OFFICE OF PHARMACEUTICAL QUALITY

FDA Pharmaceutical Quality Oversight

One Quality Voice

FDA

Executive Summary

The launch of the Center for Drug Evaluation and Research (CDER) Office of Pharmaceutical Quality (OPQ) is a milestone in FDA's efforts to assure that quality medicines are available to the American public. As a new super-office within CDER, OPQ is strategically organized to streamline regulatory processes, advance regulatory standards, align areas of expertise, and originate surveillance of drug quality. Supporting these objectives will be an innovative and systematic approach to product quality knowledge management and informatics. Concerted strategies will bring parity to the oversight of innovator and generic drugs as well as domestic and international facilities. OPQ will promote and encourage the adoption of emerging pharmaceutical technology to enhance pharmaceutical quality and potentially reinvigorate the pharmaceutical manufacturing sector in the United States. With a motto of "One Quality Voice," OPQ embodies the closer integration of review, inspection, surveillance, policy, and research for the purpose of strengthening pharmaceutical quality on a global scale.

1. Introduction

In 2004, FDA published its final report on pharmaceutical quality for the twenty-first century (1), laying out a vision to modernize the regulation of pharmaceutical manufacturing and enhance product quality. As articulated by Janet Woodcock, Director of FDA CDER, the realization of this vision would result in "a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight." Since 2004, we have witnessed significant progress toward this vision (2); however, at the same time, CDER's mission has been confronted with new and increasingly complex challenges, such as unprecedented drug shortages and recalls, which in part reflect failures in pharmaceutical quality.

FDA is now poised, largely through the creation of the OPQ, to promote "One Quality Voice" through the integration of review, inspection, surveillance, policy, and research for the purpose of strengthening pharmaceutical quality. OPQ will exercise concerted strategies designed to streamline regulatory processes, advance quality standards, and initiate surveillance function of quality within CDER. OPQ is charged with bringing a comprehensive approach to quality oversight to ensure consistent quality over the drug product lifecycle. To that effect, OPQ will develop mechanisms to proactively engage stakeholders and accelerate the adoption of emerging technology to enhance quality and reliability.

2. Challenges to Pharmaceutical Quality

FDA oversight of drug product quality has in the past been exercised through two key functions: 1) regulatory review of drug applications and 2) inspection of facility compliance with current good manufacturing practices (CGMPs). However, data available to the FDA show that pharmaceutical manufacturing and its regulation, in general, continue to manifest a number of problems:

1. Product recall and defect reporting data demonstrate unacceptably high occurrences of problems attributed to inherent defects in product and process design; these data further indicate failures in the implementation of manufacturing process scale-up as well as routine production.
2. There have been alarming shortages of critical drugs over the past few years. Many of these shortages were caused by the use of outdated equipment, reliance on aging facilities operating at maximum production capacity, and lack of effective quality management systems.
3. The number of post-approval supplements received for review has increased over the past decade, in part owing to our current practice of "locking in" an applicant's manufacturing process before it is fully optimized. A burdensome regulatory framework requires manufacturers to submit supplements as they strive for process optimization.
4. Current regulatory review and inspection practices tend to treat all products equally, in some cases without considering specific risks to the consumer or individual product failure modes. A disproportionate amount of regulatory attention is devoted to low-risk products and issues, diverting resources needed for the assessment of high-risk products.

5. FDA has only limited information about the current state of pharmaceutical quality. FDA has no formal means for quality surveillance, except through inspections, and lacks resources to comprehensively review annual reports and other data (e.g., recalls and Field Alert Reports), which may provide significant amounts of pharmaceutical quality information. Furthermore, inspection findings have not been a reliable predictor of the state of quality.
6. Inspection is not well-connected to knowledge gained from product review. Inspections often cannot cover all products and processes, so they rely on a limited subset of representative products and processes, often without reference to the specifics in the approved application. Likewise, product review is often conducted based on pre-marketing data from exhibit or clinical batches; there may be a significant disconnect between these data and the conditions under which the material is manufactured during commercial production.

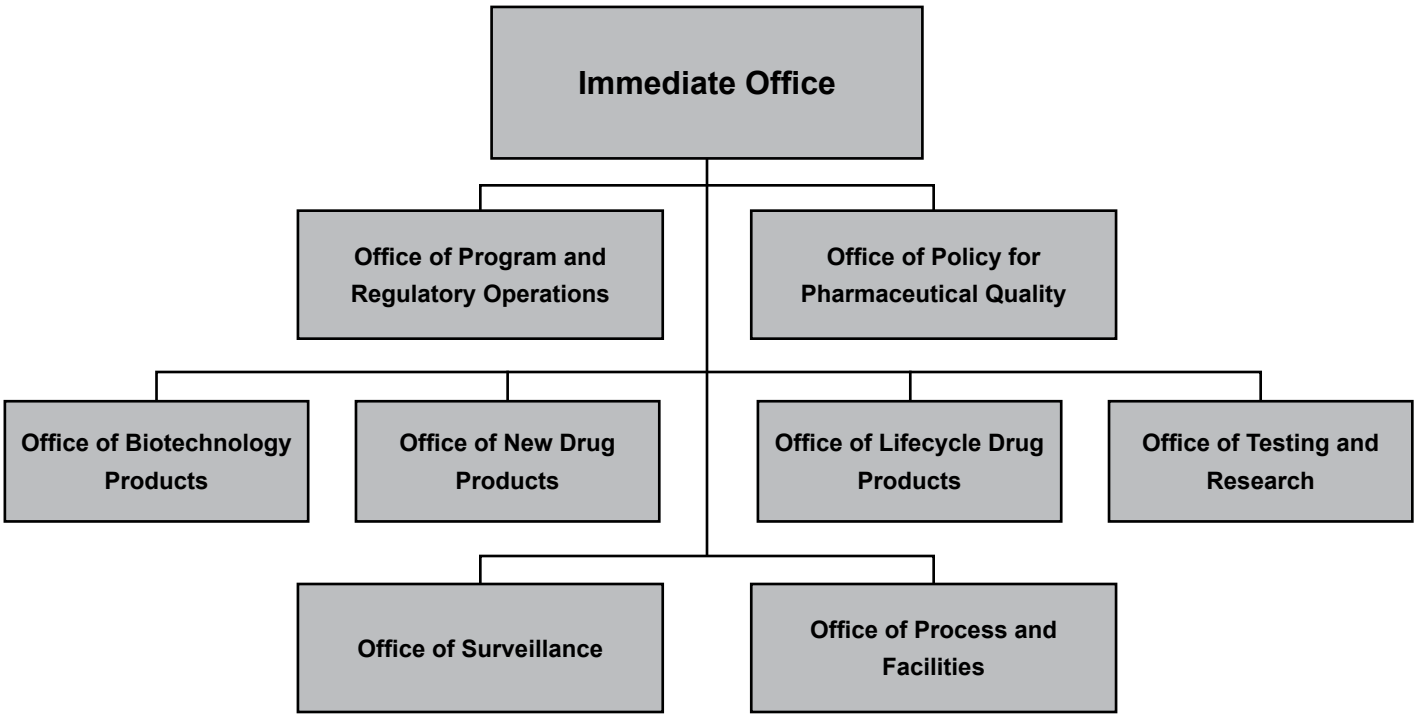
3. FDA/CDER Office of Pharmaceutical Quality

To address the gaps identified above, FDA CDER has created OPQ, which will combine non-enforcement-related drug quality work into one super-office, creating “One Quality Voice” and enhancing our oversight of quality throughout the lifecycle of a drug. The creation of OPQ is consistent with broad efforts at the Agency, as the FDA transforms to distinct commodity-based and vertically integrated regulatory programs with well-defined leads, consistent policy and strategy development, and well-designed and coordinated implementation.

Within CDER, OPQ will provide recommendations on approvability based on consistent drug product quality assessments, and externally, OPQ will communicate with stakeholders early in the review cycle for all products, including generic drugs. OPQ centralizes functions for regulatory review, policy, research and science activities, project management, quality management systems, and administrative activities. In this way, OPQ will establish a uniform approach to pharmaceutical quality across all manufacturing facilities, whether domestic or foreign, and across all drug product areas—new drugs, generic drugs, and over-the-counter drugs.

OPQ has an immediate office and eight sub-offices, as shown in the figure below. The Immediate Office consists of Program Management Analysis Staff (PMAS), providing administrative services, and Science and Research Staff (SRS), coordinating scientific activities within OPQ. An overview of the functions of OPQ sub-offices is provided below.

Office of Pharmaceutical Quality



3.1. Operations, Quality Management System, Learning and Professional Development

The Office of Program and Regulatory Operations (OPRO) is accountable for leading and coordinating regulatory review processes, facilitating a quality management system, and developing and maintaining a learning and professional development program in collaboration with review offices within OPQ. Specifically, OPRO is responsible for managing all processes associated with drug product quality reviews and facility inspections. It designs, develops, and implements internal processes to support drug product quality assessment, in collaboration with the other OPQ offices and the Office of Regulatory Affairs (ORA). OPRO monitors, reports, and leads corrective and preventive actions relating to the performance of internal processes, as defined by standard procedures. Finally, it develops and implements OPQ-specific learning and developmental programs to ensure that skill sets and competencies of staff are maintained and continually strengthened.

3.2. Pharmaceutical Quality Policy

The Office of Policy for Pharmaceutical Quality (OPPQ) develops, implements, and updates science- and risk-based policies, standards, and guidance documents, including chemistry, manufacturing, and controls (CMC) review policy and CGMP/ inspection policy and standards. OPPQ is responsible for evaluating the consistency and adherence to policy/standards of Agency findings of deficiencies and inspectional citations, and it coordinates quality-related communication between Agency and external stakeholders (e.g., Government Accountability Office, Congress, public, industry, pharmacopeias, and other government agencies). The overarching OPPQ mission is to ensure consistent interpretation and application of drug product quality policies and programs, including collaboration with international regulatory authorities.

3.3. Drug Substance, Drug Product, and Biopharmaceutics Review

Within OPQ, quality review of drug substance, drug product, and biopharmaceutics will mainly reside in the Office of Biotechnology Products (OBP), Office of New Drug Products (ONDP), and Office of Lifecycle Products (OLDP). Reviewers in these three offices will assess drug substance, drug product formulation and specification, and data from exhibit or clinical batches. Their combined expertise will ensure that marketed drug products will meet the expected clinical performance consistent with approval data. Clinically relevant quality standards, established through science and risk-based approaches, are essential, because the fundamental purpose of quality oversight is to provide patients with drug products fit for the intended use. Clinically relevant specifications (CRSs) identify and reject drug product batches that are likely to perform inadequately in the indicated patient populations. Important goals include the establishment of acceptance criteria (e.g., for impurities) and dissolution parameters based on clinical relevance, instead of process capability or manufacturing process control.

The biopharmaceutics function will provide the primary link to clinical evaluation of new drugs and bioequivalence determinations of generic drugs; a lifecycle focus on quality will thus preserve parity in quality oversight between innovator and generic products. Furthermore, drug substance, drug product, and biopharmaceutics review functions will work closely with the OPQ research laboratories and policy office to help advance science and establish standards related to pharmaceutical quality, especially for complex products that contain multiple high-risk factors.

3.4. Process, Facility, and Microbiology Review

Process, facility, and microbiology reviewers within the Office of Process and Facilities (OPF) will evaluate pharmaceutical manufacturing process design and controls for the ability to be successfully implemented at a commercial scale. Process and facility reviewers may participate in pre-approval inspections (PAIs) to ensure the proposed control strategy is appropriately implemented. Additionally, microbiologists will evaluate drug substances, drug products, and processes in order to assure quality expectations.

As with drug product review, evaluation of process will employ structured risk assessment as the basis for communication tools within OPQ that capture knowledge relevant in evaluating post-approval changes. Information from the risk assessments will be shared with investigators to assist in pre-approval inspection, quality surveillance, and decision making. To foster the science of new manufacturing technologies and clarify regulatory expectations, process and facilities experts will work closely with OPQ SRS and research laboratories.

3.5. Surveillance and Inspection

Pharmaceutical “quality surveillance” pertains to quality oversight of approved and marketed products. Quality surveillance will greatly enhance FDA’s ability to monitor quality across facilities, providing impetus for both FDA and industry to respond quickly to process trends before serious quality problems can occur. OPQ will identify a set of quality metrics for use in surveillance so the FDA can better monitor and prioritize facilities for risk-based surveillance inspection. The Office of Surveillance (OS) will maintain information on all facilities involved in the manufacture of drugs destined for U.S. patients and will conduct risk analysis and monitoring across the population of such facilities. Surveillance at the product-specific and site-specific level will be concerted through assessment of facility inspection reports and problem reports for drug products. OS will generate and manage knowledge related to the state of quality of drug facilities and products, so that the entire drug supply chain can be better monitored and understood. Intelligence generated through these efforts, along with industry-supplied data, will also strengthen FDA’s ability to make risk-based decisions that govern inspection frequency and coverage.

3.6. Research

The OPQ drug product quality laboratories (including the Office of Testing and Research (OTR) and the OBP laboratory component) conduct research to support the development of scientific standards and policies on the quality, safety, and effectiveness of human drug products. Research objectives are to understand new technologies, modernize current regulatory pathways, and explore new regulatory pathways. The OPQ laboratories provide advice, collaborative research opportunities, and scientific training for review staff on pharmaceutical quality and bioavailability/bioequivalence issues, including formulation, analytical testing, manufacturing, and modeling. They direct drug product quality surveillance testing and laboratory-based investigational activities for CDER as needed for public health. In addition, the OPQ laboratories conduct research on the development, manufacture, testing, and molecular mechanisms of therapeutic biotechnology products, assuring a scientific basis for establishing standards for safety, purity, potency, and effectiveness; they also anticipate emerging technologies and enable the timely provision of biotechnology products to meet patient needs.

4. OPQ Objectives

OPQ’s mission is to assure that quality drugs are available to the American public. OPQ strives to be a global benchmark for regulation of pharmaceutical quality. OPQ will undertake the following objectives:

1. Assure that all human drugs meet the same quality standards to safeguard clinical performance;
2. Enhance science- and risk-based regulatory approaches;
3. Transform product quality oversight from a qualitative to a quantitative and expertise-based assessment;
4. Provide seamless integration of review, inspection, surveillance, policy, and research across the product life cycle; and
5. Encourage development and adoption of emerging pharmaceutical technology

4.1. Assuring that All Human Drugs Meet the Same Standards of Quality to Safeguard Clinical Performance

The ultimate purpose for enhancing pharmaceutical quality is to better serve patients, and the OPQ emphasis on “clinically relevant” data aligns with many patient-focused initiatives within CDER. “Clinically relevant specifications” can be defined as a set of criteria and acceptance ranges to which drug products should conform in order to deliver the therapeutic benefit indicated in the label. Clinically relevant specifications, according to this definition, offer a way to predict how well drug products will perform under real-life, real-use conditions. Clinically relevant specifications increase flexibility within the pharmaceutical manufacturing sector while maintaining quality by establishing acceptance criteria based on clinical relevance, instead of process capability or manufacturing process control.

4.2. Enhancing Science- and Risk-based Regulatory Approaches

Recognizing that some pharmaceutical products and manufacturing processes pose greater risk with regard to patient safety and therapeutic effectiveness, a formal risk assessment process will define the initial scope for reviews and identify

the extent of assessment. The risk-based regulatory approaches will increase the efficiency and effectiveness of review and inspection activities by directing resources to focus more on the assessment of high-risk areas.

FDA recognizes that advancements in regulatory science are needed to keep up with the increasing complexity of drug substance, formulation design, and manufacturing processes of drug products. Regulatory science advancements will aid the identification and in-depth evaluation of risk factors for drug substances, products, and their manufacturing. To meet this challenge, OPQ supports the development of tools and scientific standards by applying its laboratory research, scientific computing capabilities, and expertise, while leveraging resources and collaborating with domestic and international partners in government and academia.

4.3. Transforming Product Quality Oversight from a Qualitative to a Quantitative and Expertise-based Assessment

To keep up with the increasing complexity of drug product and manufacturing processes, as well as to ensure that standards are consistently applied through the product lifecycle and between different drug products, OPQ aims to transform quality oversight from a qualitative to a quantitative and expertise-based assessment. Thus, OPQ is organized based on discipline and expertise (e.g., drug substance, drug product, microbiology, process, and biopharmaceutics). Structured risk assessment will be utilized to facilitate quantitative regulatory evaluations and will serve as a communication vehicle internally and externally. This will increase the efficiency and effectiveness of quality assessments by focusing on the specific risks to the consumer and individual product failure modes. These organizational changes are augmented by the subsequent program initiatives to better achieve this objective.

4.3.1. Product Quality Platform and Informatics

OPQ will not only develop risk assessment tools based on regulatory science, but will also apply its existing knowledge base. OPQ's informatics infrastructure will integrate quality-related information into a risk evaluation framework. Enhanced electronic access to data means that drug substance, drug product, manufacturing, facility, microbiology, and biopharmaceutics information will be available to FDA staff. Cross-cutting risk assessments and data mining will support programs of modernization, affecting all phases of product review, process and facility assessment, and product surveillance.

The many aspects the FDA must navigate in providing efficient, science- and risk-driven assessment are often in flux, owing to the global and complex nature of the drug development landscape. Within this landscape, OPQ will collect, evaluate, and learn from the product quality data submitted to the FDA; these efforts in knowledge acquisition constitute product quality informatics. In this initiative, new informatics tools are linked to a modern understanding of risk management; in this way, reviewers may efficiently resolve routine issues and focus effectively on those scientific issues that pose particular challenges.

Product quality informatics enables an efficient science-driven assessment that requires significant transformation in how OPQ utilizes product quality data. Core areas of product quality informatics include:

- Structured and standardized data submission and collection;
- Knowledge management and communication including established standards for approval and risk mitigation;
- Post-market surveillance and quality monitoring; and
- Quality intelligence production through advanced data analysis and modeling.

4.3.2. Quality Metrics

Facility managers use a wide variety of control metrics to manage quality of manufacturing processes and products within drug facilities. These product quality control metrics are crucial for effective quality management at manufacturing facilities as well as for quality oversight. As part of a more rigorous and comprehensive approach to drug quality surveillance, FDA is developing plans to collect a subset of such metrics to better monitor the current status of product and facility quality across the inventory of FDA-regulated sites and inform FDA risk-based surveillance inspection planning. It is also expected that this additional emphasis on quality measurement will provide greater market awareness of drug quality and give manufacturers further incentive to invest in quality manufacturing, reducing the risk of critical drug shortages.

4.3.3. New Inspection Protocol Project

Inspections have traditionally focused on facility compliance with current good manufacturing practices (CGMPs), with particular attention to process deviations and system failures. Such inspections have not been a reliable predictor of the state of product quality. Consequently, FDA is working to develop a new inspection and reporting paradigm to better assess and record the state of quality in manufacturing facilities; this new paradigm is embodied within an initiative referred to as the new inspection protocol project (NIPP). NIPP is expected to provide a more quality-focused, semi-quantitative approach with streamlined and structured inspection reports. The NIPP protocols utilize expert investigator questions and assessment approaches. NIPP is expected to increase the quality focus of investigator assessments, so that facilities and behaviors found to exceed basic compliance can be recognized as such. Following successful piloting, NIPP-developed protocols will be incorporated into new mobile technology to capture investigator findings and assessments and better support investigators while traveling and during facility inspections.

4.4. Providing Seamless Integration of Review, Inspection, Surveillance, Policy, and Research

OPQ is organized to integrate regulatory review and inspection functions and to evaluate and monitor the quality and inventory of facilities producing marketed products. The knowledge captured during review, inspection, and surveillance activities will be available in a common informatics platform that integrates knowledge between product reviews and facility inspections. The new informatics platform will also enable systematic quality surveillance to help address gaps in FDA's understanding of the current state of pharmaceutical quality and facility inventory. These organizational changes are augmented by the following program initiatives to better achieve this objective.

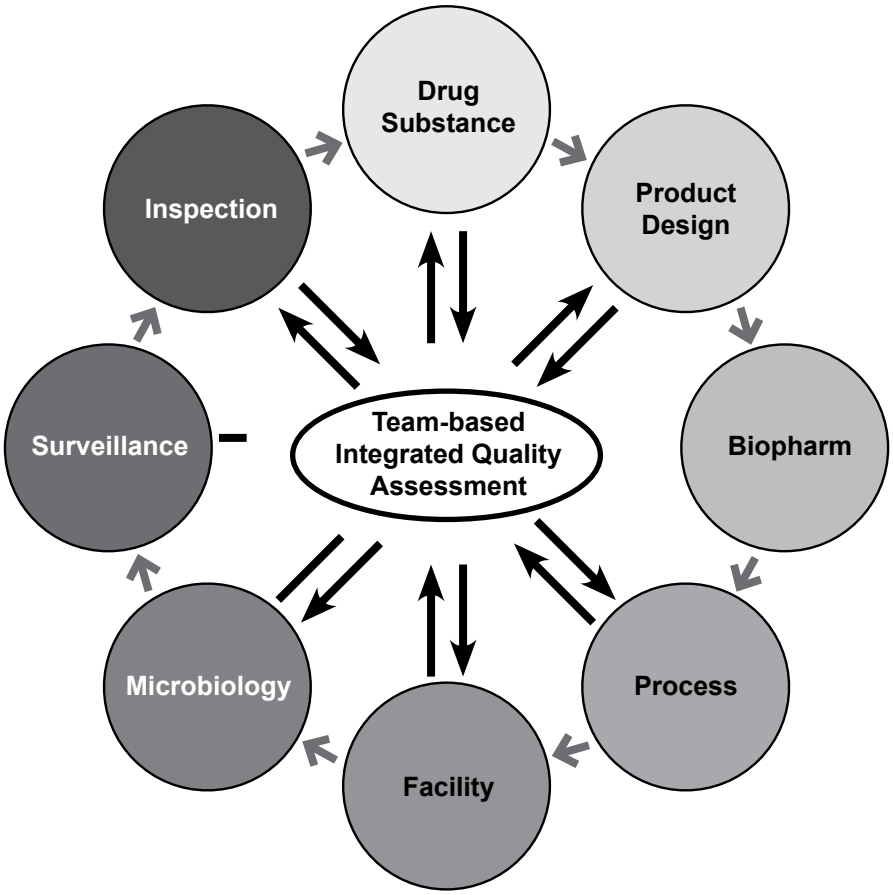
4.4.1. Team-based Integrated Quality Assessment (IQA)

Team-based IQA effectively aligns patient-focused and risk-based drug product quality recommendations. It encompasses biologics license applications (BLAs), new drug applications (NDAs), and abbreviated new drug applications (ANDAs) and is inclusive of drug substance, drug product, manufacturing, and facilities. IQA teams consist of an application technical lead (ATL), a regulatory business process manager (RBPM), discipline reviewers, and additional technical advisors as needed. Review disciplines may include drug substance, drug product, process, facility, microbiology, biopharmaceutics, and ORA investigators. Technical advisors may come from OPQ laboratories, policy, surveillance, and other offices as needed. The ATL is responsible for overseeing the scientific content of the assessment, while the RBPM is responsible for driving the review process and adhering to the established timeline.

The unifying hallmark of IQA—that is, the integration of review and inspection—is encapsulated in the OPQ motto, "One Quality Voice." As quality-driven team members, field investigators are fully apprised of any issue uncovered by CDER reviewers; conversely, reviewers are updated as to any inspectional findings. In many cases, CDER reviewers may participate in an inspection. IQA maximizes each team member's expertise and provides aligned patient-focused and risk-based drug product quality recommendations, inclusive of drug substance, drug product, manufacturing, and facilities. The closer alliance of CDER reviewers and field investigators will enhance the quality assessment of product, ultimately leading to more effective and efficient regulatory decisions on the acceptance of facilities and the overall approvability of applications.

An OPQ pilot study is exploring the potential for IQA to be facilitated through the procedural use of a comprehensively structured document that is based on question-based review and would summarize all critical information relevant to product quality. The quality summary elicited within the pilot is thus akin to the Quality Overall Summary (QOS) that is based upon International Conference on Harmonisation (ICH) risk management principles, and like the QOS, it aspires to capture inherent risks to product quality, detail risk mitigation strategies that are in place, and clarify residual risk pursuant to formulation, process design, and control strategy. The structured format utilized within the OPQ pilot study, emphasizing the critical aspects of quality that manufacturers should address, has proven to be applicable across a number of NDAs and ANDAs. The OPQ pilot has shown that the structured format for summarizing quality information can enhance quality, transparency and consistency of assessments; reduce review documentation time; and facilitate team-based review and communication.

Team-based Integrated Quality Assessment



4.4.2. Lifecycle Management

OPQ intends to follow risk- and science-based approaches to better manage post-approval changes. Within OPQ, OLDP will generally lead the assessment of post-approval changes of generic drugs as well as new molecular entities (NMEs) and non-NME [e.g., 505 b(2)] product NDAs three years and one year after approval, respectively, imparting parity to the review of NDAs and ANDAs. NDA and ANDA parity will also be established by OPF, which will conduct evaluation of process, facility, and sterility-related changes. OBP will continue to lead evaluation of post-approval changes for most biotechnology products, in collaboration with OPF.

4.4.3. Research and Surveillance Empowered by FDA Internal Laboratories

OPQ intends to establish clear standards for quality review and surveillance, and in some instances the mission of OPQ will require research activities that can supply mission-critical data. In addition to data in submissions and those obtained during inspections, product quality data produced from FDA's own laboratories will be essential to the OPQ mission. With the formation of OPQ, a programmatic form of laboratory surveillance will now be implemented, with more sampling and testing than is required through use of U.S. Pharmacopeial Convention (USP) market standards. With additional testing, statistical methods can be used to assess quality and establish a science-based system of surveillance that can predict manufacturing outcomes, identify sources of quality variance, generate alerts when a problematic lot is produced, and assess strengths of manufacturers. A comprehensive system of surveillance will enable the Agency to be more proactive in assessing product quality, allocating resources for inspections, and identifying quality problems in the field. 4.5. Encouraging Development and Adoption of Emerging Technology

4.5. Encouraging Development and Adoption of Emerging Technology

Recognizing that drug shortages and product recalls are commonly related to compromised product or facility quality (e.g., the utilization of outdated technologies and equipment), OPQ's efforts include a focus on encouraging and sustaining improvements in manufacturing quality. The innovative approaches that OPQ envisions are critical to modernizing

the pharmaceutical manufacturing base and improving quality. At the same time, innovation by definition represents challenges to all stakeholders. Regulators are challenged to develop knowledge and experience so that they can develop and implement clear standards. Manufacturers, on the other hand, consider the economic feasibility of incorporating novel technologies, which especially early in implementation may entail unfamiliar risks, costs, and time demands. A collaborative approach is clearly needed that encourages innovation, continuous dialogue, and shared learning to increase predictability and lower regulatory risk of adopting new technologies.

OPQ, led by the SRS, will provide leadership, advocacy, scientific skill, and coordination across the individual OPQ offices to identify relevant emerging technologies and align research and science activities to address outstanding regulatory science questions and to prepare the organization for the future. OPQ will collaborate with academia, industry, and other government agencies to leverage external expertise in addition to internal research to stimulate development of novel manufacturing technologies with the goal of addressing any knowledge and experience gaps. The aim of this OPQ effort is to support advances in pharmaceutical manufacturing technology, which provide new opportunities to address the primary drivers of drug shortages and product recalls and, potentially, to reinvigorate the pharmaceutical manufacturing sector in the United States.

The knowledge gained from OPQ and supported external collaboration will be transferred to the policy, review, and inspection functions within OPQ in a systematic manner. This will lead to guidance development and other actions to encourage manufacturers to adopt new manufacturing technologies, to facilitate their use of modern quality management techniques, and to ensure that FDA regulatory policies reflect state-of-the-art manufacturing science. One example of new technology that FDA is encouraging is “continuous manufacturing.” Continuous pharmaceutical manufacturing offers potential flexibility, quality, and economic advantages over traditional processing methods. Another example of OPQ engagement, along with similar engagement from other offices within CDER, is collaboration with the Biomedical Advanced Research and Development Authority (BARDA) for creative solutions to address drug shortages.

5. Conclusions

The Office of Pharmaceutical Quality is poised to achieve the goals laid out in FDA’s 21st Century Initiative. The establishment of OPQ will result in enhanced transparency and communication between the Agency and industry related to manufacturing technologies, issues, and capabilities, thereby preventing drug shortages and ensuring the availability of high-quality drugs. Additionally, OPQ will:

1. assure that all human drugs will consistently meet quality standards that safeguard clinical performance;
2. utilize enhanced science- and risk-based regulatory approaches;
3. transform product quality oversight from a qualitative to a quantitative and expertise-based assessment;
4. provide seamless integration of review, inspection, surveillance, policy, and research throughout the product lifecycle; and
5. encourage the development and adoption of emerging pharmaceutical technology.

”One quality voice,” resonating throughout the broad community that ultimately brings efficacious, safe, and high-quality drug products to the American public, is OPQ’s commitment and a motto that all OPQ staff proudly share.

6. Reference

1. U.S. Food and Drug Administration (Sep 2004). Final Report on Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach.
2. See, for example: Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (Sep 2004); Guidance for Industry: Q8(2) Pharmaceutical Development (Nov 2009); Guidance for Industry: Q9 Quality Risk Management (Jun 2006); Guidance for Industry: Q10 Pharmaceutical Quality System (Apr 2009); and Guidance for Industry: Q11 Development and Manufacture of Drug Substances (Nov 2012).