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Review

Advancing pharmaceutical quality: An overview of science and research in the U.S. FDA's Office of Pharmaceutical Quality

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ABSTRACT

Failures surrounding pharmaceutical quality, particularly with respect to product manufacturing issues and facility remediation, account for the majority of drug shortages and product recalls in the United States. Major scientific advancements pressure established regulatory paradigms, especially in the areas of biosimilars, precision medicine, combination products, emerging manufacturing technologies, and the use of real-world data. Pharmaceutical manufacturing is increasingly globalized, prompting the need for more efficient surveillance systems for monitoring product quality. Furthermore, increasing scrutiny and accelerated approval pathways provide a driving force to be even more efficient with limited regulatory resources. To address these regulatory challenges, the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA) harbors a rigorous science and research program in core areas that support drug quality review, inspection, surveillance, standards, and policy development. Science and research is the foundation of risk-based quality assessment of new drugs, generic drugs, over-the-counter drugs, and biotechnology products including biosimilars. This is an overview of the science and research activities in OPQ that support the mission of ensuring that safe, effective, and high-quality drugs are available to the American public.

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Contents

Abbreviations: ADF, abuse deterrent formulation; API, active pharmaceutical ingredient; T-DM1, Ado-Trastuzumab Emtansine; ADC, antibody-drug conjugate; CDER, center for drug evaluation and research; CBRN/EID, chemical, biological, radiological/nuclear and emerging infectious disease; CMC, chemistry, manufacturing, and controls; DMD, Duchenne muscular dystrophy; DLS, dynamic light scattering; FDA, food and drug administration; FTIR, Fourier transform infrared spectroscopy; GA, glatiramer acetate; IVIVC, *in vivo/in vitro* correlation; MHC, major histocompatibility complex; MVDA, multivariate data analysis; NMR, nuclear magnetic resonance; OBP, office of biotechnology products; OPQ, office of pharmaceutical quality; OTR, office of testing and research; PAT, process analytical technology; QbD, quality by design; SLEP, shelf-life extension program; TNF, tumor necrosis factor; VLP, virus-like particle.

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1. Introduction

For over a decade, the Center for Drug Evaluation and Research (CDER) in the U.S. Food and Drug Administration (FDA) has followed a vision to modernize pharmaceutical development and manufacturing in order to enhance product quality (FDA, 2004). Over the same time span, there have been increasing challenges with regard to drug shortages and recalls that reflect failures in pharmaceutical quality. Nearly two-thirds of all drug shortages can be attributed to quality failures, particularly due to issues in facility remediation and product manufacturing (FDA, 2013b). In addition, there is increasing scrutiny from the industry and lawmakers, coupled with a greater desire for engagement and dialogue among the regulatory agencies, industry, and patients. At the same time, major technical and scientific advancements have challenged existing regulatory paradigms. Such advancements have impacted biosimilars, precision medicine, combination products, emerging manufacturing technologies, and the use of real-world data.

Pharmaceutical manufacturing is globalizing at an unprecedented pace, making product quality surveillance even more challenging. Furthermore, there is pressure to implement new regulatory mandates (*e.g.*, accelerated approval pathways) with limited resources. To strengthen pharmaceutical quality in the face of present and future challenges, the FDA established the Office of Pharmaceutical Quality (OPQ) within CDER on January 11, 2015 (Yu and Woodcock, 2015). The science and research program within OPQ is built to support the mission and priorities of the FDA related to pharmaceutical quality (FDA, 2013a). Science and research in OPQ forms the foundation for risk-based quality evaluation including review, inspection and surveillance, as well as for quality-related standard and policy development for all drug product areas – new drugs, generic drugs, over-the-counter drugs, and biotechnology products. In this review, OPQ science and research includes: (i) testing and scientific investigation of methods and data that aid drug quality evaluation and (ii) proactive research for development of scientific tools and approaches for evaluating the safety, performance and quality of products.

There is a mandate to better utilize science and research to advance public health by improving access to safe, effective, and high-quality drugs. From the product quality perspective, the FDA needs science and research to keep pace with rapid advances in technology and increasing complexity of FDA-regulated products. For example, since the dawn of OPQ, approvals have been seen for products of new manufacturing paradigms including the first 3D printed product (Norman et al., 2016), the first three biosimilars (FDA, 2016b; Holzmann et al., 2016; von Schaper, 2016), the first new drug product made using continuous manufacturing (Vertex, 2015), and the first switch from a batch process to a continuous process for a previously FDA-approved product (PharmaTech, 2016). OPQ science and research helps the FDA, once perceived as a potential obstacle to innovation, actively promote and support new technology paradigms with the potential to improve overall drug manufacturing quality and reliability (Yu et al., 2016). The information gained supports review and inspection, as well as accelerated development timelines for new drugs and biotechnology products, including biosimilars.

OPQ's designation as a super-office indicates that multiple offices operate within its purview (Fig. 1). Under this organizational structure, OPQ can integrate the science and research findings into review, inspection, and surveillance across the product lifecycle. The laboratories of OPQ – established in the Office of Biotechnology Products (OBP) and the Office of Testing and Research (OTR) – conduct mission-directed, collaborative laboratory-based science and research activities to support the development of scientific standards and policies for safe and effective quality drug products. OPQ also collaborates with other Centers and stakeholders (*e.g.*, academia) to conduct research to advance pharmaceutical quality as appropriate. These efforts collectively build the capacity for evaluation and monitoring, address mission-critical science matters, and maintain a state of research readiness that anticipates FDA needs while allowing for rapid response to emergent regulatory issues. There are seven key areas in OPQ's science and research portfolio:

- Manufacturing Science and Innovation.
- Drug Quality Standards.
- Advanced Characterization of Complex Mixtures and Biologics.
- Physicochemical Characterization of Complex Formulations and Dosage Forms.
- Post-Market Product Quality and Public Health Issues.
- Immunogenicity and Immunology.

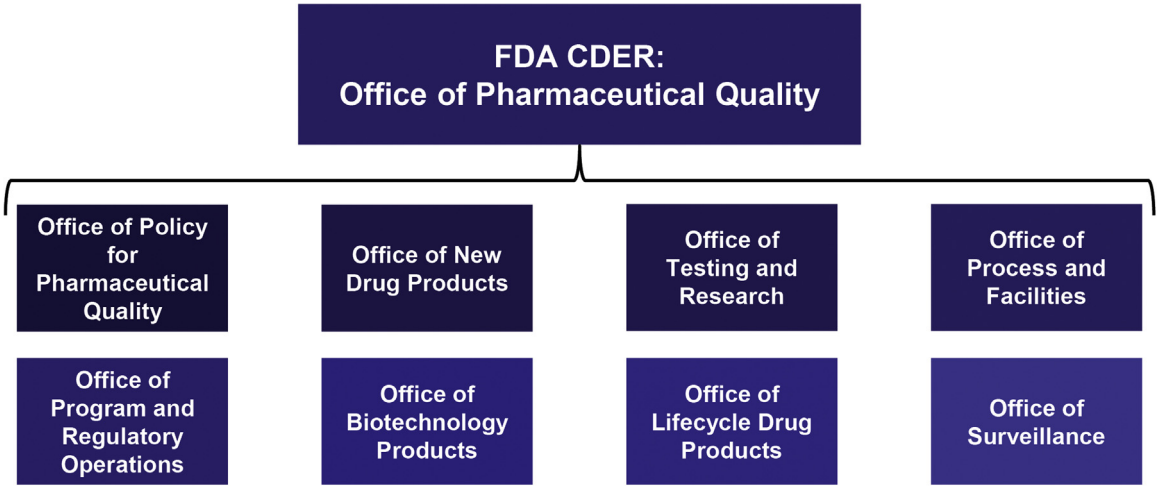

Fig. 1. Organization of CDER's Office of Pharmaceutical Quality (OPQ). There is an immediate office and eight sub-offices within the purview of OPQ. The immediate office consists of Program Management Analysis Staff (PMAS), providing administrative services, and Science and Research Staff (SRS), who help coordinate scientific activities within OPQ. Governance of scientific and research work in OPQ is the mission of OPQ's Research Review Coordinating Committee which supports, promotes, priorities and funds OPQ laboratory research that will have an impact on review and policy decisions. Committee membership is drawn from OPQ's immediate office and 8 sub-offices.