



OFFICE OF PHARMACEUTICAL QUALITY

2019

ANNUAL REPORT

One Quality Voice



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“Patients and consumers expect safe and effective medicine with every dose they take. Quality is what gives us confidence in our next dose of medicine.”

1,300

OPQ staff based at FDA headquarters in Silver Spring, MD. 50 OPQ scientific experts perform research at labs in St. Louis, MO, leading the FDA’s efforts in pharmaceutical analysis.

A Look Back: Five Years of “One Quality Voice”

A quality product, of any kind, consistently meets the expectations of the user. Drugs are no different. Patients and consumers expect safe and effective medicine with every dose they take. The Office of Pharmaceutical Quality (OPQ) stood up at the start of 2015 to assure all drugs marketed in the U.S. meet quality standards so that every dose is safe and effective, and free of contamination and defects. OPQ provides the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA) “one quality voice” on regulatory issues, working in harmony with FDA’s Office of Regulatory Affairs and CDER’s Office of Compliance. As OPQ celebrates five years of existence, we look back on our mission of assuring quality medicine is available to the American public.

Since 2015, OPQ has provided assessment, inspection, research, surveillance, and policy to support the quality oversight of drugs legally marketed in the U.S. Standards and policies based on science and risk are the foundation of the quality assessment of drug applications. The laboratories of OPQ, in **Maryland and Missouri**, conduct research to support the development of science-based quality policies. OPQ implements these policies and prepares CDER’s guidance documents related to drug product quality.

OPQ conducts the quality 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 351(k) applications (i.e., biosimilars). The quality assessment covers:

- How the applicant designs, manufactures, and tests the active ingredients and final drug products.
- Whether the proposed facilities are appropriate and prepared for commercial manufacturing.

When needed, the quality assessment can also address whether the product is sterile and whether the drug has the appropriate rate and extent of absorption after administration to the human body. In addition to prescription drugs, OPQ also establishes quality standards for over-the-counter drugs and certain compounded drug products.

OPQ's quality oversight does not end at application approval. OPQ continues to oversee the quality of marketed drugs over the entire drug lifecycle. We also monitor the state of quality for **all regulated manufacturing sites** and drug products. When used collectively, the FDA's regulatory tools give us high confidence in the quality of the U.S. drug supply.

The state of quality has been a topic of major interest over the last five years, particularly in 2019, as several reports prompted questions related to the quality of the nation's drug supply. Quite simply, the quality of our drug supply is better than ever before. For the first time, OPQ released a public [Report on the State of Pharmaceutical Quality](#), which shares the quality indicators we have based on FDA data. The quality of a drug cannot be judged solely on where it is made and whether it is **brand name or generic**. We use the same tools to assess drug quality whether the manufacturer makes a drug in the United States or abroad. We apply the same quality standards and inspect manufacturing facilities around the globe.

The **past five years** have presented some significant challenges to OPQ, including an unprecedented number of regulatory submissions, new User Fee programs, urgent public inquiries, natural disasters, scientific advancements, and newly uncovered patient risks. To continue meeting the challenges of the future, OPQ has identified the priorities to work better together — **to collaborate**, to encourage innovation — **to innovate**, to educate about the importance of quality — **to communicate**, and to foster productive relationships with the public — **to engage**. These priorities are necessary to assure that quality medicines continue to be available to the American public over the next five years and many more to come.

Quality is what gives us all confidence in our *next* dose of medicine.

“There is no difference in the quality of drugs based only on where they are made. We use the same tools to assure quality whether a manufacturer makes them in the United States or abroad or whether they are brand name or generic.”

72%

Manufacturing facilities for active ingredients in drugs located outside the U.S.

80%

How much lower the cost of a generic drug is, on average, compared to a brand-name drug.

Over 200

Additional FDA staff dedicated to pharmaceutical quality hired since 2015.



Collaborate

“We want to maximize patient access to quality medicines and we will continue to hone our integrated assessment process to do so.”

Over the past five years, the defining hallmark of OPQ has been a collaborative “integrated” quality assessment of drug marketing and licensing applications. This integrated quality assessment is a multi-disciplinary team process that requires efficient collaboration within OPQ and across the FDA. A team comprises a project manager and members from a minimum of three assessment disciplines: drug product, drug substance, and manufacturing. When needed, a team also includes microbiology (sterility), biopharmaceutics (drug absorption), and facility inspection. The integrated team is ultimately responsible for providing the quality recommendation for marketing applications. This team-based process has improved the overall output and strength of the FDA’s quality assessment.

357
Inspections to support application approval conducted by the FDA in 2019. OPQ led or participated in **30%** of these inspections.

An advantage of the integrated quality assessment is the ability to **coordinate application assessment with facility inspection** prior to approval. When needed, this coordination ensures that a manufacturing facility is ready to deliver a drug with the same quality as proposed in the application. OPQ initiates inspections of facilities referenced in pending applications and participates in these inspections when needed.

OPQ’s recommendation supports marketing applications through *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). This legislation facilitates improved patient access to medicine by allowing the FDA to collect fees from companies submitting applications in exchange for

committing to performance goals. Over the past five years, OPQ has supported the FDA in exceeding or meeting nearly all PDUFA, BsUFA, and GDUFA performance goals.

It is important that patients have access to quality medicines. Over the last five years, OPQ has helped the FDA **approve more products** across the User Fee programs.

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 generic manufacturers face in bringing complex generic drugs to the market. These complex drugs often face less competition because they are harder to "genericize." In 2019, OPQ helped the FDA approve a greater number of complex generic drugs than in past years.

The FDA has engaged with the pharmaceutical manufacturing industry over the past five years to educate potential applicants on ways to submit high-quality applications that allow our quality assessment to be as efficient as possible. To make sure patients have consistent access to the medicines they need, we also **prioritize the quality assessment of submissions with the potential to avert drug shortages**.

Over the next five years and beyond, OPQ wants to maximize patient access to quality medicines and we will continue to hone our integrated assessment process to maximize patient access to quality medicines. There are over one trillion potential combinations of personnel in OPQ across the different assessment disciplines in integrated teams. Consistency in team composition leads to improved efficiencies in assigning work and collaborating. In moving forward, OPQ assessment teams will be assembled in a way that makes team composition more consistent. A team works best when its members collaborate well. This consistency should enable even better communication and decision-making across the quality assessment disciplines.

We are at our best and strongest when we foster a collaborative culture and drive teamwork through integrated approaches.

1,014

Generic drug applications approved by the FDA in 2019. In 2015, the year OPQ stood up, this number was **726**.

10

Biosimilar applications approved by the FDA in 2019. In 2015, when OPQ stood up, this number was **0**. There are now **26** total approved biosimilars.

108

First generic drug products of their kind approved by the FDA in 2019. First generics provide access to needed therapies where little or no competition has previously existed.

194

Quality assessments of applications expedited by OPQ in 2019 to avert potential drug shortages for patients.



62%

Drugs that went into shortage found to be associated with manufacturing or product quality problems.

3 Months

Time it took to approve the sixth continuous manufacturing application to meet a medical need for cystic fibrosis patients.

Typically, application approval takes close to 10 months. When OPQ stood up, **no continuous manufacturing applications** had been approved by CDER.

Innovate

Innovations by industry and the FDA are required to keep pace with expanding globalization, accelerating drug development timelines, and advancing technologies. Although the pharmaceutical industry is more sophisticated than ever before, nearly two out of three **drug shortages** are due to quality-related issues. The quality of pharmaceutical manufacturing still lags other industries, such as electronics, semiconductors, and automobiles. One approach to address this problem is to encourage innovative technologies in pharmaceutical design and manufacturing with the potential to improve quality.

To encourage innovation, the FDA's **Emerging Technology Program (ETP)** allows early engagement with the FDA, even before identifying a drug candidate, if an innovative technology will be used for pharmaceutical manufacturing or design. Early engagement allows us to proactively identify and resolve potential scientific and policy issues related to new technologies to help applicants minimize regulatory uncertainty.

Continuous manufacturing is an important emerging technology that eliminates breaks between steps during drug manufacturing to reduce errors related to the stops and starts of a process. When OPQ stood up in 2015, no FDA-approved drug had incorporated continuous manufacturing. By the end of 2019, the ETP led the FDA to the approval of seven applications involving continuous manufacturing. The sixth such application, completed in 2019, was approved under an **expedited timeline** to address an unmet medical need for cystic fibrosis patients. The seventh application included a continuous manufacturing process for the active ingredient used in an inhaler — the first ever continuous manufacturing process approved for making the active ingredient.

In addition to innovations in the manufacturing industry, CDER has also acknowledged the need for innovations in the regulatory process. In 2019, OPQ publicly unveiled a technology, in development for several years, to improve the quality assessment of applications. This new **Knowledge-aided Assessment & Structured Application (KASA)** system

improves the efficiency, effectiveness, and consistency of the quality assessment. It does this 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 2019 OPQ began using a **pilot version of KASA** for some generic drug applications, which was well-received by OPQ assessment staff.

Over the five-year life of OPQ, the FDA has acknowledged the need for all quality-related operations to work better together to remain effective. A key example of this was the 2017 agreement across the FDA on a **concept of operations** outlining responsibilities for facility evaluation and inspection. This agreement enabled CDER and ORA to more effectively manage the growing complexity of the pharmaceutical landscape.

While the FDA benefited from the agreement by eliminating redundancies and finding efficiencies, it also benefited pharmaceutical manufacturers. Prior to this agreement, inspected facilities would not know the result of their surveillance inspections (i.e., classification) within a specific timeline. As of 2019, the vast **majority of facilities** now receive a letter stating the result of their inspection within 90 days of the close of inspection. Also, the median time to issue warning letters has dropped from over one year to just over six months. These improvements greatly reduce uncertainty for pharmaceutical manufacturing facilities while also allowing the FDA to act more quickly to protect patients from potential risks.

In 2019 CDER undertook a major effort to streamline the **New Drugs Regulatory Program**, which included a structural reorganization. OPQ supported this effort by creating 25 new work units to better align with CDER's Office of New Drugs and optimize efficiency within OPQ. We also changed the names of some existing work units to better reflect the work we do. All of OPQ's new work units were stood up by early January 2020.

"KASA is easy to use and quite intuitive."

—Feedback on KASA from an OPQ user in the 2019 pilot program for generic drug applications

86%

Inspected facilities that now receive notice of their surveillance inspection results within 90 days of the inspection closing. Prior to the FDA's Concept of Operations agreement in 2017 there was no specific timeline.

Science & Research Highlight: An Out-of-Body Experience



A robust science and research program in OPQ fuels science-based decisions and policies. OPQ's science and research program includes five Centers of Excellence and an extramural research program that provides over \$13 million in funding. In 2019 OPQ researchers set out to answer a question: Are drugs safe after they leave our bodies? OPQ is responsible for assessing the environmental impact of new drugs. Eventually drugs reach our wastewater and potentially interact with marine life. The structures of hormone receptors are highly similar in all vertebrate animals. This makes aquatic vertebrates susceptible to reproductive and developmental defects by disrupted endocrine signaling. In 2019 OPQ researchers developed a computer model to screen 1,293 drugs for potential interactions with estrogen receptors in fish tissue. The model identified 200 drugs that have the potential to interact with aquatic estrogen receptors. This approach will now help OPQ determine the type of environmental assessment data needed to keep the environment safe when approving new drugs.

Read more: Pinto, C.L., Bloom, R.A. and Laurenson, J.P., An Approach for Using In Vitro and In Silico Data to Identify Pharmaceuticals with Potential (Anti) Estrogenic Activity in Aquatic Vertebrates at Environmentally Relevant Concentrations. *Environmental Toxicology and Chemistry* (2019)



“The FDA has the same expectations for quality whether a drug is made in the U.S. or abroad or whether a drug is brand-name or generic.”

23%

Physicians surveyed by FDA and WebMD who believed seeing or hearing an advertisement for a drug is an indicator of its quality. Drug advertisements are *not* an accepted indicator of quality.

47%

Physicians surveyed by FDA and WebMD who sometimes or often write a prescription specifying a brand-name drug when a generic version is available.

Communicate

OPQ wants everyone to understand and appreciate the importance of pharmaceutical quality. We want to help healthcare providers, patients, and consumers in the U.S. trust their medicines regardless of what they are or where they were made.

In 2019, the FDA and WebMD concluded a survey of over 600 physicians on their perceptions of pharmaceutical quality. Nearly half of physicians believed drugs legally for sale in the U.S. but manufactured abroad were of lower quality than those manufactured domestically. This finding is troubling as the vast majority of FDA-registered manufacturers of active pharmaceutical ingredients are located outside the U.S.

Nearly **one-quarter of physicians** believed seeing or hearing an advertisement for a drug is an indicator of its quality. These perceptions influence patient treatment. For example, **nearly half of the physicians** — sometimes or often — write a prescription specifying a brand-name drug when a generic version is available (i.e., “dispense as written”). Nearly three-quarters of the physicians who’ve done this said it’s because their patients specifically requested brand-name drugs. To maintain patient confidence in medicine, there is a clear need for us to better understand these sentiments and to help facilitate conversations between physicians and patients about the quality of drugs.

Physicians, too, need to know the medications they prescribe are consistently safe and effective. Of course, the FDA has the same expectations for quality regardless of whether a drug is made in the U.S. or abroad or whether a drug is brand-name or generic. As one

way to help facilitate conversations between physicians and patients, OPQ's Director Dr. Michael Kopcha participated in a series of "expert Q&As" on drug quality that appeared in **WebMD magazine** in 2019.

The performance of a pharmaceutical manufacturing site cannot be judged solely on where it is in the world. In 2019, OPQ publicly shared information on quality surveillance in a [Report on the State of Pharmaceutical Quality](#) which includes:

- Sites that manufacture non-application products (e.g., homeopathic products) perform at a lower level than other sites.
- The majority of FDA inspections of drug manufacturing sites are conducted outside of the U.S.
- Of over 1,000 different applicants, just ten high-volume applicants account for 20% of all submissions to CDER.
- Some of these high-volume applicants have the highest rate of products that are not approved (i.e., Complete Response outcomes).

In this era of globalization, engaging with the pharmaceutical industry and emphasizing the importance of quality is essential. To this end, OPQ held a free public [regulatory education event](#) focused on pharmaceutical quality. Here the FDA discussed recent developments and provided case studies to illustrate the most effective ways to address quality issues and interact with the FDA. With a keynote speech by CDER Deputy Director Dr. Patrizia Cavazzoni, the major topics of the event were:

- Manufacturing and the Quality Assessment of Applications
- Quality Beyond Application Approval
- Emerging Technologies in Pharmaceutical Manufacturing and Design
- Happenings in Biologics: Biosimilars and "Deemed to be a License" Products

As the event was broadcast live online, **attendees** could participate from anywhere around the world. Nearly 30% of registrants were outside the U.S. and nearly 10% were from India. OPQ looks forward to continuing to engage our international stakeholders with more public events in 2020.



What does Pharmaceutical Quality have in common with **Lin-Manuel Miranda**, **Trevor Noah**, and **Emma Thompson**?

In 2019 they were featured in the same issues of WebMD Magazine to help facilitate conversations between physicians and patients about the quality of their medicines.

2,223

Attendees (online and in-person) who participated in the FDA's 2019 Pharmaceutical Quality Symposium, including **32%** from outside the U.S.



Engage

61

Quality-related guidance documents released since 2015, including several under FDA's Drug Competition Action Plan.

28 out of 28

EU countries the FDA has recognized as capable of conducting surveillance inspections that meet U.S. requirements. The FDA can recognize reports of these surveillance inspections conducted by these countries within their own borders. When OPQ stood up, **no countries** had been recognized.

OPQ must work closely with our FDA partners to effectively engage our external stakeholders, including other regulators. In this era of increasing globalization, in addition to **providing guidance** from our country, it is important that drug regulators around the world use the same quality guidelines. This concept, called harmonization, is the goal of the International Council for Harmonisation (ICH). It's also important in this growing global pharmaceutical market that manufacturers of approved products have the flexibility to make changes to improve quality without requiring excessive regulatory oversight.

In 2019, OPQ staff represented the FDA at the ICH meeting in Singapore where the quality guideline on product lifecycle management (ICH Q12) was finalized. This guideline should better establish which parts of an application can be changed without engaging regulators. In fact, in 2019 the FDA approved the first submissions related to such "established conditions" — NDA and BLA supplements that clarified the aspects of the analytical methods used in manufacturing that, if changed, require regulatory approval.

Since the launch of OPQ five years ago, the scope of the Mutual Recognition Agreement between the **FDA and European Union** (and a stand-alone agreement with the United Kingdom) has grown to allow drug inspectors to recognize reports from their counterparts' drug surveillance inspections conducted within their own borders. This past year, the FDA acknowledged five additional countries as capable of

conducting inspections that meet U.S. requirements. In 2019 alone, the FDA was able to reduce 25% of routine surveillance inspections in the European Union because of reliance on trusted partner reports through this agreement.

A topic of significant national and international interest in 2019 was the presence of N-Nitrosodimethylamine (NDMA) and other nitrosamine impurities in some drug products around the world. NDMA is a common contaminant found in water and foods including cured and grilled meats, dairy products, and vegetables. Although the international scientific community does not expect these impurities to cause harm when ingested at low levels, they may increase the risk of cancer when exposures rise above acceptable levels over **long periods of time**.

Since being alerted to the presence of NDMA in the blood pressure medication valsartan in mid-2018, OPQ scientists have developed the **most advanced and sensitive tests** for nitrosamine compounds in the name of patient safety. We've made these methods publicly available so drug manufacturers, scientists, and other international regulators can detect even trace amounts of these impurities. As a result, some additional drug products were also found to have low levels of nitrosamine impurities in 2019.

OPQ is now working closely with international drug regulatory agencies and manufacturers to ensure that drugs on the U.S. market do not have nitrosamine impurities above an acceptable limit. The FDA will continue to recommend recalls of drugs found to have nitrosamine impurities above an acceptable limit in the U.S.

As overall quality in pharmaceutical manufacturing lags other industries, it is important that the management of quality in the industry matures through capital investment and innovation. One part of such “quality management maturity” is the use of quality metrics to measure product and process quality to identify opportunities for improvement. In 2019, 25 FDA staff members visited **pharmaceutical manufacturing sites** around the globe, from Puerto Rico to Switzerland. FDA staff engaged with firms to better understand how they use quality metrics and establish quality culture programs. OPQ will continue to work with selected companies in 2020 to further evaluate how the FDA can use quality metrics to assure patients have access to better quality medicines.

70 Years

The amount of time patients could take a drug containing NDMA below an acceptable daily limit and not expect to have an increased risk of cancer.

1 Part Per 200 Million

The sensitivity of a method developed by OPQ scientists to detect the nitrosamine impurity NDMA in certain drugs. This is the equivalent of finding 1 specific grain of sand in a 20-pound sandbag. Scientists around the world are now using this method to assure drugs do not have NDMA levels above an acceptable daily limit.

15

Manufacturing sites visited by FDA staff in the Quality Metrics Site Visit Program in 2019 to better understand how they manage quality using quality metrics.



79%

Physicians surveyed by FDA and WebMD who believed their patients experienced difficulty filling prescriptions due to drug shortages. OPQ is building programs that incentivize quality management maturity in the drug manufacturing industry to make sure quality medicine is available for patients when they need it.

Over 90

Drug products that will transition from NDAs to BLAs on March 23, 2020 to improve patient access by allowing the development of biosimilar versions of these important medicines.

A Look Forward

OPQ's mission is to assure that quality medicines are available to the American public. Yet the concepts of quality and availability are, at times, in opposition as quality issues drive most **drug shortages**. In 2019, the FDA released a **drug shortages report** that examined the root causes of drug shortages and proposed some potential solutions. One solution called for developing a rating system to incentivize drug manufacturers to invest in quality management maturity for their facilities. The market does not presently recognize and reward manufacturers that have "mature quality systems" which focus on continuous improvement and early detection of supply chain issues. In moving forward, OPQ will work to build programs that incentivize quality management maturity in the drug manufacturing industry to make sure medicine is available for patients when they need it.

A ten-year journey that began with the Biologics Price Competition and Innovation Act of 2009 will end and a new one will begin on March 23, 2020. To improve patient access to certain medicines, on this date some drugs currently considered "small molecules" (i.e., historically approved as NDAs) will transition to be biological products (i.e., approved as BLAs). These **drug products** include insulin and insulin analogs, human growth hormone, pancreatic enzymes, and reproductive hormones. These products have faced limited market competition in the past. To open up competition,

developers of these products can take advantage of the biosimilars pathway for regulatory approval.

A public hearing was held in May 2019 on the future of insulin biosimilars and how they will be developed as biosimilar and interchangeable products. This hearing informed FDA policy for the transition of these products.

OPQ has prepared for this transition by proposing a rule that will allow select transition products to continue relying on drug master files for certain information after the transition. This is significant as biological products do not typically reference drug master files. We've also proposed a rule defining the term "biological product," generated a guidance document on the relevant provision of the legislation, and prepared a staff manual explaining the new quality assessment responsibilities for transitioning products. We look forward to playing our part in improving patient access to these important medicines.

Throughout OPQ's five years, we've been asked what we mean when we invite you to "join us in a commitment to quality." The role of drug manufacturers and regulators is very clear, but nearly every person taking a medication has a potential role to play. Here are some actions you can take to join us in a commitment to quality:

Store medications in your household at the appropriate labeled storage conditions and take them per the prescribed directions.

If you have concerns about the quality of a medication you or a family member is taking based on something you've read or observed, please discuss this with your healthcare provider or pharmacist. It can be more dangerous to stop taking a medication than to be exposed to a minor risk related to quality.

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.

We can't do this alone and **don't forget, we are patients too.** We rely on medicines to maintain our own health and the health of our loved ones. OPQ takes our mission seriously. We will continue to work tirelessly to assure that safe, effective, *quality* medicines are available to the American public, so we can *all* have confidence in our *next* dose of medicine.

"We need your help. Report suspected quality issues with a drug directly to the FDA using www.fda.gov/medwatch."

We are patients too.

"My grandson was born prematurely. Thanks to the lung surfactant he received, an application my colleague worked so hard on, he has grown into a healthy little boy." —OPQ Quality Assessor

"I was hospitalized with H1N1 along with six other patients. I am the only one who survived. I am more than a statistic; I am a mother!"

—OPQ Quality Assessor

"My friend's medical struggles and early death factored into my decision to join the FDA."

—OPQ Scientist

"My eldest son was diagnosed with insulin dependent diabetes in 1982 and he developed an injection site reaction to pork insulin. He was a subject in the Phase III clinical trial for recombinant insulin." —OPQ Scientist



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