U.S. FOOD & DRUG ADMINISTRATION

OFFICE OF PHARMACEUTICAL QUALITY

2018 ANNUAL REPORT

One Quality Voice

Table of Contents

WHO WE ARE

"Quality is what gives patients and consumers confidence in their next dose of medicine."

The Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA) is responsible for assuring the *quality* of most human drugs marketed in this country. A quality product of any kind consistently meets the expectations of the user. Drugs are no different. Patients and consumers expect safe and effective drugs with every dose they take. All drugs marketed in the U.S. must be manufactured to meet established quality standards that ensure every dose is safe and effective – and free of contamination and defects. Quality is what gives patients and consumers confidence in their next dose of medicine.

Over 1,300
Staff in OPQ make it the largest office in CDER

8
Sub-offices in OPQ cover assessment, inspection, research, surveillance, and policy

4,399
INDs assessed by OPQ

OPQ provides assessment, inspection, research, surveillance, and policy to assure that the American public has access to safe, effective, quality drugs. OPQ provides the quality assessment of Investigational New Drug Applications (INDs) and *every* type of human drug marketing application. This includes 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 drug substance, drug product, manufacturing, and facilities. The quality assessment can also include biopharmaceutics and microbiology, when needed. In 2018, we saw record approvals of generic drugs, biosimilar drugs, and novel drugs. In the case of novel drugs, we topped the record set in 1996.

OPQ stood up in 2015 to provide a uniform approach to assure quality across the drug product lifecycle from development through commercial marketing. This means that OPQ assesses all quality-related changes proposed after application approval over the life of the drug. OPQ also monitors the state of quality for all regulated manufacturing sites and drug products.

Quality standards and policies based on science and risk are the bedrock of quality assessment. The laboratories of OPQ conduct collaborative research to support the development of science-based quality standards and policies. OPQ implements the policies and guidance documents related to drug product quality. These collective functions of OPQ are why you can have confidence knowing that all drugs legally marketed in the U.S. have been held to consistent quality standards regardless of their source.

In 2018, OPQ established four strategic priorities:

- **COLLABORATE:** Strengthen OPQ's collaborative culture
- **INNOVATE:** Promote availability of better medicines
- **COMMUNICATE:** Elevate awareness and commitment to the importance of pharmaceutical quality
- **ENGAGE:** Strengthen partnerships and engage stakeholders

Guided by these priorities, OPQ improved integration of our internal processes to find more efficiencies. We held public events to encourage quality-related innovation inside the FDA and in the pharmaceutical sector. All stakeholders were invited to join us in a commitment to quality. As part of this effort, we established programs to engage stakeholders in discussions on further improving pharmaceutical quality. This all fueled OPQ's mission to assure that safe, effective, quality medicines are available to the American public.

8,254
Postapproval supplements assessed by OPQ

Did you know?

In July 2018, the FDA set the record for the most generic drug approvals in a month, then broke that record in October and November

COLLABORATE

123
NDA approvals including **10** breakthrough therapies and **44** new molecular entities

1,021
ANDA approvals including **188** priority assessments

24
BLA approvals including **8** breakthrough therapies and **7** biosimilars

OPQ aims to leverage a collaborative culture, engaged workforce, and streamlined processes to foster efficiencies within OPQ. A fundamental collaborative function of OPQ is the patient-focused, risk-based quality assessment of drug marketing and licensing applications. This *Integrated Quality Assessment* includes drug substances, drug products, manufacturing, and facilities, and can include biopharmaceutics and microbiology. The focus on quality stretches across the drug product lifecycle through development (INDs, pre-submission meetings), premarket (original submissions, amendments), and postmarket (supplements, annual reports). The Integrated Quality Assessment is a multi-disciplinary process that requires efficient collaboration within OPQ and across the FDA.

OPQ supports the FDA's ability to meet performance goals for different product areas. 2018 was the first full year of the most recent reauthorizations of the Prescription Drug User Fee Act (PDUFA), the Biosimilar User Fee Act (BsUFA), and the Generic Drug User Fee Act (GDUFA). This legislation allows the FDA to collect fees from companies submitting applications for certain new, biologic, biosimilar, and generic drug products in exchange for commitment to performance goals. In 2017, the FDA introduced a Drug Competition Action Plan to bring more generic drugs to market. In 2018, the FDA released a Biosimilars Action Plan to address competition and affordability for biologics and biosimilar products. This plan includes a key action to provide support for product developers regarding product quality and manufacturing processes. OPQ is committed to supporting the FDA effort to improve patient access to medicine.

In 2018, OPQ supported these action plans and contributed to the FDA exceeding or meeting virtually all PDUFA, BSUFA, and GDUFA performance goals. This included the approval or tentative approval of:

123 **new drugs** 1,021 **generic drugs** 24 **biologic drugs**

While there were record months for generic drug approvals in 2018, there were also a record **2,390** complete response letters issued to generic applicants whose products were not approved. Together, these numbers provide a more complete picture of the workload of OPQ.

A hallmark of OPQ is assessing applications in coordination with inspections and facility assessments to ensure that manufacturing is adequate to deliver the quality drug product proposed in an application. OPQ initiates inspections of facilities referenced in pending applications and OPQ subject matter experts participate in these inspections, when needed. OPQ investigators lead the inspections related to BLAs prior to licensing approval. After an inspection and prior to application approval, OPQ conducts a facility assessment to confirm data accuracy in the application and readiness for quality commercial manufacturing. OPQ also maintains a catalog of all drug manufacturing facilities. In 2018, OPQ published information on the risk-based Site Selection Model used to prioritize sites for inspections based on risk. In 2018 OPQ:

- Conducted **119** facility inspections
- Prepared **710** site dossiers to inform facility assessments

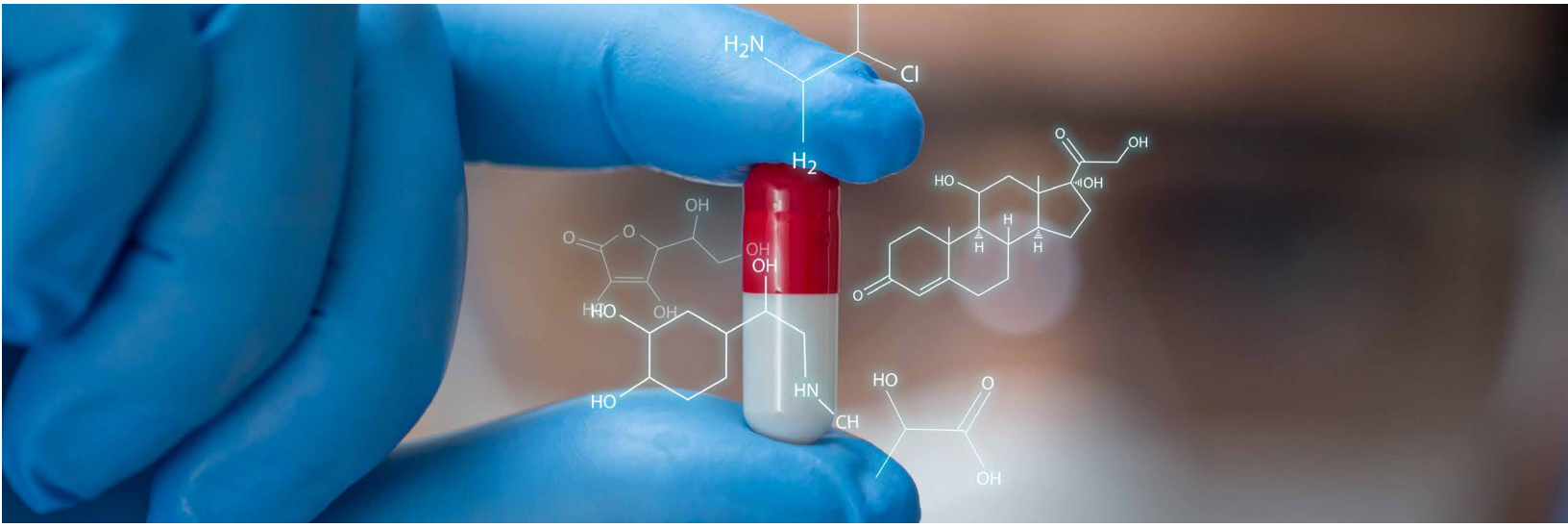
Since peaking in 2011, the number of new drug shortages has steadily declined, owing to the work of the FDA, industry, and other stakeholders. Despite these efforts, we continue to see shortages of medically necessary products. This phenomenon fueled the formation of the Agency Drug Shortages Task Force in July. In 2018, OPQ accelerated or prioritized **125** quality assessments to avert potential drug shortages.

Did you know?

OPQ also establishes quality standards for over-the-counter drugs and certain compounded drug products.

182
Industry meetings OPQ participated in to support the assessment of applications

52
Inspections of BLA facilities prior to licensing approval led by OPQ (15 domestic, 37 international)



INNOVATE

27
Meetings with companies developing emerging technologies

5
Cumulative approvals of applications using continuous manufacturing

Did you know?

Until an application approval this year, all injectable drugs were tested with blue blood harvested from *living horseshoe* crabs to ensure they are safe.

OPQ encourages quality-related innovation in the pharmaceutical sector and within FDA. OPQ aims to minimize barriers to pharmaceutical innovation, promote sensible oversight, and make risk-based decisions. Keeping pace with expanding globalization, accelerating drug development timelines, and advancing technologies requires innovations internal to FDA. A key example of this is the Emerging Technology Program (ETP), which is both innovative within the FDA and aims to encourage innovations in pharmaceutical design and manufacturing. The ETP allows for early engagement with the FDA *even before identifying a drug candidate*. This allows the FDA to identify and resolve potential scientific and policy issues related to new technologies. We continue to expect significant innovations from the pharmaceutical industry.

Innovations from the Pharmaceutical Industry in 2018

- The FDA approved two NDAs based on *continuous manufacturing*. This type of manufacturing eliminates breaks between steps during the process of making a drug. Among other things, this reduces opportunities for human errors during the stops and starts in a process.
- The FDA approved a BLA that uses a revolutionary endotoxin test method (Recombinant Factor C) for drug product release. This new method could reduce or eliminate the need for horseshoe crab blood to ensure injectable drugs are safe.

- The FDA approved the first ANDA for generic EpiPen and EpiPen Jr (epinephrine auto-injector) for the emergency treatment of life-threatening allergic reactions. The development of this complex generic drug-device combination product required rigorous data and assessment to ensure it met quality standards.

Innovations Within FDA in 2018

- OPQ developed an innovative Knowledge-Aided Assessment and Structured Application (KASA) tool for knowledge management and quality assessment. A Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting was held in September to discuss the modernization of application assessment related to KASA.
- The Pre-ANDA program held pre-submission and development meetings for applicants developing complex generic drugs products for the first full year. The Pre-ANDA program facilitates approval of these types of products. Accessory research programs in OPQ study complex drug products across their lifecycles to inform the development and assessment of these products.
- A robust science and research program in OPQ fuels science-based decisions and policies and enables rapid responses to public health issues. OPQ's science and research program includes five Centers of Excellence and an extramural research funding program that provided nearly $6 million in grants to study cutting-edge manufacturing technologies in 2018.

10-0
Advisory committee vote in favor of enhancing submission format related to KASA

40
Number of Pre-ANDA meetings held

149
Peer-reviewed scientific publications with OPQ authors

Science & Research Highlight

In July, the FDA began alerting healthcare professionals and patients of a voluntary recall of certain angiotensin II receptor blocker (ARB) drug products that contained probable human carcinogen impurities. OPQ scientists developed methods to quantify these impurities and performed the FDA's testing of marketed ARB drug products and drug substances. OPQ published these methods to provide options for companies and other regulators seeking to detect these impurities. At the close of 2018, the cause of these impurities remains an ongoing investigation within the FDA.

COMMUNICATE

"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."

OPQ wants the American public to understand the importance of pharmaceutical quality to help them trust their drugs regardless of what they are and where they came from. Patients and healthcare professionals both expect quality drugs. Patients need to be able to trust the medications they are taking. Doctors need to know the medications they prescribe are consistently safe and effective. Pharmacists need to know the prescriptions they house and dispense are stable and reliable. Researchers and engineers need to understand the importance of quality when they pioneer better medicines and envision better manufacturing processes for them. When these stakeholders work with the FDA, we can all drive toward making better medicines available.

88%
Percent of WebMD.com survey respondents who correctly knew the FDA does not set prices for drugs

OPQ made a concerted effort to reach healthcare professionals in 2018. OPQ Director Dr. Michael Kopcha delivered major addresses to audiences of pharmacy professionals at both the Alliance for Safe Online Pharmacies Research Symposium and the American Society of Health-System Pharmacists Midyear Clinical Meeting, which is the largest gathering of pharmacists in the world.

In 2018, the FDA conducted a survey of consumers and patients on their knowledge of pharmaceutical quality on WebMD.com. Unfortunately, nearly 75% of respondents either did not believe or were not sure that drugs manufactured outside the U.S. and sold in the U.S. adhere to strict manufacturing standards and regulations. Most respondents also were either not sure of the quality of these drugs or thought their quality was lower than drugs manufactured within the U.S. Yet, 80% of the FDA-registered manufacturers of active pharmaceutical ingredients are located outside of the U.S. The FDA has the same expectations for quality regardless of whether a drug is made

in the U.S. or abroad and whether a drug is brand-name or generic. To provide this information directly to patients and consumers, Dr. Kopcha participated in a series of "expert Q&As" on drug quality that appeared in WebMD magazine in 2018. More of these features are set to appear in 2019.


Checkup

Small Science in Action


CHECKUP

Drug Quality 101


Checkup

Drug Innovations

Did you read about OPQ at your doctor's office?
OPQ's magazine features are available in 85% of physician offices nationwide - and online

OPQ was also involved in a major study about the uptake of biosimilars published in the *Journal of the American Medical Association* (JAMA). Biosimilars, which are versions of brand-name biological drugs that do not require costly clinical trials, introduce competition in the marketplace, and may offer more affordable options to patients. This study examined uptake of the first approved biosimilar between 2015 and 2016. Nearly one-third of the use of filgrastim products was attributed to the biosimilar version, rather than its brand-name counterpart, less than two years after approval. Further, nearly three-quarters of patients taking the biosimilar had not previously used the brand-name counterpart. This shows that doctors are prescribing, and patients are using, biosimilar drugs. Like other human drugs, the FDA assures that the manufacturer of a biosimilar is capable of meeting quality standards. The FDA has the same expectations for quality whether the drug is a biosimilar or not.

3
Biological products now have two or more biosimilars - improving patient access and driving competition in the market

ENGAGE

OPQ works with our FDA partners to engage our stakeholders and meet the needs of the American public. OPQ recognizes that external stakeholders, including consumer organizations, health professionals, regulated industry, international regulatory authorities, and others, play critical roles in helping us achieve our mission. In 2018, OPQ established programs to engage diverse stakeholder groups to develop and support quality standards for pharmaceutical development and manufacturing. Such engagement is needed to ensure stakeholder perspectives are appropriately considered in our policy-setting and decision-making processes.

15
Applicants to OPQ's Quality Metrics Site Visit Program and **1** site visit completed

17
Pharmaceutical quality guidance documents released

Engaging Stakeholders in 2018

- Many industries use quality metrics to measure product and process quality. In June 2018, OPQ announced two new programs focused on quality metrics. The Quality Metrics Feedback Program and the Quality Metrics Site Visit Program build on stakeholder requests for continued dialogue to inform FDA's use of quality metrics.
- After soliciting stakeholder comments during the guidance development process, OPQ released draft and final guidance documents on quality-related regulatory topics. These topics included impurities, packaging, postapproval changes, inhalers, data integrity, compounding, and chewable tablets.

- OPQ published a public white paper in January 2018 on the Quality Overall Summary section of drug marketing/licensing applications. This document provides some key considerations for applicants when preparing this section of applications to allow for more efficient assessments.
- OPQ provided an Experiential Learning Site Visit Program for OPQ staff to visit pharmaceutical companies across the United States. In this program, staff learned elements of drug development and manufacturing up-close and on-site.
- OPQ was a key participant in the rollout of the New Inspection Protocol Project (NIPP). This project generated standardized electronic inspection protocols to collect information about manufacturers for more efficient and more consistent inspections.
- OPQ published information on the developing Site Engagement Program, which identifies firms for voluntary participation in a quality enhancement program. The FDA will invite these firms to meet and discuss manufacturing issues that could impact drug product quality. Initially, this program will focus on sites where quality issues could disrupt availability.
- Additional countries were recognized as capable of conducting inspections that meet U.S. standards under the Mutual Recognition Agreement (MRA) between the FDA and the European Union. This agreement allows drug inspectors from capable authorities to rely on information from drug inspections conducted within each other's borders. This yields efficiencies for U.S. and European regulators, as well as manufacturers, by avoiding duplication of inspections.
- OPQ helped implement the Global Watch platform to enhance our surveillance ability and better integrate the intelligence gained from FDA field work with sensible regulatory oversight and assessment.

238
OPQ staff participated in the Experiential Learning Site Visit Program to visit and learn from **13** different pharmaceutical companies

12
Additional countries recognized by the FDA under the Mutual Recognition Agreement

We thank those who engaged with us in 2018 and we look forward to continuing working with you in 2019. If you are one of the stakeholders we haven't reached, we invite you to join us in our commitment to quality.

A LOOK FORWARD

"Join us in a commitment to pharmaceutical quality."

In 2018, OPQ used strategic priorities to both meet current challenges and guide future direction. OPQ met work capacity challenges requiring record numbers of application assessments with efficient collaborations within OPQ and across the FDA. OPQ addressed scientific challenges surrounding the increasing use of novel technologies in pharmaceutical design and manufacturing through innovative internal programs that encourage the use of these technologies. OPQ provided major public communications on pharmaceutical quality to tackle the challenge of getting patients, consumers, and healthcare professionals to understand and appreciate pharmaceutical quality. OPQ reached out to stakeholders, asking them to join us in a commitment to pharmaceutical quality by establishing new programs aimed at encouraging these necessary interactions. As we move into 2019, we envision an OPQ that is even better at assessment, inspection, research, surveillance, and policy.

OPQ's evolution includes refining internal quality management practices to make sure we are as effective as possible. It includes honing our integrated quality assessment processes to ensure we are as efficient as possible. It involves better communicating the benefit and risk considerations behind our decisions to ensure quality is appreciated and understood by the public and our FDA partners. It also involves developing new tools that enable and empower better quality assessments of submissions – including the use of structured data provided by applicants.

While some things may change in the future, many will stay the same. The FDA will continue to expect the same quality whether a drug is made in the U.S. or abroad and whether a drug is brand-name or generic or biosimilar. You can continue to have confidence knowing that all FDA-approved drugs have been held to consistent quality standards regardless of the source. Drug quality requirements will continue to apply to all manufacturing facilities - domestic and foreign - and across human drug product areas - brand-name, generics, biologics, biosimilars, and over-the-counter.

Still, we need your help. Even when manufacturers are vigilant, quality issues can arise. Please use the MedWatch system to report suspected drug quality issues to the FDA. You can visit www.fda.gov/medwatch to find the online reporting form for patients and healthcare professionals. We continue to ask you - one of our stakeholders - to join us in a commitment to pharmaceutical quality.

With our collective efforts, OPQ can continue to assure that safe, effective, *quality* medicines are available to the American public.

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

U.S. FOOD & DRUG
ADMINISTRATION

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