

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL QUALITY

2020 ANNUAL REPORT

Assuring quality medicines are available to the
American public

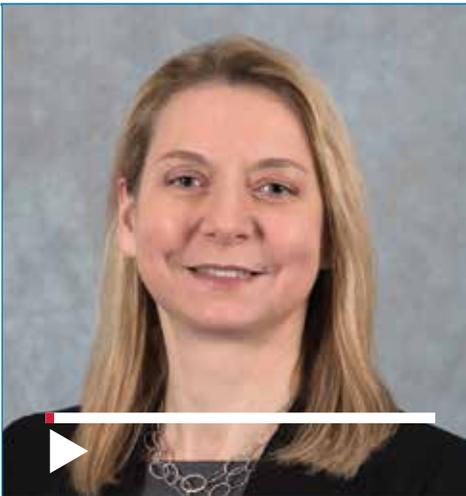




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In July 2020, CDER's Acting Director, Patrizia Cavazzoni, explained how pharmaceutical quality is a global priority — click below:



“Pharmaceutical quality is assuring every dose is safe and effective and free of contamination and defects.”

Who We Are

The mission of the Office of Pharmaceutical Quality (OPQ) in the FDA’s Center for Drug Evaluation and Research (CDER) is to assure quality medicines are available to the American public. In 2020, the COVID–19 pandemic posed an unprecedented challenge to this mission. COVID–19 brought new and long-standing issues to the forefront. These issues encompassed complex global supply chains, dramatically changing demand, drug shortages, and the need for rapid decision-making based on evolving science and risk. Especially in the face of the COVID–19 pandemic, patients and consumers expect safe, effective, quality medicine with every dose they take. Pharmaceutical quality is assuring every dose is safe and effective and free of contamination and defects. Quality gives patients and consumers confidence in their next dose of medicine.

OPQ handles 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 351(k) applications (i.e., biosimilars) — working closely with CDER’s Office of New Drugs and Office of Generic Drugs to do so. Our work in 2020 made new prescription and over-the-counter drugs available to patients, kept existing drugs on the market for patients, accommodated rapidly changing supply chains and manufacturing sites, and even expanded manufacturing capacity for some critical medicines. In spite of COVID–19, OPQ supported the FDA in exceeding or meeting nearly all user fee performance goals in 2020.

COVID–19 challenged all of OPQ’s functions: assessment, inspection, research, surveillance, and policy. In 2020, OPQ’s dedicated staff rose to meet the challenges posed by COVID–19. OPQ’s assessment staff supported accelerated approvals and emergency use authorizations for important medicines related to treating patients with COVID–19. Although COVID–19 travel restrictions postponed non-mission-critical facility inspections, OPQ staff made use of alternative tools for manufacturing facility assessments, avoiding the need to conduct 153 on-site facility inspections prior to approving applications. Staff in the laboratories of OPQ, in Maryland and Missouri, continued to conduct mission-critical testing and research, leading to product recalls and import alerts keeping pharmaceutical markets safe for consumers. OPQ staff provided critical support for establishing which FDA inspections were deemed mission critical and understanding where essential medicines are manufactured.¹ OPQ’s policy teams protected public health by playing a role in eleven guidance documents related to COVID–19.

¹ Leading to the publication of “Executive Order 13944 List of Essential Medicines, Medical Countermeasures, and Critical Inputs”

Since the outset of the pandemic, FDA has worked to assure essential medicines are available to patients and continued to conduct mission-critical foreign and domestic facility inspections. However, facility inspections not deemed mission-critical were postponed. Fortunately, inspections are just one of the tools we use to regulate quality and we were able to make use of alternative tools to continue performing manufacturing facility assessments. For instance, we requested information from applicants and requested records directly from facilities. We also used information from trusted foreign regulatory partners through mutual recognition and confidentiality agreements. The FDA is resuming postponed inspections as soon as feasible, when and where it is safe to conduct inspections. Yet, we are continuing to develop new approaches and explore new technologies and processes to conduct facility assessments under our current authorities.

While we are still discerning the complete impact of COVID-19 on global pharmaceutical manufacturing, OPQ releases a public report every year on the State of Pharmaceutical Quality which helps to inform regulatory decision-making, provide transparency, and engage industry in a commitment to quality. The report on fiscal year 2019, released in 2020, illustrated the global and dynamic nature of the pharmaceutical manufacturing industry. Of all FDA-registered drug manufacturing facilities, 58% were outside the U.S. Of all Generic drug of manufacturing facilities, 65% were outside the U.S. and 72% of manufacturing facilities for active pharmaceutical ingredients were outside the U.S. Of course, the FDA has the same expectations for quality whether a drug is made in the U.S. or abroad and whether a drug is brand-name or generic or biosimilar. While COVID-19 may be changing the global landscape of pharmaceutical supply chains, our commitment to transparency and sharing information on the State of Pharmaceutical Quality remains unchanged.

To continue supporting the FDA's COVID-19 response and meet the challenges of the future, OPQ remains committed to its strategic priorities to **collaborate, innovate, communicate, and engage**. We collaborated to rapidly approve applications to bring safe, effective, quality drugs to the market. We innovated by supporting the adoption of advanced manufacturing technologies and developing new tools to help our quality assessments. We provided temporary guidance to manufacturers and communicated to alert healthcare providers, consumers, and patients when unsafe products were found on the market. We engaged with stakeholders to better understand global quality management practices. These strategic priorities will help us assure that quality medicines *continue* to be available to the American public.

² Drugs and biologics determined by the FDA to be regularly used in the treatment of patients with COVID-19, not necessarily treatments for COVID-19. Please visit [COVID-19 Frequently Asked Questions](#) for information about medical products approved for the treatment of COVID-19.

622

Submissions approved for drugs used in the treatment of patients with COVID-19²

9

Sub-offices in OPQ cover assessment, inspection, research, surveillance, and policy

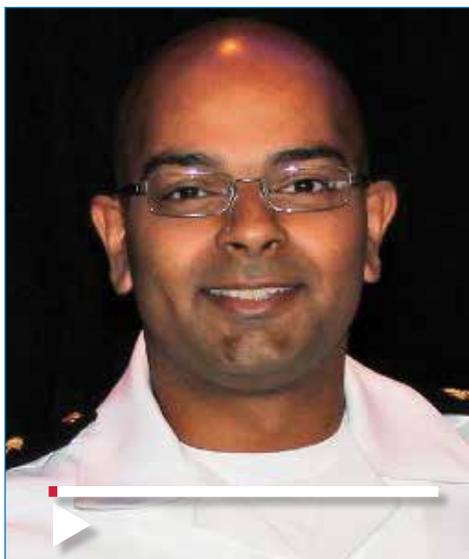
Over 6,000

Drug manufacturing facilities newly registered with the FDA



Collaborate

In July 2020, OPQ's Mahesh Ramanadham explained how facility decisions were made in the absence of inspections — [click below](#):



A collaborative quality assessment of drug marketing and licensing applications is OPQ's hallmark. The integrated quality assessment (IQA) is a multidisciplinary team process within OPQ and across the FDA. IQA teams comprise an application technical lead, a regulatory business process manager, discipline assessors, and additional technical advisors as needed. At minimum, assessment disciplines include drug substance, drug product, manufacturing (process, facility, and microbiology), and may also include biopharmaceuticals (drug absorption). Technical advisors may come from OPQ laboratories, policy, surveillance, and other FDA offices. The application's technical lead is responsible for overseeing the scientific content of the assessment. A regulatory business process manager is responsible for driving the assessment process and adhering to the desired timeline. Team-based IQA aligns patient-focused and risk-based drug product quality recommendations. Team-based IQA maximizes each team member's expertise to provide an integrated quality recommendation. As part of CDER's New Drugs Regulatory Program modernization, the Office of New Drugs adopted a similar team-based concept to conduct integrated drug reviews of NDAs in 2020.

Needs of the team-based IQA approach include cohesion within and consistency between teams, which must be carefully devised to bring the right individuals from across disciplines to address the large volume of applications. Proper team building ensures the clarity, collaboration, communication, and timeliness of the IQA. In 2020, OPQ began

to address this issue by adopting an “aligned teams” approach to the IQA which draws from smaller pools of individuals across disciplines to assign IQA teams, making it more likely that IQA teammates will have worked together before. Aligned teams allow OPQ to conduct quality assessments as effectively, collaboratively, and efficiently as possible while providing more consistent feedback to applicants. This aligned teams approach paid immediate dividends by making work assignments related to COVID–19 easier.

OPQ’s quality assessment recommendation supports marketing applications across every human drug User Fee program, including the Prescription Drug User Fee Act (PDUFA), the Biosimilar User Fee Act (BsUFA), and the Generic Drug User Fee Amendments (GDUFA) — all of which are up for reauthorization in fiscal year 2023. This legislation facilitates improved patient access to medicines by allowing the FDA to collect fees from companies submitting applications in exchange for committing to performance goals. In 2020, OPQ supported the FDA in exceeding or meeting nearly all user fee performance goals, in part by using alternative tools to facility inspections prior to application approval. Further, expedited quality assessments prevented 293 potential drug shortages, assuring supply chain security for U.S. patients.

OPQ is also responsible for regulating the quality of compounded and over-the-counter (OTC) drugs. A new User Fee program, the Over-the-Counter Monograph User Fee Act (OMUFA), was enacted in 2020 to reform the way certain OTC drugs are regulated in the United States. OMUFA will help provide the public with access to quality OTC drugs by allowing for industry-paid fees to fund a portion of FDA’s regulatory activities related to OTC drugs.

As part of the FDA’s efforts to promote drug competition and maximize patient access, there has been a focus on reducing the hurdles that manufacturers face in bringing competitive products to the market. In 2020, OPQ enabled the FDA approval of 942 generic and 3 biosimilar drug products. Among these, 72 were first generics and 2 were complex generics. First generics are the first FDA approvals of a generic drug product of its kind in the United States. They are very important to public health because they lower the price of products by over 30% on average, significantly improving patient access. Complex generics are drugs often facing less competition because they are harder to “gener-icize” by demonstrating equivalence to an innovator product. OPQ will continue to align and work collaboratively to make new drugs available, keep existing drugs on the market, and expand patient access to critical medicines in 2021.

153

Pre-approval inspections recommended but not conducted due to the use of additional tools in light of COVID–19 travel restrictions

Over 95%

Percentage of applications acted on by their user fee goal date

Over 10,000

Approved quality-related changes for previously approved products (i.e., application supplements)

293

Expedited quality assessments to avert or mitigate drug shortages

In July 2020, OPQ's Sau (Larry) Lee explained how the FDA supports the implementation of advanced manufacturing — click below:



40

Meetings with companies developing emerging technologies

3

Approvals of applications using continuous manufacturing

2

FDA-sponsored workshops held by the National Academies of Sciences, Engineering, and Medicine to identify coming innovations in pharmaceutical manufacturing

Innovate

Innovations are critical in keeping pace with the global pandemic, complex supply chains, accelerating drug development timelines, and advancing technologies. The pharmaceutical industry remains challenged by drug shortages, due often either to quality-related concerns or sudden increases in demand as during the COVID-19 crisis. The security of our nation's drug supply is closely linked to solutions that will improve the resilience of the pharmaceutical manufacturing base. One approach to secure a more reliable drug supply is to encourage advanced manufacturing and the use of innovative technologies. Advanced manufacturing is a collective term for new medical product manufacturing technologies that can improve drug quality, address shortages of medicines, and speed time-to-market. The benefits of advanced manufacturing can be plentiful: improved drug quality, enhanced responsiveness and flexibility, smaller facility footprints, lower environmental impacts, and more efficient use of human resources. For these reasons, advanced manufacturing can address the underlying causes of drug shortages and help mitigate or prevent future supply chain problems.

CDER supports advanced manufacturing through the Emerging Technology Program (ETP) and through extramural research funding. To encourage innovation, the ETP allows early engagement with the FDA, even before identifying a drug candidate, if an innovative advanced manufacturing technology will be used. Early engagement allows us to proactively identify and resolve potential scientific and policy issues related to these new technologies and helps applicants minimize regulatory uncertainty. In 2020, the ETP received 9 regulatory submissions, accepted 16 new proposals, and held 40 industry meetings. To strengthen our knowledge base on advanced manufacturing, over \$13 million in extramural research funding in 2020 enabled OPQ staff to collaborate with academia and industry studying and developing these new technologies.

Of note, continuous manufacturing is an important advanced technology in drug manufacturing that eliminates breaks between steps to reduce errors related to testing and the stops and starts of a process. As a result, continuous manufacturing technologies can greatly improve the reliability of the supply of products for the U.S. market and even have the potential to increase the domestic manufacturing base. The first regulatory application using continuous manufacturing for an active pharmaceutical ingredient was approved in 2020 as well as the first continuous biomanufacturing process. In addition, semi-continuous manufacturing processes were approved for two different marketed products.

To help us prepare for future technology innovations, the National Academies of Sciences, Engineering, and Medicine held two workshops in 2020, which brought together industry, academia, and government stakeholders to discuss the future of pharmaceutical manufacturing. The workshops focused on [identifying innovations](#) on the horizon in the next 5–10 years in the pharmaceutical industry and identifying [barriers](#) to implementing those innovations. We are now beginning to understand the known or latent risks associated with the adoption of advanced manufacturing technologies, recognize challenges with existing approaches to regulatory compliance, and ultimately develop regulatory frameworks that better support industry innovations.

In addition to innovations in the manufacturing industry, OPQ has acknowledged the need for continued innovations in regulatory assessment. To this end, OPQ has been developing the Knowledge-aided Assessment & Structured Application (KASA) tool. KASA improves the efficiency, effectiveness, and consistency of the quality assessment by structuring the quality-related data we receive, maintaining a collective knowledge base of these data, and enabling a more consistent scientific assessment of risk associated with applications. In 2020, OPQ developed and tested new knowledge-aided assessment interfaces for drug substance information and liquid dosage form ANDAs. We also started to develop interfaces for INDs and BLAs. In early 2021, OPQ will begin using knowledge-aided assessment interfaces for solid oral dosage forms, manufacturing, and biopharmaceuticals. The structured application element of KASA is still being developed.³ FDA's use of KASA is expected to be a win for the FDA, applicants, and patients: more regulatory efficiency, increased consistency between submissions, and faster availability of quality products.

Science & Research Highlight



In July 2020, OPQ scientists published the analytical testing procedures they developed to measure a potential impurity, called *N*-Nitrosodimethylamine, or NDMA, in metformin drug products used by patients with diabetes. The FDA established an allowable intake limit (96 ng/day) for NDMA based on patient safety. OPQ staff responded to reports of NDMA in metformin by a private lab claiming to have found it in very high levels. OPQ scientists used validated, orthogonal (two sufficiently different) methods to show some tests may overestimate the amount of NDMA by not accounting for a substance that interferes with the results. This interfering substance, dimethylformamide (DMF), is a solvent commonly used in pharmaceutical manufacturing. OPQ estimated the levels of DMF in the metformin samples were well below the level of concern to patients — as determined by current international standards.⁴ Sound science is critical for effective action. OPQ has [posted testing methods for metformin and other drug products on the FDA website](#) for industry, third party laboratories, and international regulators. We welcome others to use them — or to ensure they use similarly sound and validated measures. FDA has recommended recalls of metformin products tested and found to have NDMA above the allowable intake limit.⁵

³ Via [CBER-CDER Data Standards Program Action Plan](#) and revision of guideline for industry, [ICH M4Q: The CTD – Quality](#)

⁴ Guidance for Industry ICH Q3C *Impurities: Guideline for Residual Solvents*

⁵ Yang J, Marzan TA, Ye W, Sommers CD, Rodriguez JD, Keire DA. [A Cautionary Tale: Quantitative LC-HRMS Analytical Procedures for the Analysis of *N*-Nitrosodimethylamine in Metformin](#). *The AAPS Journal* (2020)



Communicate

In July 2020, OPQ's Director, Michael Kopcha, discussed the international commitment to pharmaceutical quality — click below:



Everyone has a role to play in the commitment to pharmaceutical quality. We want to help healthcare providers, patients, and consumers recognize the importance of pharmaceutical quality — and help them trust their medicines regardless of what they are or where they are made. Of course, trust must be built from collective efforts of both regulators and the pharmaceutical industry.

In spite of objective evidence to the contrary,⁶ an FDA and WebMD survey of over 600 physicians showed that nearly half believed drugs legally for sale in the U.S. but manufactured abroad were of lower quality than those manufactured domestically. To work against this bias and keep international pharmaceutical manufacturers equipped with the latest knowledge related to the regulation of pharmaceutical quality, the [Pharmaceutical Quality for Global Stakeholders webinar](#) was held in July and targeted international pharmaceutical manufacturers. This online interactive event was planned with the CDER's Small Business and Industry Assistance (SBIA) staff and FDA's India and China offices. The webinar was held from 12:00–5:00 AM in the time zone of FDA headquarters to fall within the working day for international stakeholders in India and China. This event focused on communicating developments related to pharmaceutical quality that impact global stakeholders, including remote facility assessments in the absence of inspections due to COVID-19 travel restrictions. The event reached the desired audience, as nearly 90% of the event's online attendees were from India and China.

One of the FDA's most important types of communication is guidance which presents FDA's current thinking on a topic to the public. COVID-19 challenged FDA to share its current thinking as rapidly as possible to secure patient access to new and existing products. In 2020, OPQ led or contributed to the release of eleven guidance documents⁷ focusing

on topics related to COVID–19, including inspections, supply chains, repackaging or combining propofol drug products, compounding certain drugs at outsourcing facilities, temporary use of portable cryogenic containers, and resuming normal manufacturing operations. In addition, in response to shortages of hand sanitizer products brought on by the start of the COVID–19 pandemic, OPQ participated in the development and subsequent four revisions of three guidance documents outlining temporary policies for the production of hand sanitizer products. OPQ also supported efforts to address the contamination of some hand sanitizer products with potentially harmful substances. OPQ tested products and publicly reported hand sanitizer products found to be contaminated in a [list of products you should not use](#). OPQ also worked to revise the tests legally required to be used by manufacturers in testing alcohol for contamination before use in hand sanitizer products.

Of course, not all guidance in 2020 related directly to COVID–19. In September, the FDA released guidance on the control of nitrosamine impurities in human drugs. This guidance provides recommendations on the steps manufacturers should take to detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical products. To emphasize the importance of these recommendations and answer stakeholder questions, OPQ and SBIA held the interactive webinar [Overview of the Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs](#) in October 2020. A total of 2,253 attendees heard about conditions that can lead to nitrosamine formation and expectations for the industry in detecting and preventing unacceptable levels of nitrosamine in human drugs.

OPQ continues to test marketed products for the presence of nitrosamine and will continue to work with the Office of Compliance to request recalls of [products found to have nitrosamines](#) above the allowable intake limit based on patient safety. A robust science and research program in OPQ fuels such science-based decisions and policies. OPQ is committed to communicating important research findings to improve drug development and regulatory assessment. In 2020 OPQ staff authored over 100 peer-reviewed publications. As COVID–19 has reinforced, sound science is critical for effective action.

“The timing of the program really helped us to attend and understand FDA thinking on addressing the current COVID situation.”

—Attendee of the Pharmaceutical Quality for Global Stakeholders webinar held from 12:00 AM – 5:00 AM in the time zone of FDA headquarters

11

Guidance documents to ensure the quality, supply, and safety of pharmaceuticals during the COVID–19 crisis

Over 100

Peer-reviewed scientific publications with OPQ authors — sound science is critical for effective action

6 Fisher AC, Viehmann A, Ashtiani M, Friedman RL, Buhse L, Kopcha M, Woodcock J. [Quality Testing of Difficult-to-Make Prescription Pharmaceutical Products Marketed in the US](#). *JAMA Network Open* (2020)

7 [COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders](#)



Over 200
Pharmaceutical manufacturers
participating in a global
benchmarking study to
characterize quality management

Engage

In 2020, OPQ made it a priority to engage with external stakeholders to better understand how they value and perceive pharmaceutical quality. In February, an FDA-sponsored workshop [Understanding How the Public Perceives and Values Pharmaceutical Quality](#) was held by the Duke-Margolis Health Policy Center to begin a dialogue with patients, providers, payors, and purchasers on their needs related to pharmaceutical quality — and this dialogue continues today. Nearly 80% of healthcare providers reported that their patients had experienced difficulty filling a prescription due to drug shortage. When the FDA released the [Drug Shortages: Root Causes and Potential Solutions](#) report in late 2019, it examined the root causes of drug shortages and proposed some potential enduring solutions. One root cause is that the market does not recognize and reward manufacturers that have “mature” quality management systems which focus on continual improvement and early detection of supply chain issues.

To be clear, the desire for mature quality management systems in the industry does not mean that substandard products are on the

market. Patients and consumers can have confidence in the quality of their medicines owing to both the actions of pharmaceutical manufacturers and the FDA's pharmaceutical quality program. Mature quality management uses performance and patient focus to identify areas of improvement — and, importantly, to implement effective changes to ensure robust supply of a drug. It gives manufacturers confidence that every batch they make will be acceptable to release to patients, which in turn gives patients and consumers confidence that their next dose of medicine will be available. A potential solution to the lack of incentivization for mature quality management is development of a rating system to incentivize drug manufacturers to invest in achieving quality management maturity at their facilities. Such a rating system would allow a cross-sectional comparison of manufacturers. Those choosing to disclose their facility ratings could benefit from a competitive advantage, as ratings would enable purchasers and payors to differentiate among drug manufacturers and their ability to consistently deliver quality products.

In 2020, OPQ initiated several programs to begin developing a framework for understanding and appraising quality management practices in the industry. We first funded a study by Dun & Bradstreet and the University of St. Gallen in Switzerland to conduct research and baseline global pharmaceutical quality management practices among human drug manufacturers. Over 200 pharmaceutical manufacturing establishments around the globe participated in this free assessment and each will receive a custom benchmarking report with clearly identified opportunities for continual improvement. We next awarded contracts to third parties to conduct (onsite, if safe) assessments of a facility's quality management maturity, accompanied by FDA staff trained on how to conduct such assessments. Finally, we launched two quality management maturity pilot programs to help the FDA gain insight from third parties to inform development of an FDA rating system to characterize quality management maturity. One program invited domestic finished dosage form manufacturers and the other invited active pharmaceutical ingredient manufacturers worldwide. Both pilot programs will run through December 31, 2021.

Patients and consumers deserve to be confident that their next dose of medicine will be *available* when they need it. More transparency around the quality management maturity of the facilities producing their drugs is necessary to provide this confidence.

In November 2020, OPQ's Jennifer Maguire explained the FDA's quality management maturity programs — [click below](#):



2

Quality management maturity pilot programs launched to inform a future rating system



If you suspect an issue with the quality of your medication, please report it to us at www.fda.gov/medwatch so we can track the experiences of patients and consumers.

A Look Forward

The COVID–19 public health emergency has led to a time of great cultural disruption, which historically has brought times of great technological innovation. OPQ’s mission remains assuring that quality medicines are available to the American public. During the COVID–19 public health emergency, it is a more acute mission than ever before. OPQ’s focus in 2021 and beyond is on keeping the FDA prepared to handle the public health and pharmaceutical quality challenges of the future. We will continue to encourage preparedness and innovation in the pharmaceutical industry and continue to foster the same values at the FDA.

Critical efforts in 2021 focus on promoting manufacturing innovation and incentivizing manufacturers to strive for mature quality management at their facilities. Of course, part of this effort lies in developing a rating system to characterize quality management maturity at facilities. Mature quality management is holistic, proactive, and not only identifies areas of improvement, but also helps drive effective changes. This is where quality management can intersect with the adoption of advanced manufacturing to usher in a new era of flexible, agile manufacturing capable of ensuring the availability of medicines. Sustained advancements in the industry require investment and innovation which will drive overall pharmaceutical manufacturing toward a state of mature quality management. OPQ will continue to support the implementation of advanced manufacturing through the next iteration of our Emerging Technology Program while new research in

manufacturing science and innovation will keep us prepared to handle future pharmaceutical manufacturing paradigms.

Of course, pharmaceutical quality is a global concept and OPQ works with international regulators to move toward global regulatory convergence. In the time of COVID–19 and global manufacturing disruption, it is important that drug regulators around the world continue to work to harmonize quality guidelines. OPQ will continue to work in the International Council for Harmonisation (ICH) to develop guidelines on Continuous Manufacturing of Drug Substances and Drug Products (ICH Q13), Analytical Procedure Validation and Development (ICH Q2(R2) and Q14), and Viral Safety for Biotechnology Products (ICH Q5). In this dynamic global pharmaceutical market, it is important that regulations not stymie innovation. Global alignment on regulatory expectations is a critical mechanism to incentivize continuous improvement and innovation.

OPQ will continue to work internally with two introspective strategic initiatives focused on innovating our operations to better serve public health in the future. The first initiative works to integrate a Quality Management System into our organization to ensure the delivery of high-quality work products across the functions of our office. The second initiative works to develop an Enterprise Risk Management strategy that will holistically assess the risks OPQ will face in future years — and to prepare accordingly. OPQ staff worked extremely hard over the past year with other CDER offices to secure the U.S. medical supply chain during the COVID–19 public health emergency. With improved enterprise risk management, we aim to keep our staff from being as overburdened in the future.

Much was said and written about staff at the FDA in 2020. Especially with the challenges of COVID–19, don't forget that we are patients too. Most OPQ staff report being motivated by the importance of our public health mission and the desire to help others. We rely on the same medicines as everyone else to maintain our health and the health of our loved ones. OPQ takes this mission seriously. Regardless of the circumstances, we will continue to work tirelessly to assure that safe, effective, *quality* medicines are available to the American public, so we can *all* continue to have confidence in our *next* dose of medicine.

“Don't forget that we are patients too. We rely on the same medicines as everyone else to maintain our health and the health of our loved ones.”



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