U.S. FOOD & DRUG ADMINISTRATION

OFFICE OF PHARMACEUTICAL QUALITY

2017 ANNUAL REPORT

One Quality Voice

February 2018

www.fda.gov

Director's Message

We, at the Office of Pharmaceutical Quality (OPQ), are honored to serve the public health through our mission of assuring the availability of quality medicines for the American public. Our organization focuses on quality, which fundamentally supports the pharmaceutical pillars of safety and efficacy. Quality is what assures that drugs safely and reproducibly deliver the benefit claimed in their label, over their lifecycle. It is what gives the American public confidence in the safety and efficacy of their *next* dose of medicine.

OPQ is providing this report to highlight our primary work accomplishments in 2017. OPQ occupies a unique space at the U.S. Food and Drug Administration (FDA) by reaching across all human drug User Fee programs: new drugs and biologics, generics, and biosimilars—and also over-the-counter drugs and compounded drug products. Further, we reach across the drug product lifecycle: development, premarket, and postmarket. With this report, we emphasize the breadth and depth of the collective efforts across OPQ in 2017. Many drugs are currently available to patients and consumers due to accomplishments stretching across assessment, inspection, surveillance, policy, and research.

2017 brought major challenges for OPQ, both expected and unexpected. For instance, we saw new commitments in conjunction with the reauthorization of the human drug User Fee programs in the Generic Drug User Fee Act, the Prescription Drug User Fee Act, and the Biosimilar User Fee Act. We expected this challenge and were prepared to meet it with the necessary trainings and resources. On the other hand, like you, we witnessed the devastation caused by Hurricanes Harvey, Irma, and Maria. OPQ had over 100 Public Health Service Officers deployed to deal directly with their aftermaths. Those who remained at their OPQ duty stations stepped up to handle the increased workload resulting from these deployments and the infrastructure impacts of these storms. OPQ continues to monitor potential short- and long-term drug shortages in these disaster zones. We will work across Offices to develop mitigation strategies to address these and any other unexpected challenges in the future.

I am personally honored to lead the push for a stronger commitment to pharmaceutical quality in the name of patients and consumers. I look forward to continuing and growing our contribution to global pharmaceutical quality in 2018. We will do this, in part, by working with our business partners and stakeholders to enhance the FDA's pharmaceutical quality programs. It is our shared goal to assure the American public access to safe, effective, *quality* medicines.

Michael Kopcha, Ph.D., R.Ph.
Director, Office of Pharmaceutical Quality

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What Do We Mean by Quality?

A quality drug product:

- Is free of contamination and defects
- Reproducibly delivers the therapeutic benefit claimed in the label

Every pharmaceutical drug product marketed in the U.S. has established identity, strength, purity, and other quality characteristics designed to ensure its safety and efficacy.

OPQ: Assuring Quality Medicines are Available to the American Public

The Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA) has over 1,300 staff responsible for regulating the quality of human drugs marketed in this country. Pharmaceutical quality underpins the safety and efficacy of all drugs on the market. Quality is what gives patients and consumers confidence in the drugs that are on the market—and their next dose of medicine. To do this, OPQ provides assessment, inspection, research, surveillance, and policy to assure that the American public has access to safe, effective, quality drugs. OPQ contributes to the assessment of nearly every type of human drug marketing application including New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Biologics License Applications (BLAs), including 351(k) applications (i.e., biosimilars). OPQ also performs the quality assessment of Investigational New Drug Applications (INDs) and establishes quality standards for over-the-counter drug products and facilities. As such, OPQ is supported by the human drug User Fee programs in the Generic Drug User Fee Act (GDUFA), the Prescription Drug User Fee Act (PDUFA), and the Biosimilar User Fee Act (BsUFA). These were each reauthorized in the 2017 FDA Reauthorization Act as GDUFA II, PDUFA VI, and BsUFA II.

In turn, OPQ supported each of these programs in 2017 with quality assessments contributing to the approval or tentative approval of:

- 132 new drug applications, including 13 breakthrough therapies
- 1,027 generic drug applications, including 150 priority first generics
- 21 biologics applications, including 7 breakthrough therapies and 5 biosimilars

Training was provided to OPQ personnel to help meet the commitments in these reauthorized User Fee programs. OPQ also played a significant role, through research and the Emerging Technology Program, in facilitating pharmaceutical technology advancements—including continuous manufacturing and 3-D printing and public health threats—including the opioid epidemic. To strengthen the FDA's current thinking and procedures, OPQ published ten guidance documents on topics including nanomaterials and the pre-submission of facility information related to prioritized generic drug applications. In addition, OPQ entered a historic concept of operations agreement with CDER's Office of Compliance (OC) and the Office of Regulatory Affairs (ORA) which delineates an operating model with roles and responsibilities for human drug manufacturing facility inspections and evaluations. This truly enables OPQ to work together with OC and ORA regarding facilities using *One Quality Voice*.

Since 2015, OPQ has provided a uniform approach to assure quality across the drug product lifecycle. OPQ consists of an immediate office and eight sub-offices (Figure 1). The Immediate Office (IO) primarily consists of the Director of OPQ, Dr. Michael Kopcha; the Deputy Director of OPQ, Dr. Lawrence Yu; the Science and Research Staff (SRS); and the Program Management and Analysis Staff (PMAS). Under Dr. Kopcha's direction, the IO leads and supports the activities of OPQ's eight sub-offices.

The sub-offices collectively comprise all quality functions of OPQ. The Office of Program and Regulatory Operations (OPRO) coordinates processes associated with quality assessments and facility inspections and facilitates OPQ's quality management system. The Office of Policy for Pharmaceutical Quality (OPPQ) develops, implements, and updates science- and risk-based policies, standards, and guidance documents related to drug product quality and quality assessment. OPRO and OPPQ provide the organizational foundation for the quality assessment of drug products, including biotechnology products.

A fundamental function of OPQ is patient-focused, risk-based quality assessment of drug marketing and licensing applications. This includes BLAs, NDAs, ANDAs, and supplements for drug substance, drug product, manufacturing, and facilities. The drug substance and drug product disciplines of quality assessment for NDAs, ANDAs, and BLAs generally fall under the purview of the Office of New Drug Products (ONDP), the Office of Lifecycle Drug Products (OLDP), and the Office of Biotechnology Products (OBP). These three OPQ offices ensure that applications include appropriate quality standards for drug substances and products. Another element of the quality assessment is provided by the Office of Process and Facilities (OPF) which oversees the assessment

Mission

The Office of Pharmaceutical Quality assures that quality medicines are available to the American public

Vision

The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality

of the manufacturing process and facilities for NDAs, ANDAs, and BLAs and specifically covers the microbiology-related elements of product quality. OPF also helps to assure that pharmaceuticals are manufactured to quality standards at commercial scale over the product lifecycle. For products that have marketing approval, the Office of Surveillance (OS) monitors the state of quality for all regulated manufacturing sites and products.

Broadly supporting OPQ's core mission are the laboratories of OPQ in the Office of Testing and Research (OTR) and OBP which conduct collaborative mission-directed science and research to support the development of science-based standards and policies for safe, effective, quality drug products. The laboratories of OPQ also maintain a state of readiness to address regulatory needs and allow for rapid responses to emergent regulatory and public health issues.

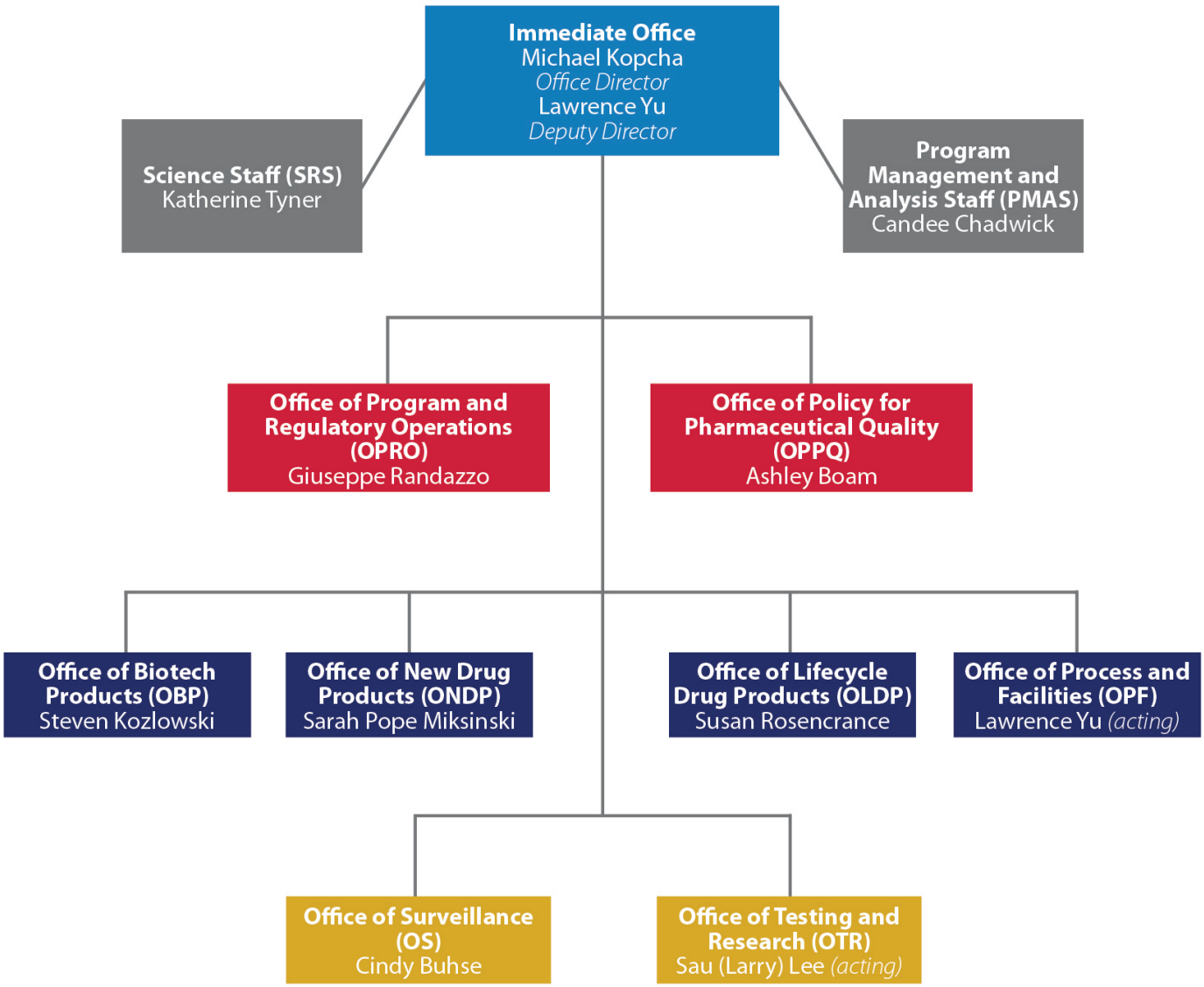


FIGURE 1. Organizational Structure of the Office of Pharmaceutical Quality at 2017 Year End

A Summary of Key Quality Initiatives in 2017

Initiative	Objectives	2017 Accomplishments
Emerging Technology Team (ETT)	• Support industry's development and implementation of innovative approaches in pharmaceutical product design and manufacturing • Identify and resolve potential scientific and policy issues related to new approaches	• Accepted 19 ETT meeting requests and held 20 ETT meetings • Worked to approve the third application with continuous manufacturing, an NDA for a breakthrough therapy, in under 5 months • Published final ETT guidance, Manuals of Policies and Procedures (MAPP) documents, and a public web site
Concept of Operations for Facility Evaluations and Inspections (ConOps)	• Ensure consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision-making for marketing applications • Improve the FDA's operational capacity by eliminating overlapping efforts among CDER and ORA offices	• Reached consensus between CDER and ORA on enhanced roles and responsibilities for all inspections types (Pre-Approval, Surveillance, Post-Approval, and For-Cause) • Finalized and published the signed ConOps agreement in June 2017 • Revised and published the 7356.002 Compliance Program (for surveillance inspections) to better align policy with the agreement
New Inspection Protocols Project (NIPP)	• Provide inspectional assessments to support tracking and improvement of performance across pharmaceutical manufacturers and products • Enhance the production, utility, and consistency of the establishment inspection reports	• Initiated a third pilot for NIPP inspections at sterile drug process facilities • Developed a work plan for expanding the NIPP approach to additional dosage forms

Knowledge-Aided Assessment and Structured Application (KASA)	• Develop tools to modernize the quality assessment of regulatory drug applications and knowledge management throughout the drug product lifecycle that:
	  ◦ Capture and manage knowledge during the lifecycle of a drug product
	  ◦ Facilitate risk identification, mitigation, and communication
	  ◦ Provide a structured template for quality assessment
		• Developed and piloted a dashboard interface, centered around:
		  ◦ Quality risks for critical quality attributes and corresponding mitigation strategies
		  ◦ Control strategies for drug substance and drug product
		• Designed a computer-aided interface to emphasize lifecycle knowledge management and standardization of ANDA quality assessment

Enhanced Core Work Functions	• Support the continuous improvement of drug marketing and licensing application quality assessments • Prepare for commitments in the User Fee programs to ensure the FDA meets or exceeds these commitments	• Implemented 15 standard operating procedures, eight of which directly support core processes • Worked to update the 21st Century Review Desk Reference Guide which describes the review activities required for NDA and BLA applications • Piloted holistic assessment, with one single process and facilities assessor, for non-sterile products of original ANDAs and NDAs • Developed an innovative biopharmaceutics software application to enhance ANDA and NDA assessments

Enhancing Communication and Collaboration

Pharmaceutical manufacturing is globalizing at a rapid pace, making open engagement with stakeholders more important than ever before. Each of the reauthorized User Fee programs emphasizes the need to enhance communication between the FDA and industry to improve predictability and transparency and promote the efficiency and effectiveness of the assessment process.

GDUFA II includes elements to enhance communication between the FDA and industry throughout the ANDA review process, including the use of discipline review letters and establishment of a dispute resolution process. A pre-submission facility correspondence from the applicant can now shorten the review clock for priority generic submissions. Applicants began submitting the first pre-submission facility correspondence in 2017. Of note, GDUFA II also includes significantly enhanced communications surrounding complex generic drugs with the addition of development and pre-submission meetings. In addition, it includes a commitment to communicate final surveillance inspection classifications to facility owners within 90 days of the end of an inspection.

PDUFA VI continues to promote transparency and communication between the FDA review team and the applicant, increase the efficiency and effectiveness of the first cycle review process, and minimize the number of review cycles necessary for approval. Under BsUFA II, one major change is that the 10-month goal date is now within 10 months of the 60-day *filing date*, rather than the receipt date, to allow for additional communications between assessment teams and biosimilar applicants for original applications. In both PDUFA VI and BsUFA II, all original applications and supplements are expected to include a comprehensive list of all manufacturing facilities. If there is a need to inspect a facility that was not included on the list, the FDA may extend the goal date for the application.

In addition to the enhanced communications with applicants surrounding the User Fee programs, the FDA is also increasing communication and collaboration with global regulatory counterparts. As an initial step, the FDA announced in 2017 that, through a Mutual Recognition Agreement (MRA), they will recognize eight European drug regulatory authorities as capable of conducting inspections of manufacturing facilities that meet FDA requirements: Austria, Croatia, France, Italy, Malta, Spain, Sweden and the United Kingdom. Capability assessments of the remaining European Union (EU) member states will follow. In turn, the European Commission determined that the FDA carries out inspections at a level equivalent to the EU. This agreement should enable the FDA and the EU to avoid duplication of drug inspections. Ultimately, this agreement will maximize resources and allow for more coverage of manufacturing facilities, help to identify potential drug quality problems more quickly, and prevent poor quality drugs from entering the U.S. market.

Quality Policy

In 2017, OPQ issued ten guidance documents which reflect the FDA's current thinking on regulatory topics. These touched on issues of great interest, including final guidance on emerging technology and the pre-submission of facility information related to prioritized generic drug applications. Each guidance document undergoes extensive FDA review and is initially published as a draft document open to public comment.

In some cases, these guidance documents also lead to development and publication of Manuals of Policies and Procedures (MAPPs), which describe internal procedures. In 2017, OPQ published or updated ten MAPPs, covering processes including evaluation of emerging technologies and drug shortage management. Other public documents that were published or revised included those related to inspections such as: (i) Staff Manual Guide 9004.1, Policy and Procedures for Requesting Records in Advance of or In Lieu of a Drug Inspection and (ii) Compliance Program 7356.002 Drug Manufacturing Inspections (Surveillance).

OPQ manages and coordinates CDER liaisons to the United States Pharmacopeia (USP), which publishes quality standards for drugs and dietary supplements. In 2017, there were 135 CDER liaisons to USP serving on nearly two dozen Expert Committees and over 150 Subcommittees or Expert Panels. OPQ representatives also participated in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Assembly Meeting in June 2017. ICH quality-related guidelines advanced in 2017 to the implementation and public comment stages.

In 2017, OPQ also responded to 527 controlled correspondence related to generic drug development. *None* missed the GDUFA deadline for providing such a response.

2017 Guidance Documents

Title	Document	Date
Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic Stockpiles; Draft Guidance for Government Public Health and Emergency Response Stakeholders	Draft	April 2017
Current Good Manufacturing Practice for Medical Gases	Revised Draft	June 2017
Child-Resistant Packaging Statements in Drug Product Labeling	Draft	August 2017
CMC Postapproval Manufacturing Changes for Specified Biological Products to Be Documented in Annual Reports	Draft	August 2017
Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products	Revised Draft	August 2017
Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization	Final	September 2017
ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence)	Draft & Revised Draft	November 2017
Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System	Final	December 2017
Drug Products, Including Biological Products, that Contain Nanomaterials	Draft	December 2017
Gluten in Drug Products and Associated Labeling Recommendations	Draft	December 2017

2017 Published MAPPS

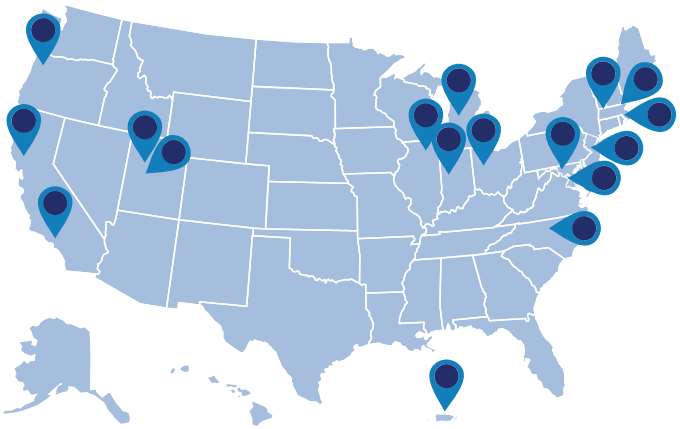
Title	Date
Office of Biotechnology Products and Office of Process and Facilities, Interactions on BLA Assessments	July 2017
Environmental Assessments and Claims of Categorical Exclusion	October 2017
Acceptability of Standards from Alternative Compendia (BP/EP/JP)	October 2017
Drug Product Distribution After a Complete Response Action to a Changes Being Effected Supplement	October 2017
Process for Evaluating Emerging Technologies Related to Quality	October 2017
Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance	December 2017 (posted)
Naming of Drug Products Containing Salt Drug Substances	December 2017

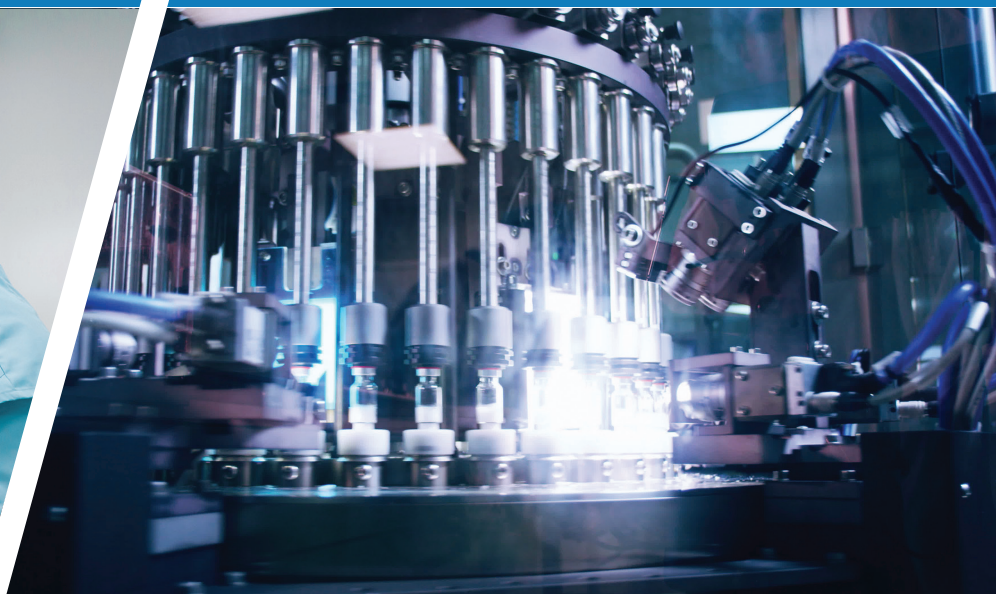
Continuous Improvement and Operational Excellence

OPQ's commitment to quality and continuous improvement extends to internal culture and operations. As part of operational excellence, OPQ identified core processes that tie into key initiatives and support assessment, inspection, research, surveillance, and policy. In 2017, OPQ implemented 15 standard operating procedures (SOPs), eight of which directly support these core processes. Many of these SOPs address elements of the reauthorized User Fee programs. Additional staff resources developed in 2017 to support quality assessments under the User Fee programs included work aids and How-to Guides to enhance consistency and explain internal activities to staff.

Training is a key element of operational excellence in OPQ. OPRO's Learning and Professional Development (LPD) Branch provides relevant, competency-based learning to optimize workforce excellence. In 2017, LPD delivered 139 courses and seminars in support of scientific and regulatory education and professional development. Multiple trainings focused on the changes in the reauthorized User Fee programs, the impact of those changes, and the roles and responsibilities within OPQ.

OPQ also provided an Experiential Learning Site Visit Program for 330 OPQ staff to visit 17 pharmaceutical companies across the United States. In this program, staff learned elements of drug development and manufacturing up-close and toured a variety of drug manufacturing operations. Participants in this program reported that, by providing a better understanding of the pharmaceutical industry and its operations, these site visits enhanced their understanding of pharmaceutical manufacturing, were relevant to their work at the FDA, and will improve assessment efficiency and quality. Considering this success, OPQ has requested more industry participants for this program in 2018.





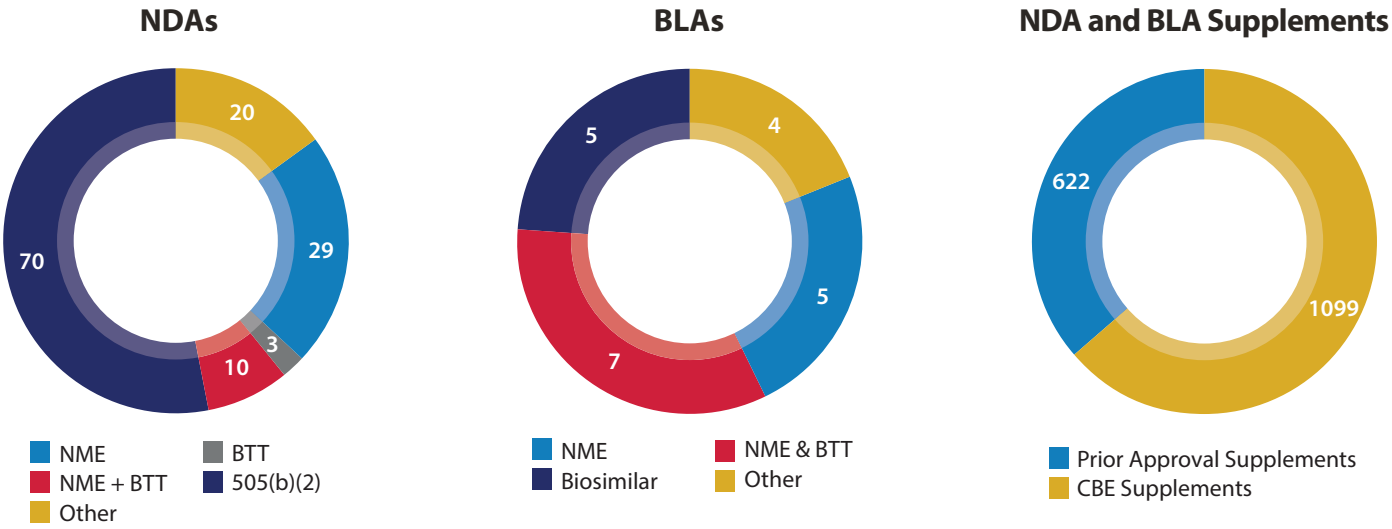
Application Quality Assessment

OPQ is responsible for the quality assessment of nearly every type of human drug marketing application received by the FDA whether an NDA, ANDA, or BLA. This includes drug substances, drug products, manufacturing, and facilities—and can include biopharmaceutics and microbiology. This quality focus stretches throughout the drug product lifecycle through development (INDs, pre-submission meetings), premarket (original submissions, amendments), and postmarket (supplements, annual reports). In exchange for User Fees from industry, OPQ supports the FDA's ability to meet certain performance goals for classes of products.

The Prescription Drug User Fee Act (PDUFA), reauthorized in 2017 as PDUFA VI, allows the FDA to collect fees from companies that produce certain human drug and biological products. In 2017, OPQ supported the FDA in meeting or exceeding all PDUFA V performance goals and approving 20 breakthrough therapies. Challenging NDA approvals included a breakthrough therapy involving continuous manufacturing approved in under five months and aripiprazole tablets with sensor. The latter is the first approval for a technology in which a sensor is activated in stomach acid to send a signal to a patch worn by the patient—and subsequently a smartphone or healthcare professional. Notable BLA approvals included two enzyme replacement therapies for rare diseases, two breakthrough antibody drug conjugates, and a new dosage form combination product.

The Biosimilar User Fee Act of 2012 (BsUFA), reauthorized in 2017 as BsUFA II, allows the FDA to assess and collect fees for biosimilar biological products. In 2017, the Agency approved five biosimilar licenses, including the first two biosimilars with oncology indications and the first two cases in which multiple biosimilar products were approved for the same reference product.

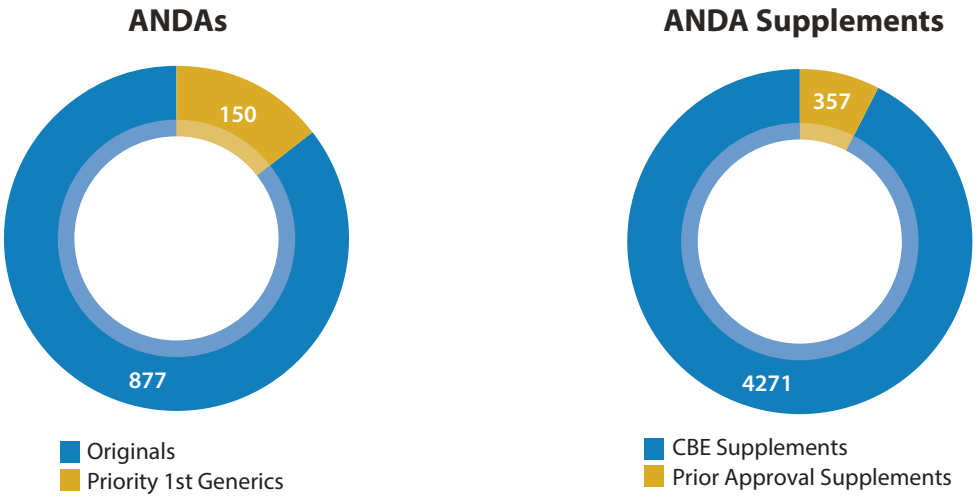
NDA and BLA Approvals and Tentative Approvals in 2017



Cumulative approvals and tentative approvals in 2017 of: (i) NDAs and (ii) BLAs including New Molecular Entities (NMEs), Breakthrough Therapies (BTT), 505(b)(2) applications, and Biosimilars, and (iii) NDA and BLA Supplements including Prior Approval Supplements and Changes-Being-Effected (CBE) Supplements. Note that a *tentative approval* is issued when the application is found approvable prior to the expiration of patents or exclusivities accorded to the innovator (reference listed drug) product. The final approval occurs when all patent/exclusivity issues have expired.

The Generic Drug User Fee Amendments of 2012 (GDUFA), reauthorized in 2017 as GDUFA II, is designed to speed patient access to generic drugs and reduce costs to industry. In June 2017, the FDA also unveiled the Drug Competition Action Plan to outline ways to bring more generic drugs to market by addressing some of the barriers that have hindered generic drug competition. This includes identifying drugs without competition and expediting review until there are three approved generics for all drug products. In 2017, OPQ supported the FDA in meeting or exceeding all GDUFA I performance goals and contributed to the approval or tentative approval of 150 priority first generics. Particularly noteworthy among these were the approvals of glatiramer acetate and sevelamer carbonate products which are challenging due to the highly heterogeneous nature of their active ingredients and the associated challenges with demonstrating equivalence to the brand name products.

ANDA Approvals and Tentative Approvals in 2017

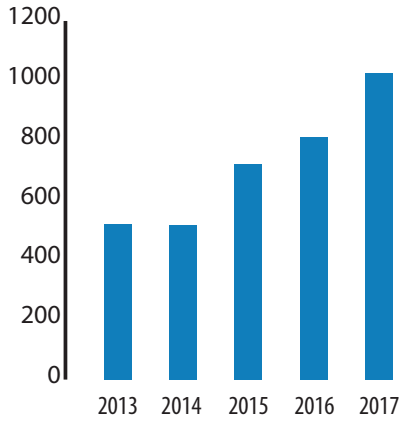


Cumulative approvals and tentative approvals in 2017 of: (i) ANDAs including applications receiving initial Priority First Generic status and (ii) ANDA Supplements including Prior Approval Supplements and Changes-Being-Effected (CBE) Supplements.

BY THE NUMBERS: 2017 ASSESSMENT HIGHLIGHTS

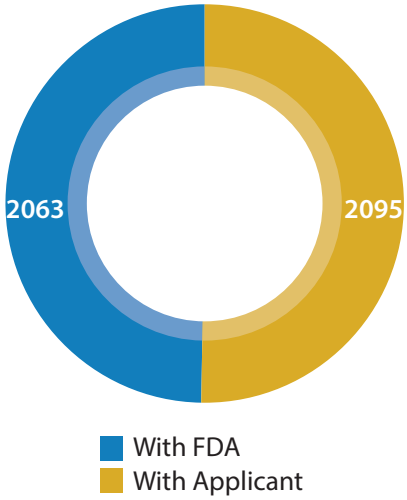
There was a record number of ANDA approval actions (approvals and tentative approvals) in 2017

ANDA Approval Actions by Year



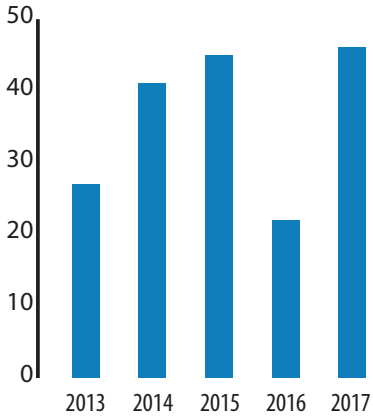
At the end of 2017, for the first time, more ANDAs were pending response from industry than FDA assessment

ANDAs



Novel drug approvals rebounded in 2017

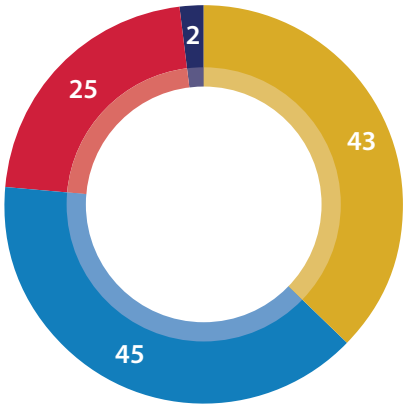
Novel Drug Approvals by Year



The active ingredient or ingredients in a novel drug have never before been approved in the United States. Novel drugs, are often among the more innovative products in the marketplace, and/or help advance clinical care by providing therapies never before marketed in the United States. Note that while many new drug approvals are not novel drugs, they still offer important medical value to patients in need.

In 2017 OPQ expedited many quality assessments due to potential drug shortage considerations

Expedited Submissions Due to Shortage Considerations



Facility Inspection and Evaluation

OPQ works closely with ORA and CDER's OC to provide "One Quality Voice" regarding facility evaluation and inspection. The increasingly complex and global pharmaceutical landscape required the FDA to remodel its oversight of the manufacture of drugs. To this end, in 2017, CDER and ORA entered a historic agreement on a concept of operations (ConOps) for the integration of facility evaluation and inspection for human drugs. The ConOps provides streamlined work flows and clear roles and responsibilities for all parties involved in Pre- and Post-Approval, Surveillance, and For-Cause Inspections at domestic and international drug manufacturing facilities.

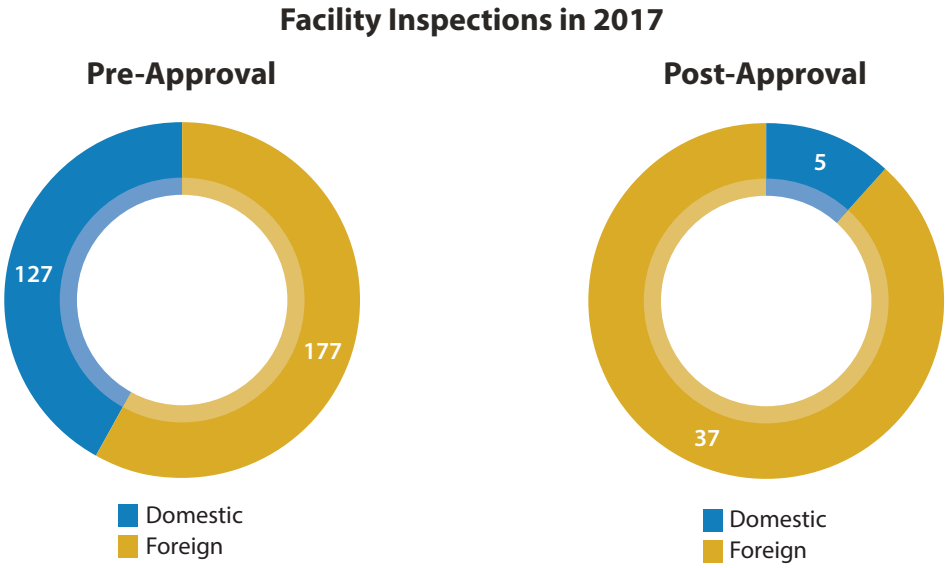
In 2017, OPQ worked with its ConOps partners to develop templates for decisional letters to communicate final inspection classifications within 90 days of the end of Surveillance, Post-Approval, and For-Cause Inspections. These 90-day letters have begun to roll out to facility owners. The ConOps agreement also required the development of standard operating procedures related to inspection and surveillance activities, the transfer of certain activities between OPQ and ORA, and updates to public inspection documents—such as Manuals of Policies and Procedures (MAPPs), Compliance Programs, the Investigations Operations Manual (IOM), and the Regulatory Procedures Manual (RPM).

Pre-Approval Facility Inspections directly support the assessment of drug marketing applications to ensure data accuracy in the application and quality manufacturing at the facility. Meanwhile, Post-Approval Facility Inspections are initiated after drug application approval to verify that the commercial-scale manufacturing operation results in a

drug product as it was designed and approved. While ORA investigators conduct most inspections in the field, OPQ initiates Pre- and Post-Approval Inspections and OPQ subject matter experts participate in these inspections when needed. For example, this may occur in cases when applications involve complex product designs or manufacturing processes. For BLAs, OPF investigators lead the inspections prior to licensing approval. In 2017, OPQ participated in or lead 108 Pre-Approval Inspections for NDAs, ANDAs, or BLAs.

Surveillance Facility Inspections focus on system-wide controls that ensure manufacturing processes produce quality drug products. OPQ maintains a catalog of manufacturing facilities which includes all sites in applications as well as those used by OTC manufacturers. A risk-based Site Selection Model prioritizes these sites for Surveillance Inspections conducted by ORA. In advance of an inspection, OS prepares an up-to-date site dossier for the investigator(s) that includes background information, inspectional history, applications under review, and adverse drug events. In 2017, OPQ prepared 849 site dossiers.

Improved inspection coverage is being achieved by executing a surveillance plan that aims to inspect all previously uninspected sites (foreign and domestic) by the end of FY 2019. In addition, the implementation of the Mutual Recognition Agreement with the European Union (EU) enables the FDA to use inspections conducted by EU drug inspectors. This agreement will allow the FDA to reduce the number of drug manufacturing inspections it performs in Europe and increase overall coverage of facilities prioritized by the Site Selection Model.



The cumulative number of domestic and foreign: (i) Pre-Approval and (ii) Post-Approval Inspections performed in 2017 for ANDAs, NDAs, and BLAs. OPQ lead the 33 Pre-Approval Inspections of BLA facilities (15 domestic, 18 foreign).

Research

OPQ maintains a robust science and research program which supports public health and OPQ's overall mission to assure access to safe, effective, quality drugs. A key effort within OPQ in 2017 was operationalizing five Centers of Excellence (CoEs) to promote centralized, focused, and collaborative scientific platforms to address CDER regulatory needs. They also serve to promote the research capabilities of OPQ and encourage scientific collaboration within the FDA. These CoEs cover the technical areas of:

- Pharmaceutical Analysis and Characterization
- Manufacturing Science and Innovation
- Immunology
- Tumor Biology
- Infectious Disease and Inflammation

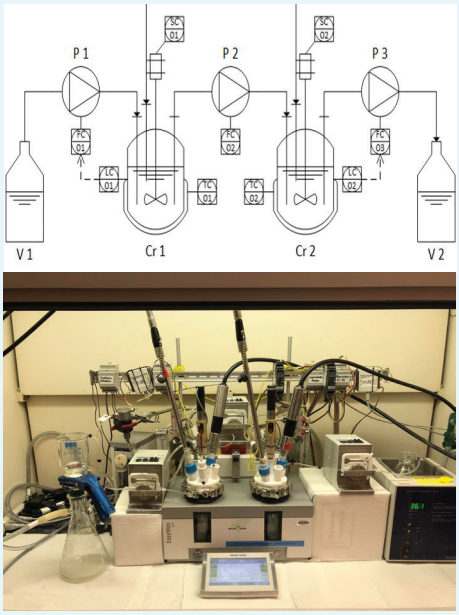
In 2017, OPQ authors contributed to over 150 peer-reviewed articles, largely emanating from these technical areas. These include comprehensive overviews of the challenges posed by biosimilars and nanomaterials in the *Annual Review of Medicine* and *Nature Nanotechnology*, respectively.

OPQ supported innovation in 2017 by expanding its ongoing research program in emerging technologies for both chemical and biological drugs including mass spectrometry for characterization and testing, novel container and closure systems, 3D printing, and continuous manufacturing (see Box 1). The program also funded new extramural research on continuous manufacturing complex drug formulations, which was enabled by the 21st Century Cures Act. In part, this Act specifically authorized grants to support studying the continuous manufacturing of drugs in an effort to modernize U.S. pharmaceutical manufacturing.

Another 2017 research focus was abuse deterrence of opioid drug products. Work in this area included investigating how opioid drug products can be designed and manufactured to discourage abuse and applying research knowledge to aid the quality assessment of abuse deterrent products. OPQ research also continued to uncover the mechanistic understanding of certain adverse drug events (see Box 2). OPQ research directly informed and supported multiple 2017 guidance documents, on topics such as opioids, synthetic peptides, emerging technology, analytical similarity, interchangeability, and nanomaterials. This also included multiple product-specific guidance documents including those for complex generic products.

BOX 1. Research on Manufacturing Science and Innovation

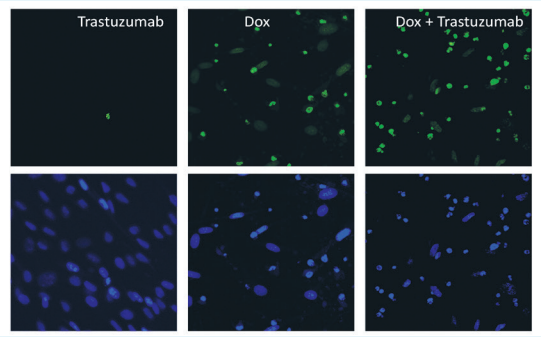
OPQ uses research to prepare for advanced drug manufacturing technologies, including continuous manufacturing and 3D printing. For example, to study a process for drug substance manufacturing called continuous crystallization, OPQ developed and validated a technology to monitor the concentration of the drug substance carbamazepine during the process. Running this process, with this technology, allowed OPQ to identify several risks to consider when developing or assessing such a system. These risks were shared in a resulting publication, which was chosen for distinction as an American Chemical Society Editors' Choice for new research of importance to the global scientific community. This project supported the Emerging Technology Team (ETT) in preparing for the assessment of new technologies related to continuous drug substance manufacturing.



A schematic and photo of the continuous crystallization process in OPQ including three pumps (P1-3), two crystallizers (Cr1-2), and two tanks (V1-2), as reported in Yang, X. et al., *Org Process Res Dev* 2017.

BOX 2. Uncovering the Mechanisms Underlying Adverse Events

Frontline therapy for patients with HER2-positive breast cancer includes treatment with doxorubicin (Dox), a small molecule drug, and trastuzumab, a monoclonal antibody. It is known that Dox leads to cardiac damage in some patients. However, clinicians have observed an increased risk of cardiac damage in patients treated with a therapy of Dox and trastuzumab together. Unfortunately, the molecular basis behind this additive risk was not known. Recent work in OPQ demonstrated that the source of this cardiotoxicity is Dox itself, but that trastuzumab contributes by decreasing the levels of an enzyme found in cardiac cells. This enzyme is a protein involved in cellular repair called type IIB DNA topoisomerase (TOPB2). This study revealed, for the first time, the mechanistic basis for the enhanced risk of cardiac toxicity in patients treated with this therapy. This knowledge improves OPQ's understanding of an adverse event and informs the risk assessment for the safe use of these products.



Human cardiomyocytes treated with trastuzumab (left), Dox alone (middle), and Dox and trastuzumab concurrently (right). The green color (TUNEL signal, top) indicates cells undergoing apoptosis (a type of cell death). The blue color is used to count total cell number (stained nuclei, bottom). Cells treated with both Dox and trastuzumab concurrently have a higher rate of apoptosis relative to cells treated with either drug alone. Figures adapted from Jiang, J.S. et al., *Oncotarget* 2017.

A Look Forward

In 2017, OPQ encountered expected and unexpected challenges impacting the state of pharmaceutical quality. Legislation modified the process of application assessment. Emerging technologies required cutting edge knowledge. Complex products remained difficult to develop and assess. Drug development and assessment timelines continued to shorten. Globalization challenged established regulatory processes. Natural disasters required rapid public health responses. Drug shortages and recalls remained a serious risk for patients. OPQ's commitment to public health catalyzed the effort necessary to face all of these challenges with finite resources.

In 2017, OPQ showed how to meet these and other challenges in the future. Key quality initiatives will allow OPQ to develop internal processes and tools to better address global pharmaceutical quality. Enhanced communication and collaboration will allow OPQ to engage stakeholders across the globe to share the commitment to the importance of pharmaceutical quality. New and revised policies will address challenging regulatory issues of widespread impact. The commitment to operational excellence ensures that OPQ will continue to improve its capabilities and effectiveness. OPQ's competence in application quality assessment and facility evaluation will ensure that the FDA's performance commitments are met. Science and research in OPQ will enable the best science- and risk-based regulatory decisions possible regarding pharmaceutical quality.

Looking forward into 2018, OPQ will continue its evolution as the global benchmark for the regulation of pharmaceutical quality. Traveling through the first full year of the reauthorized User Fee programs, OPQ will continue to explore the most effective and efficient ways to meet the commitments within these more mature programs. In early 2018, OPQ will roll out a 2018–2022 Strategic Plan which will include strategic priorities, objectives, and performance goals to guide OPQ over a 5-year period. To this end, OPQ will strengthen its collaborative culture, promote availability of better medicines, elevate awareness and commitment to the importance of pharmaceutical quality, and strengthen partnerships and engage stakeholders. In doing so, OPQ will lead the push for a stronger commitment to pharmaceutical quality in the name of patients and consumers. Above all else, OPQ will continue to assure that safe, effective, *quality* drugs are available to the American public.

U.S. FOOD & DRUG
ADMINISTRATION

U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
www.fda.gov

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue, Building 75
Silver Spring, Maryland 20993