021-10272021

9 https://www.fda.gov/industry/fda-user-fee-programs/cders-work-meet-user-fee-goals-during-pandemic

10 Term used herein to refer to both pre-approval inspections and pre-license inspections.

47
Pre-approval inspections conducted with OPQ staff

21
Mission-critical inspections conducted with OPQ staff

52%
Reduction in the number of facilities needing pre-approval inspections by using alternative tools

in many pre-approval inspections for new and generic drugs with the FDA's Office of Regulatory Affairs. COVID-related travel restrictions severely limited FDA's ability to inspect facilities in 2021. Yet, after considering the medical benefit and necessity of the product subject to inspection and the safety of FDA investigators and regulated industry, OPQ conducted pre-approval inspections across 13 states and 16 countries in 2021.[11] Since the start of the COVID-19 public health emergency, OPQ has used alternative approaches to assess manufacturing facilities including:

- Information from regulators in the EU and UK obtained through Mutual Recognition Agreements[12]
- Information from other trusted regulatory authorities obtained through confidentiality agreements
- Information requested from the facility in lieu or in advance of an inspection[13]
- Remote Interactive Evaluations (RIEs), which use livestreamed video of operations as well as remote, live interactions with operators to assess a facility[14]

These alternative tools further reduced the number of facilities needing pre-approval inspections by over 50% in 2021 and allowed OPQ to complete the assessment of 269 drug product submissions.[15] The tools leveraged and refined during the public health emergency will continue to be useful in the future, though inspections will remain the irreplaceable standard.

11 https://www.fda.gov/media/148197/download

12 https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra

13 Pursuant to section 704(a)(4) of the FD&C Act

14 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remote-interactive-evaluations-drug-manufacturing-and-bioresearch-monitoring-facilities-during-covid

15 https://www.fda.gov/files/drugs/published/FDA%E2%80%99s-Pre-Approval-Inspection-(PAI)-Program-and-How-to-prepare-for-a-successful-outcome.pdf

Assessment

OPQ's assessment of drug marketing and licensing applications employs a team of experts in drug substance, drug product, manufacturing (process, facility, and microbiology), and biopharmaceutics (the relationship between the properties of a drug and its action). In 2021, owing in part to the use of alternative tools to inspections, OPQ supported the approval of over 850 drug applications, including 776 ANDAs, 108 NDAs, and 20 BLAs inclusive of 4 biosimilars, and over 8,000 application supplements. As part of the international Project Orbis, OPQ worked with FDA's Oncology Center of Excellence to quickly approve 8 drugs for patients with cancer in the U.S. and around the globe.[17] OPQ also supported patients by enabling the approvals of 31 submissions for breakthrough therapies to treat conditions for which there are limited or no treatment options. FDA-approved therapies treat patients suffering from rare conditions including:

- Achondroplasia, a form of short-limbed dwarfism
- Polycythemia vera, a rare chronic disease whereby the body produces too many red blood cells
- Pruritus (itching) in progressive familial intrahepatic cholestasis, a disorder that causes progressive liver disease
- Cholangiocarcinoma, a group of aggressive cancers that start in the bile duct
- Light chain amyloidosis, a cancer occurring when an abnormal protein builds up in the organs.

In 2021, CDER passed the milestone of approving 1,000 drug submissions to assist in treating patients with COVID-19 while also maintaining on-time action >90% of the time across all submissions with goal dates. To avoid potential drug shortages for patients in the U.S., OPQ prioritized and expedited the quality assessment of 343 submissions. OPQ supported seven Emergency Use Authorizations by the Secretary of the Department of Health and Human Services in 2021 for COVID-19 treatments including three monoclonal antibody products and four small molecule products, including one to avoid shortage of a critical drug used in mechanical ventilation of patients with COVID-19. OPQ also sponsored an important virtual workshop on Drug Master Files in March 2021 to provide guidance on the submission and assessment process, which had over 7,500 global attendees.[18]

>90%
of actions on time across all submissions with goal dates

617
Approved drug submissions to assist in treating patients with COVID-19

4
Approved biosimilars

100
Approved complex generics

16 https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence

17 https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis

18 https://sbiaevents.com/dmf2021/

OPQ's surveillance catalog comprises:

>6,000
global drug manufacturers

>135,000
approved application products

>140,000
non-application products (e.g., over the counter, monograph, and homeopathic products)

Surveillance

OPQ continuously monitors the state of quality for CDER-regulated sites and products. As the *FY20 Report on the State of Pharmaceutical Quality*, released in August 2021, explains, OPQ maintains the active catalog of all CDER-regulated sites and products.[19]

In 2021 OPQ's surveillance program continued to indicate possible contamination in some hand sanitizer products. In response, FDA staff used multiple surveillance tools including voluntary requests for information, record requests, and enhanced sampling and testing of marketed products. These tools enabled the FDA to remove many dangerous and low-quality products from the market and issue the first-ever FDA Warning Letters to manufacturers based on their failure to respond to record requests.[20] To enable enhanced product testing, OPQ scientists developed novel methods to detect contaminants such as methanol and 1-propanol in hand sanitizers, which are toxic when absorbed through the skin or ingested. Methods developed by OPQ scientists allowed for analysis of hand sanitizers in their original containers to detect contamination or insufficient amounts of active ingredient.[21]

OPQ's surveillance program has also been instrumental in detecting the presence of nitrosamines, a class of chemicals that can be carcinogenic, in some drug substances and products.[22] The presence of nitrosamine impurities led to the market withdrawal of the heartburn medicine ranitidine in 2020. An unanswered question has been whether ranitidine converts to nitrosamine in the human body, as it is known to do during storage at elevated temperatures or over long durations. In 2021, OPQ scientists provided strong evidence that ranitidine is not converted to nitrosamine under physiological conditions[23] or in the human body,[24] potentially paving the way for ranitidine products to eventually return to the market, if designed and manufactured appropriately. OPQ continues to develop methods for accurate and precise nitrosamine testing and in 2021 communicated formulation and manufacturing strategies to help manufacturers eliminate nitrosamine formation in their finished dosage forms.[25]

19 https://www.fda.gov/media/151561/download

20 Pursuant to section 704(a)(4) of the FD&C Act

21 https://www.nature.com/articles/s42004-021-00563-6

22 https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

23 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2781455

24 https://jamanetwork.com/journals/jama/fullarticle/2781670

25 https://www.fda.gov/media/141720/download

Research

A strong research program allows OPQ to protect patients and consumers from substandard products and enables OPQ to make difficult science-based decisions and policies related to pharmaceutical quality. Many of OPQ's laboratory scientists have continued to work on site, following implementation of COVID-19 safety precautions to perform mission-critical work throughout the public health emergency. Many times, their science and research has been indispensable to providing guidance on drug product development[26] and enabling drug approvals, especially those that lead to substantial cost-savings like complex generic drugs and biosimilars. For example, OPQ scientists spent considerable effort studying a complex product, ferumoxytol injection, that treats iron deficiency anemia in patients with chronic kidney disease. Their research helped to better define the composition, structure, and size of the extremely small (nanoscale) particles that make up this drug product. Armed with this knowledge, the FDA approved the first generic ferumoxytol injection product for patients in January 2021.

OPQ research also enabled a better understanding of peptide drug products like glucagon for injection, which is used to treat severe hypoglycemia in patients with diabetes. OPQ scientists developed methods to define the sequences of, and quantify impurities in, peptide drug products. Due largely to an improved understanding of potential impurities, the FDA approved the first generic glucagon for injection product which arrived on the U.S. market in early 2021.

Throughout its history, OPQ's researchers have investigated the structure, properties, and activity of biotechnology products like insulin glargine and monoclonal antibodies. The body of knowledge generated from this research contributed to the 2021 approvals of the first interchangeable biosimilar products, which can be substituted for the brand name products without intervention of the prescribing healthcare provider. These important approvals should improve the availability of these products for U.S. patients with diabetes or certain inflammatory diseases.

130

OPQ research publications on topics including:

- **Advanced manufacturing**
- **COVID-19 therapeutics**
- **Complex generic equivalence**
- **Botanical products**
- **Nanotechnology**

26 https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Policy

18

FDA guidance documents on topics including:

- **Potency assays for COVID-19 monoclonal antibodies**
- **Container closure system components for sterile drugs**
- **Alternative tools to inspection**

OPQ develops and promotes robust policies that give direction and clarity to manufacturers of pharmaceuticals. In 2021, OPQ led the development of 18 guidance documents for industry, including five guidance documents related to COVID-19 to ensure supply chain robustness and security, expedite the development of new products, and allow for regulatory flexibility where appropriate based on risk. For example, OPQ issued new guidance on FDA's use of remote interactive evaluations as an alternative approach to inspections.[27] Existing guidance was updated and clarified, including two revisions to a guidance on manufacturing, supply chain, and drug inspections during the public health emergency. This guidance was also presented at a public webinar with over 1,300 attendees from 88 countries.[28]

2

International guidance documents on:

- **Lifecycle management**
- **Continuous manufacturing**

OPQ works closely with the International Council for Harmonisation (ICH) to develop guidance for harmonized international standards. A major policy development in 2021 was the publication of the ICH Q12 guidance on lifecyle management, as well as an accompanying guidance for implementation in the U.S.[29, 30] This guidance provides an opportunity for regulators to focus attention and resources on higher risk postapproval changes. It also provides those manufacturers that conduct robust product development and continually improve their processes with postapproval regulatory flexibilities. In the long run, use of the principles in this guidance should reduce the likelihood of quality-related supply disruptions and drug shortages. In 2021, OPQ supported ICH documents related to viral safety, continuous manufacturing,[31, 32] quality risk management, extractables and leachables, analytical procedure development, and the quality portions of the common technical document. OPQ will continue leading international efforts to develop harmonized pharmaceutical standards in these and other areas.

27 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remote-interactive-evaluations-drug-manufacturing-and-bioresearch-monitoring-facilities-during-covid

28 Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers

29 https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf

30 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ich-q12-implementation-considerations-fda-regulated-products

31 https://database.ich.org/sites/default/files/ICH_Q13_Step2_DraftGuideline_%202021_0727.pdf

32 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q13-continuous-manufacturing-drug-substances-and-drug-products

A Culture of Continual Improvement

Pharmaceutical companies are expected to use a patient-focused approach to identify opportunities for improvement and implement effective changes; OPQ operates using the same principle. In 2021, OPQ instituted a formal Quality Management System, with supporting software, and an Enterprise Risk Management system to ensure the continual improvement of the office. To enhance the efficiency, effectiveness, and consistency of assessments as well as knowledge and lifecycle management, OPQ developed the first automated IT system for quality assessments: the Knowledge-aided Assessment and Structured Application (KASA). FDA's work on KASA won a 2021 FedHealthIT Innovation Award,[33] for delivering significant innovation and results in the federal government. KASA now provides over 15 analytics reports to OPQ assessors across the drug substance, drug product, manufacturing, and biopharmaceutics disciplines. To further enhance assessment efficiency and strengthen collaboration, OPQ assessors now conduct integrated quality assessments in aligned teams, which are smaller pools of experts from which teams are assigned to assess applications. In 2021, OPQ expanded the aligned teams framework beyond BLAs and ANDAs to include NDAs and cover nearly all submission types handled by the office.

The continual improvement of OPQ is important because the quality of medicines is critical to the long-standing public health mission of the FDA. Assuring an adequate supply of quality medicines has been challenging over the past two years. Responding to the COVID-19 public health emergency has required the availability of new therapies and, in some cases, increased supplies of existing ones. OPQ has supported the quality and supply of these and all other drugs in the context of a pandemic that impacted global supply chains and complicated the evaluation of manufacturing facilities. As the White House 100-Day Report states, "All Americans deserve safe, effective, and high-quality medicines and assurance that their next dose of medicine will be available when they need it. Access to medicine is also a foundation for a quality education and a healthy workforce." OPQ is proud to play the key role in assuring that quality medicines are available to the American public.

"All Americans deserve safe, effective, and high-quality medicines and assurance that their next dose of medicine will be available when they need it. Access to medicine is also a foundation for a quality education and a healthy workforce."

—White House 100-Day Report

33 https://www.fedhealthit.com/2021/05/2021-fedhealthit-innovation-award-winners-announced/

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