

OFFICE OF CLINICAL PHARMACOLOGY Annual Report 2017





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OUR VISION

To improve public health by building and translating knowledge of drug response into patient-centered regulatory decisions of the highest quality.

Examples presented in this Annual Report are illustrative and are not a comprehensive representation of 2017 information. For detailed information on the content of this report or the Office's other activities, please contact ocp@fda.hhs.gov.

DIRECTOR'S MESSAGE

Innovative, collaborative, and effective – in my view, these three words summarize the achievements of the Office of Clinical Pharmacology (OCP) in 2017. Each year, we respond to emerging scientific and regulatory challenges in the development of new treatments for patients. Collectively, we work to promote and protect global public health through application of clinical pharmacology principles in an efficient and timely manner. This year our office achieved many noteworthy accomplishments. We played a critical role in the reauthorization of the Prescription Drug User Fee Act (PDUFA) wherein the goals and commitments outlined in PDUFA VI promise to bolster use of clinical pharmacology-related regulatory decision tools (e.g., through “model-informed drug development” and biomarker qualification). We also contributed to elements of the 21st Century Cures Act related to targeted drugs for rare diseases. Guidance and policy efforts were remarkable this past year, as our office led and finalized 3 clinical pharmacology-focused guidances and provided input on 35 Center for Drug Evaluation and Research (CDER) guidances and policy documents. We continued to strengthen regulatory research capabilities to ensure relevant and timely scientific output to address public health issues, with specific and tangible impact. We continued to invest in our staff by offering team collaboration training, and by enhancing employee engagement through strategic use of diverse communication mechanisms. We placed significant emphasis on fostering relationships with internal and external stakeholders. As a result, we increased productivity, as well as efficiency of internal and external communication methods. Additionally, optimizing organizational effectiveness remains a top priority. The Office focused significant attention on process enhancements in our core functional areas (Regulatory, Guidance & Policy, Outreach & Communication, Consults, and Research), including new molecular entity review (both standard and priority), labeling review, training, and workshop/meeting planning.

Our annual report highlights the breadth and depth of our staff’s contributions to the Office of Translational Sciences (OTS), CDER, and the Agency and their important work in service to public health. This report also recognizes the collective efforts of OCP staff and our collaborators to promote the OCP, OTS, CDER, and Food and Drug Administration (FDA) missions. I am very proud our efforts and actions in 2017 fully embodied our core values of Stewardship, Leadership, Excellence, Connectedness, Diversity & Respect.

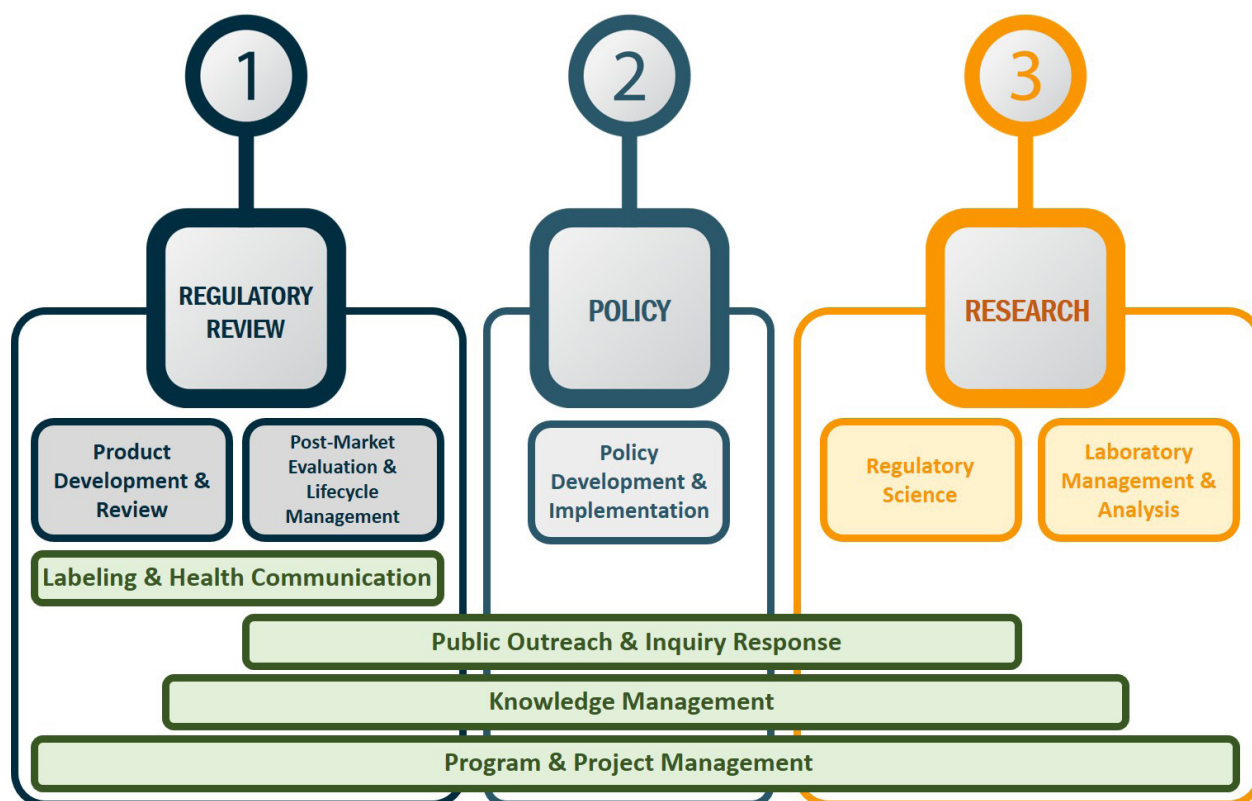
We in OCP wish to dedicate this report to our good friend and colleague Darrell Abernethy. His scientific contributions spanning a lifetime, his service to clinical pharmacology, and his career-long commitment to fostering generations of young scientists have shaped our field in innumerable ways. Darrell’s passion and presence in our lives is sorely missed.

Issam Zineh

OFFICE OF CLINICAL PHARMACOLOGY
Office of Translational Sciences
Center for Drug Evaluation and Research

ORGANIZATIONAL HIGHLIGHTS

OCP is a dynamic, purpose-driven organization whose two-fold mission is to 1) play a pivotal role in advancing development of innovative new medicines by applying state-of-the-art regulatory science and clinical pharmacology principles; and 2) to promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product lifecycle. We accomplish our mission through fulfilling three core functions: regulatory review, policy development and implementation, and research. These are strengthened through effective communication, outreach, and executive program and project management.



PDUFA VI

Scientific advances in clinical pharmacology have led to the development of new approaches to assess safety, efficacy, and performance of medical products. Model-Informed Drug Development (MIDD) was explicitly identified in PDUFA VI as one such novel approach. MIDD is the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to inform drug development and regulatory decision making. Our efforts in MIDD are aimed at developing new approaches, standards, and tools to better account for and predict 1) diseases and how they progress, 2) relationships between biomarkers and outcomes of interest, and 3) variability in therapeutic responses. In 2017, we began assembling the internal resources and establishing processes to meet PDUFA VI goals related to MIDD and complex innovative trial designs.

ORGANIZATIONAL HIGHLIGHTS

— Organizational Enhancements

Our role as clinical pharmacologists in regulatory decision-making continues to evolve, and we constantly assess, adapt, and advance our science and organization. OCP's organizational enhancements in 2017 addressed therapeutic innovation and emerging public health needs, and included establishing the Office's Therapeutic Biologics Program (TBP) and laying the foundation for harmonizing clinical pharmacology efforts in Lifecycle Management (LCM). Expanding on the previous year's Office-wide effort to define OCP's core processes and understand the organization's desired roles and responsibilities for OCP project managers, a transition team was established to identify need-based, priority processes for immediate project management integration. These included New Drug Application (NDA)/Biologics License Application (BLA) review, workshop planning, Citizen Petition review, and management of our biologics/biosimilars research portfolio. Furthermore, team building and organizational connectedness underscored many of our organizational enhancements.

1

THERAPEUTIC BIOLOGICS PROGRAM

Building on the successes of OCP's Biologics Oversight Board (BOB) and collaborations with colleagues in other offices including (but not limited to) the Office of New Drugs, Office of Biotechnology Products, and Office of Biostatistics, OCP established the TBP in 2017. TBP is charged with broad oversight of policy development and cross-divisional collaboration on biologics and biosimilar program reviews. Clinical pharmacology considerations (e.g., drug disposition, pharmacology and biomarkers, quantitative methods, drug safety, clinical trial methods) are critical to the rational development and optimal use of biologics. Additionally, with the emergence of biosimilar product development in recent years, there is a Center-wide need to ensure organizational readiness to advance and integrate the best possible science into the development, regulatory review, and policy development of biosimilars (and therapeutic biologics more generally).

2

LIFECYCLE MANAGEMENT

Building upon last year's efforts to harmonize OCP's approach to the application of clinical pharmacology and biopharmaceutics principles across a drug's lifecycle, the Office evaluated the current landscape and scope of activities in support of LCM. A crucial component of this was proactively engaging key stakeholders to identify LCM activities that OCP can help support. Staff initiated pilot mechanisms to enable expert scientific exchange across review units in OCP and with relevant stakeholders on all significant LCM issues in Investigational New Drug Application (IND), NDA, and Abbreviated New Drug Application (ANDA) submissions, as well as to ensure consistent application of policy within OCP. Formalizing this OCP initiative is expected to facilitate identification and timely resolution of all significant LCM issues that arise from the pre-IND to post-NDA approval phases.

OCP: A FOCUS ON ORGANIZATIONAL PROCESSES

— Priority Processes Identified in 2017



*BsUFA, Biosimilar User Fee act

TEAM BUILDING The Outward Mindset

The importance of connectedness as a core value was highlighted in 2017 OCP teambuilding training, the specific focus of which was collaboration. Senior leadership and Office staff were challenged to build collaboration, innovation, and group problem-solving skills through practice of "The Outward Mindset" approach. Moving forward, OCP staff committed to internalizing the concepts of "Outward Mindset" with personal behaviors to achieve collaborative target results.

REVIEW ACTIVITIES

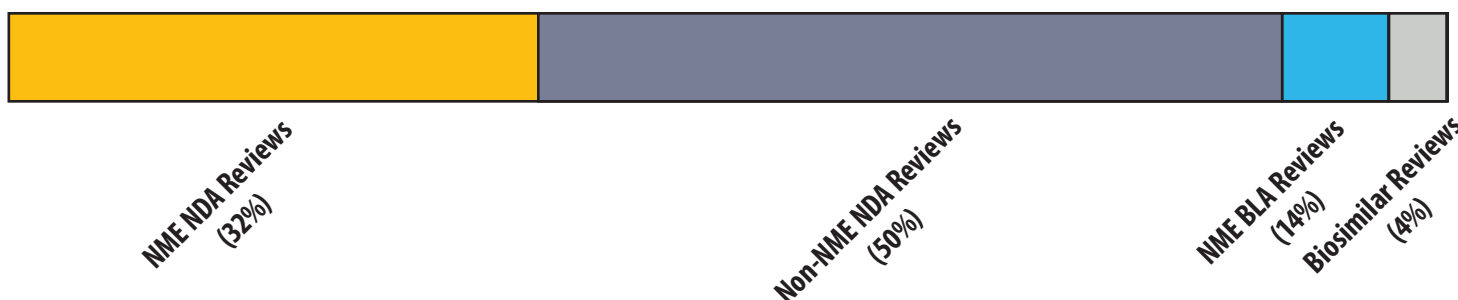
— Regulatory Review

OCP's core regulatory review function covers the spectrum of drug development phases, from pre-clinical to post-approval activities. In 2017, OCP fulfilled this core function by reviewing regulatory submissions under expedited timelines and newly integrated review frameworks. OCP staff completed over 3600 reviews and consults for drugs and biologics in 2017. In addition to impacting drug development (INDs), our review contributions impacted 46 novel drug approvals, either as new molecular entities (NMEs) under NDAs or as new therapeutic biologics under BLAs, 28 of which were approved using one or more of FDA's expedited pathways.

CLINICAL PHARMACOLOGY REVIEWS

NDA and BLA Reviews in 2017

(Percentage of 185 Total NDA and BLA Reviews)



Public Health Needs - OCP Review Under Expedited Timelines

(Percentage of Novel Drug Approvals
by Expedited Review Category*)

PRIORITY REVIEW - 61%

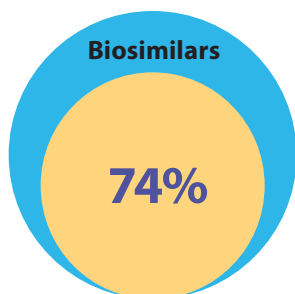
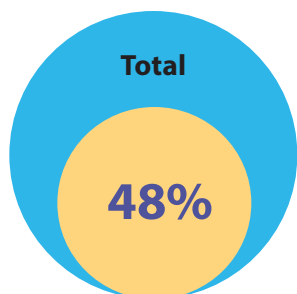
FAST TRACK - 39%

BREAKTHROUGH THERAPIES - 37%

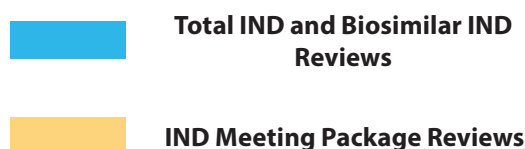


*New drug approvals can fall under multiple expedited review categories.

Direct interaction with drug developers is crucial to convey clinical pharmacology-related direction on development programs. The majority of OCP IND reviews were for meeting packages, the outcomes of which are thoughtful, streamlined, and comprehensive development plans.



OCP IND REVIEWS IN 2017



NOTABLE OCP REVIEW CONTRIBUTIONS IN 2017

MITIGATION OF RISK

- Identified deficiencies in pharmacokinetic (PK) assay and unreliability in PK data for a pediatric indication, leading to a Complete Response
- Evaluated the potential underlying biological mechanisms and pharmacokinetic/pharmacodynamic (PK/PD) data related to suicide safety events observed in a development program
- Assessed the risk associated with inhibition of a vitamin receptor and potential for central nervous system toxicity

REFINED TARGET POPULATION

Refined breakthrough therapy designation for a specific peptide to include patients with genetic alterations upstream of target

INFLUENCED DEVELOPMENT PLAN/TRIAL DESIGN

- Identified deficiencies and limitations in proposed interchangeability plans and recommended alternative design to support a proposed biosimilar
- Proposed a plan to use PD biomarkers to identify an efficacious human dose under the FDA Animal Rule for the treatment of Hematopoietic Syndrome - Acute Radiation Syndrome
- Deemed current evidence does not support pediatric extrapolation for antiemetic drug development programs

OPTIMIZED DOSING REGIMEN

- Recommended further optimization of dose for a new target-based therapy for a rare disease
- Ruled out a proposed dose in product labeling based on review of exposure-response and subgroup analysis results
- Conducted PK/PD analysis for a biologic to support dosing recommendations in adolescent patient population
- Recommended exploration of doses in a post-marketing requirement (PMR) trial for purposes of optimizing benefit and mitigating risk
- Used modeling/simulation (M/S) and physiologically-based PK modeling (PBPK) to inform dosing in patients with renal impairment based on PK data and probability of target attainment analyses

EVALUATED/PROPOSED BRIDGING OR EXTRAPOLATION STRATEGIES

- Used a novel PK bridging strategy for a glucocorticoid based on biopharmaceutics properties and PBPK, as well as all available clinical pharmacology information, to bridge from an unavailable, decades-old clinical trial formulation to a to-be-marketed formulation
- Identified a quantitative relationship between pulmonary vascular resistance (PVR) and exercise capacity in adults to support approval in pediatric pulmonary artery hypertension (PAH) patients based on PVR

EMERGENT PUBLIC HEALTH NEEDS

— Drugs in Pediatrics and Pregnancy

In 2017, OCP-led analyses supported bridging and extrapolation strategies and optimized dosing regimens for 8 entities approved for use in children, adolescents and pregnant women:

ESLICARBAZEPINE ACETATE

& PERAMPANEL: Both drugs approved for adjunctive and monotherapy treatment of partial onset seizures in pediatric patients

BENZNIDAZOLE: Treatment of Chagas disease in pediatric patients

BENRALIZUMAB: Add-on maintenance treatment of patients with severe asthma aged 12 years and older with an eosinophilic phenotype

BOSENTAN: Treatment of PAH (idiopathic or congenital) in pediatric patients

LAMIVUDINE: In combination with other antiretroviral agents for the treatment of human immunodeficiency virus-1 (HIV-1) infection in pediatric patients

NITISINONE: Treatment of pediatric patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine

RILPIVIRINE: In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve patients with HIV-1 RNA less than or equal to 100,000 copies/mL

REVIEW ACTIVITIES

— Consults and Citizen Petitions

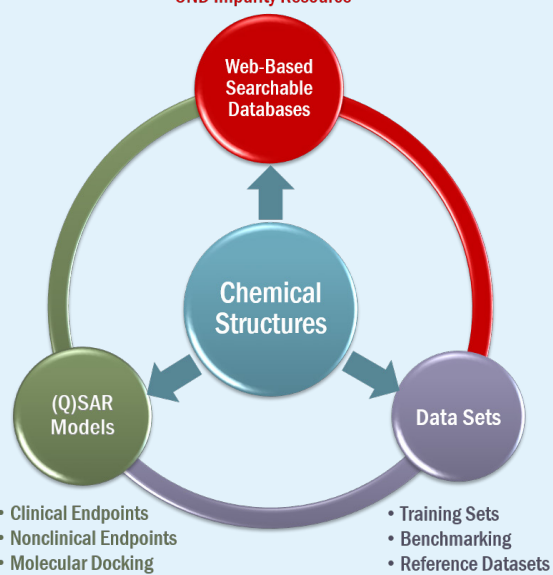
OCP responded to 327 consult requests and reviewed 21 Citizen Petitions in 2017. We viewed these as unique opportunities to foster collaboration within and between Centers and Offices on complex regulatory issues; this year's requests originated from a wide range of internal stakeholders, including the Office of Regulatory Policy, Office of New Drugs, Office of Generic Drugs, Office of Product Quality, Office of Prescription Drug Promotion, Office of Surveillance and Epidemiology, and the Center for Devices and Radiological Health.

DRIVERS OF INNOVATION

— Using Chemical Informatics to Inform Regulatory Decision Making

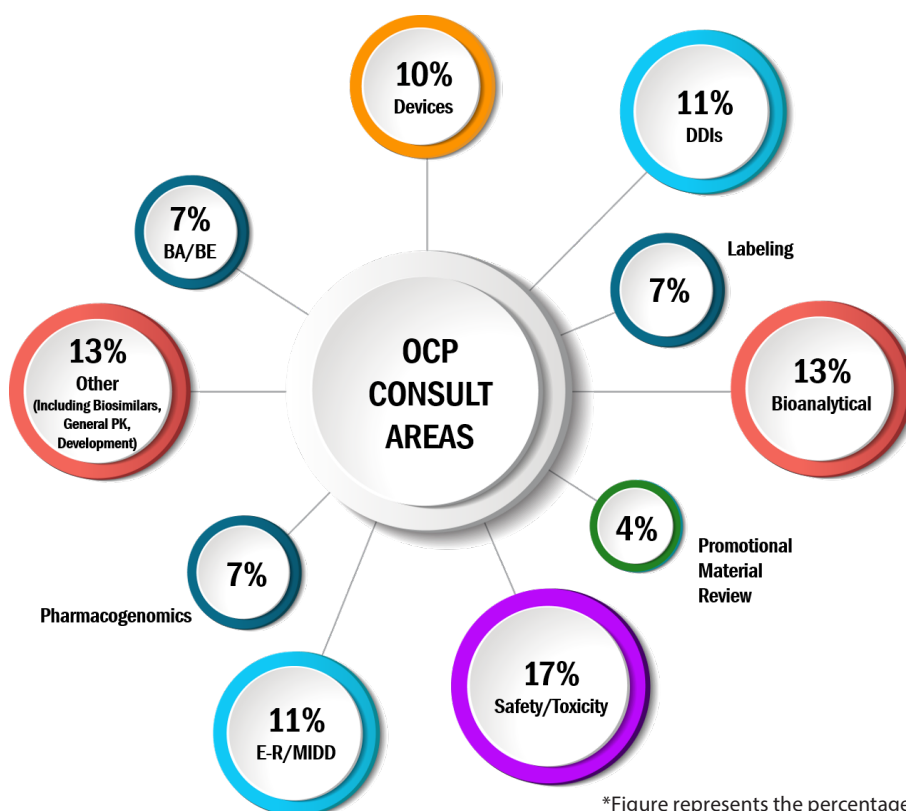
In 2017, OCP analyzed 697 chemicals to support regulatory review decisions for both new and generic drugs. These analyses were performed in response to 266 consultations received by the Chemical Informatics Program in OCP's Division of Applied Regulatory Science. OCP developed and improved chemical informatics tools to provide structure-based safety assessments focused on non-clinical and clinical endpoints of regulatory significance, including genetic toxicity, carcinogenicity, hepatotoxicity, and cardiotoxicity.

- Rodent Carcinogenicity
- In-House Consult Database
- OND Impurity Resource



*(Q)SAR, Quantitative Structure-Activity Relationship

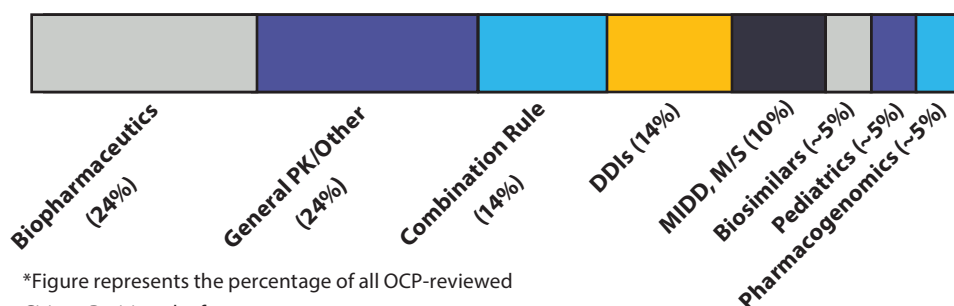
2017 OCP CONSULTS by Focus Area



*Figure represents the percentage of all non-chemical informatics consults related to a specific focus area.

BA/BE, Bioavailability/Bioequivalence
DDI, Drug-Drug Interaction

2017 CITIZEN PETITIONS by Focus Area



*Figure represents the percentage of all OCP-reviewed Citizen Petitions by focus area.

REVIEW ACTIVITIES —Advisory Committee Meetings

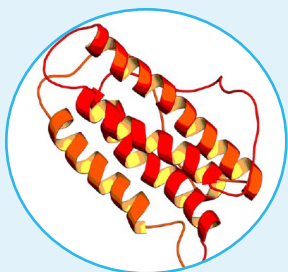
OCP was involved in 14 Advisory Committee (AC) Meetings in 2017, sharing state-of-the-art review science and gaining independent advice from outside experts on a variety of clinical pharmacology-related issues.

ATALUREN PERIPHERAL AND CENTRAL NERVOUS SYSTEM AC

Our Contributions

E-R analyses and in vitro mechanism of action studies informed questions about evidence of effectiveness in Duchenne muscular dystrophy.

BEVACIZUMAB and EPOETIN HOSPIRA ONCOLOGIC DRUGS AC



Our Contributions

- Biosimilarity assessment as basis for these approvals for treatment of metastatic colorectal, lung, renal cell, and cervical cancer (bevacizumab) and anemia due to chronic kidney disease, non-myeloid malignancies with chemotherapy, elective surgery (Epoetin Hospira)

MECHANISTIC MODELING AND SIMULATION PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY AC

Our Contributions

Presented strategies, approaches, and challenges in MIDD with specific focus on PBPK modeling and simulation and mechanism-based risk prediction/safety assessment

PHARMACOGENOMICS PEDIATRIC AC

Our Contributions

Discussed precision medicine landscape and case studies in pediatric pharmacogenetic interactions

RITUXIMAB HYALURONIDASE ONCOLOGIC DRUGS AC

Our Contributions

PK bridging of formulations as evidence of effectiveness to support approval for follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia

EMERGENT PUBLIC HEALTH NEEDS

— Opioid Crisis

OCP contributions to Advisory Committee Meetings in 2017 addressing the Nation's opioid crisis include:

BUPRENORPHINE

JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUG AC AND THE DRUG SAFETY AND RISK MANAGEMENT AC

- OCP-led PK/PD analyses supported evidence of effectiveness for treatment of opioid dependence.

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS AC AND THE DRUG SAFETY AND RISK MANAGEMENT AC

- Outlined requirements for extrapolation of evidence of effectiveness for treatment of opioid dependence in pediatric patients

CAM2038

JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUG AC AND THE DRUG SAFETY AND RISK MANAGEMENT AC

- PK analysis of new subcutaneous depot dosage formulation for weekly and monthly release of bupivacaine demonstrated higher exposure versus current daily formulation, supporting non-approval of higher doses for treatment of opioid dependence.

SUBLOCADE

JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUG AC AND THE DRUG SAFETY AND RISK MANAGEMENT AC

- Analysis of drug blockade for treatment of moderate to severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine containing product

GUIDANCE & POLICY

— *Guidances, Manual of Policies & Procedures (MaPPs), and Internal Quality Procedures (IQPs)*

The evolving scientific landscape requires contemporary policy documents to help advance drug development and regulatory decisions. The OCP Guidance Modernization Initiative was in full force in 2017, and our office worked with internal and external stakeholders to systematically identify, develop, and implement state-of-the-art scientific guidances, policies, and procedures. In 2017, we collaborated with groups within and across centers in FDA on 35 drug development-related guidances and policy documents spanning a range of therapeutic areas.

OCP'S 41 COLLABORATIVE POLICY-RELATED EFFORTS ACROSS THE AGENCY

- 3 MaPPs
- 14 Draft Guidances
- 11 Final Guidances
- 1 Template
- 2 Technical Specifications Documents
- 1 Compliance Program Guidance Manual
- 1 Needs Assessment
- 8 Others

Guidance Spotlight

Paving the Path for Safe and Effective Drug Use

OCP-LED GUIDANCES ON DRUG-DRUG INTERACTIONS (DRAFT GUIDANCES)

- Represents a significant achievement for our Office and highlights our commitment to promoting therapeutic optimization and improving public health
- Aims to help drug developers design drug-drug interaction studies that provide meaningful clinical information on how to manage risks when a patient is taking more than one drug
- Describes a systematic, risk-based approach to the assessment of DDIs

DDI GUIDANCES:

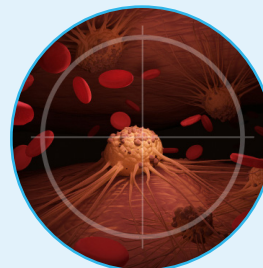
- 1 *In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies*
- 2 *Clinical Drug Interaction Studies -- Study Design, Data Analysis, and Clinical Implications*

Guidance Spotlight

Fostering Innovative Approaches to Drug Development

DEVELOPING TARGETED THERAPIES IN LOW-FREQUENCY MOLECULAR SUBSETS OF A DISEASE

- First abbreviated guidance under CDER's limited guidance process pilot that utilizes a shorter bulleted format to communicate key ideas in a more streamlined fashion
- Cross-Center effort to encourage streamlined approaches for drug researchers and developers to enable more efficient access to safe and effective, novel targeted therapies for the patients who need them
- Specifies the evidence needed to demonstrate effectiveness for a variety of molecular subsets within a particular disease



GUIDANCE & POLICY

— Working Groups, Committees & Task Forces

The commitment of OCP staff to multidisciplinary, collaborative science was evidenced by staff participation on over 130 committees, task forces, and working groups in 2017. This included work at the Office-, Center- and Agency-levels, as well as national and international, efforts.

2017 OCP Working Groups by Focus Area

Regulatory and Review-Related:
75 (55%)

Other (including animal welfare, research methods, biosafety):
16 (12%)

General Clinical Pharmacology Topics:
12 (9%)

Product/Class/Therapeutic-Specific:
11 (8%)

Education and Training:
8 (6%)

Tech/Tools/Standards:
6 (4%)

Workplace Culture:
6 (4%)

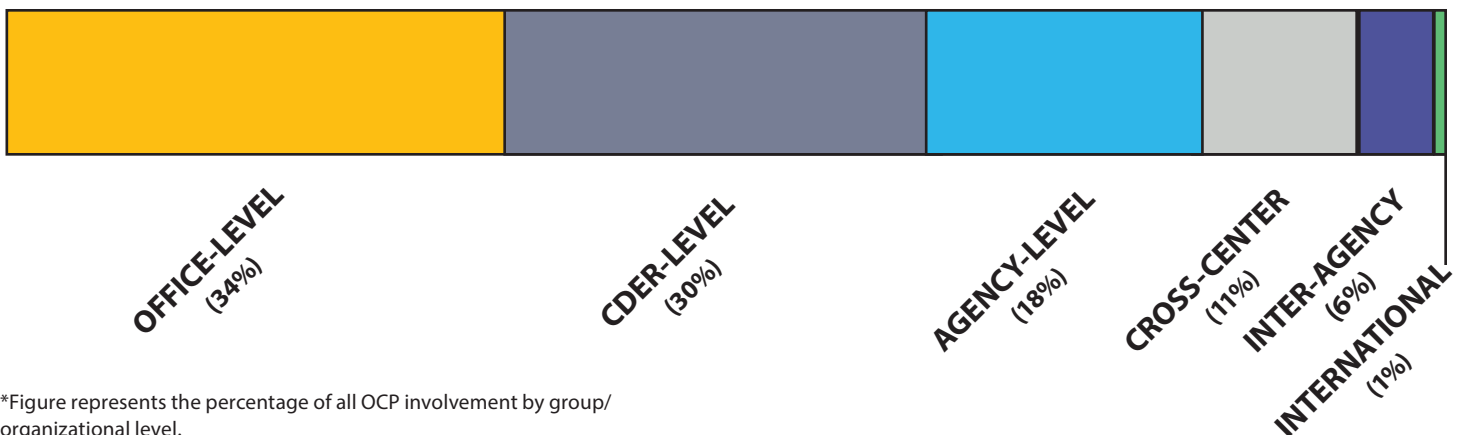
Clinical Trial Design/Drug

OCP WORKING GROUP TOPICS

Animal Rule	Drug Safety
BCS & Biowaivers	Guidance & Policy
Bioanalysis	Labeling
Biomarker Qualification	Modeling
Biosimilars	Nanoparticles
Communication	Pharmacogenomics
Diagnostics	Review Processes

BCS, Biopharmaceutics Classification System

2017 OCP INVOLVEMENT in Committees, Task Forces, and Working Groups, by Group Level



*Figure represents the percentage of all OCP involvement by group/organizational level.

RESEARCH & COMMUNICATION

— Research Projects

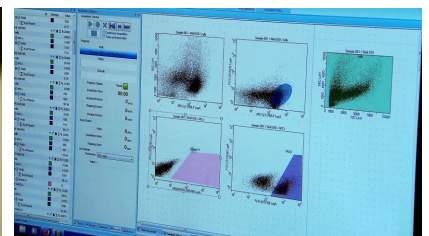
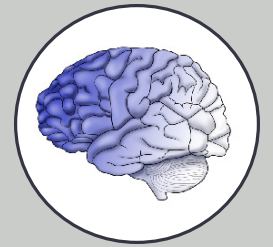
Regulatory research is fundamental to OCP's mission to promote therapeutic optimization and individualization, and advance the development of innovative new medicines. In 2017, research activities in the Office spanned a wide range of research topics, and many were enabled by the Critical Path, Regulatory Science and Review Enhancement, and the Office of the Chief Scientist programs (including Medical Countermeasures Initiative and Centers of Excellence in Regulatory Sciences and Innovation programs). Our review and research staff undertook 243 research projects in 2017, surpassing previous years' efforts, to help inform CDER regulatory review decisions and drug development science.

Research Spotlight

STREAMLINING ANTIPSYCHOTIC DRUG

Objective: establish an exposure-response relationship for antipsychotics based on efficacy findings of immediate-release and long-acting injectable antipsychotic formulations sharing the same active moiety, with a view to streamlining clinical development and minimizing unnecessary clinical trials

This project explores the potential of approval of long-acting injectable antipsychotics with a PK bridging only approach and assessment of PK profile to assure efficacy throughout the dosing interval of the long-acting injectables.



OCP RESEARCH PROJECTS

Primary Focus Areas

PATIENT FACTORS 42



IN VITRO,
IN VIVO,
DISEASE &
(Q)SAR
MODELS **28**



DDIs **29**



SAFETY/
TOXICITY **36**



$\sum_{i=1}^n (f_{mi} \times CL_{int,mi})$
MIDD,
M/S, **25**
& PBPK

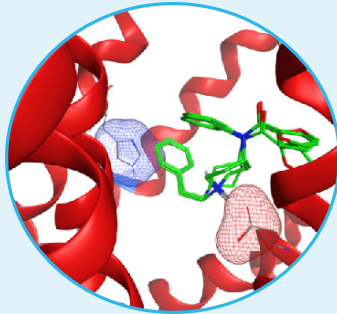
*Figure represents numbers of completed and ongoing projects in primary focus areas.

DRIVERS OF INNOVATION

A STRUCTURE-BASED APPROACH FOR ASSESSING ABUSE POTENTIAL OF DESIGNER DRUGS

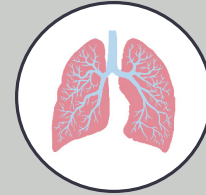
Objective and Methods

The current opioid epidemic has led to a rise in “designer” synthetic street drugs, including pharmacologically-uncharacterized fentanyl derivatives more potent than fentanyl itself. OCP developed a multi-component computational approach to assess a newly-identified drug’s risk to public safety, including three-dimensional molecular docking models. When paired with expert opinion, this approach provides guidance on whether that drug merits immediate placement into Schedule I of the Controlled Substances Act (i.e., emergency drug scheduling).



Research Spotlight

EVALUATION OF COMBINED EFFECTS OF OPIOIDS AND SEDATIVE PSYCHOTROPIC PRODUCTS ON RESPIRATORY DEPRESSION



Objective: provide relative risk information for combination use of an opioid with selected sedative psychotropic drugs, with a goal of informing labeling change decisions for those selected drugs

This project uses a rat model of opioid-induced respiratory depression to assess the potential for additive or synergistic exacerbation of respiratory depression of various opioids when co-administered with sedative psychotropic drugs. Frequently prescribed sedative psychotropic drugs were selected for testing if they lacked pre-existing animal or clinical data to either implicate or exonerate their ability to induce respiratory depression when used alone or to exacerbate opioid-induced respiratory depression when used with an opioid.



Research Spotlight

DISEASE SYSTEMS ANALYSIS: OSTEOPOROSIS



Objective: utilize disease systems analysis toward a generic framework for characterizing disease progression and treatment effects in osteoporosis

This project uses modeling and simulation methodologies to establish a quantitative link between short-term bone turnover biomarkers and fracture rate, the efficacy endpoint of osteoporosis trials.

Research Spotlight

APPLIED REGULATORY SCIENCE

OCP’s dedicated research group, the Division of Applied Regulatory Science (DARS), works together with OCP review divisions and others throughout the Agency to answer regulatory review questions, inform regulatory decision-making and address emergent public health needs. Innovative research performed by DARS and review staff spans the translational research spectrum including in vitro and in vivo laboratory research, in silico computational modeling and informatics, and integrated clinical research covering clinical pharmacology, experimental medicine, and postmarket analyses.

PREDICTIVE SAFETY/ EFFICACY MODELING

NON-CLINICAL AND CLINICAL SAFETY & EFFICACY BIOMARKERS

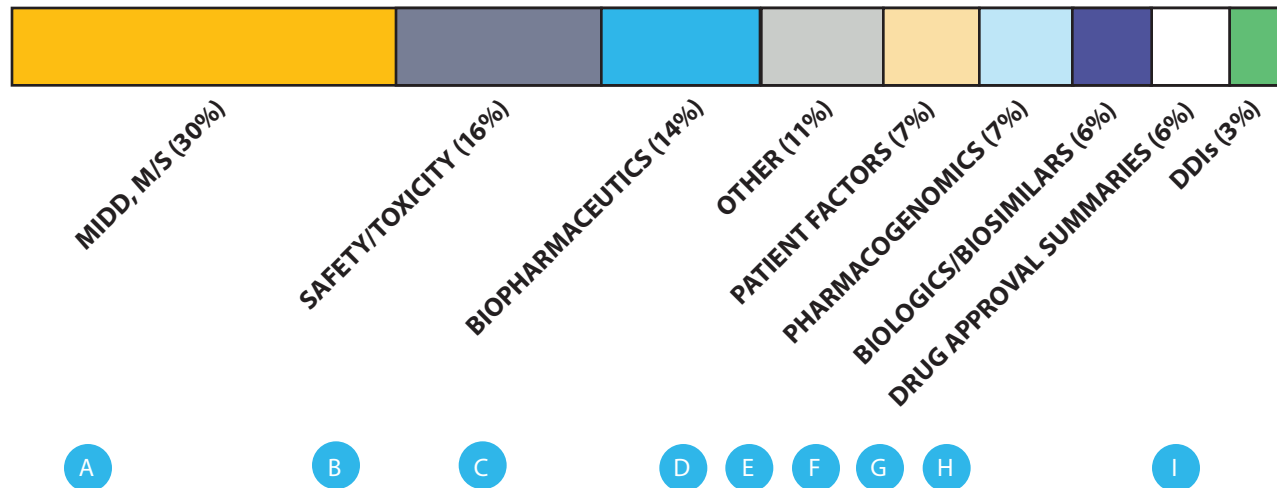
INNOVATIVE CLINICAL TRIAL DESIGNS

RESEARCH & COMMUNICATION

— *Scientific Publications*

OCP staff members authored 109 journal articles published in 2017, and over 15% of them involved collaborations among OCP divisions. Many OCP publications were multidisciplinary and included collaborators from throughout the Center.

2017 OCP PUBLICATIONS BY FOCUS AREA



*Figure represents the percentage of all OCP publications by focus area.

REPRESENTATIVE MULTIDISCIPLINARY OCP PUBLICATIONS IN 2017

<p>A</p> <p>MIDD, M/S</p>	<p>B</p> <p>SAFETY/TOXICITY</p>	<p>C</p> <p>BIOPHARMACEUTICS</p>
<p>Modeling and Simulation in Dose Determination for Biodefense Products Approved Under the FDA Animal Rule</p> <p>J Pharmacokinet Pharmacodyn 2017 Apr;44(2):153-160</p>	<p>MicroRNA Biomarkers of Pancreatic Injury in a Canine Model</p> <p>Exp Toxicol Pathol 2017 Jan;69(1):33-43</p>	<p>Impact of the US FDA “Biopharmaceutics Classification System” (BCS) Guidance on Global Drug Development</p> <p>Mol Pharm 2017 Dec 4;14(12):4334-4338</p>
<p>D</p> <p>OTHER</p>	<p>E</p> <p>PATIENT FACTORS</p>	<p>F</p> <p>PHARMACOGENOMICS</p>
<p>Clinical Trials in a Dish</p> <p>Trends Pharmacol Sci 2017 Jan;38(1):4-7</p>	<p>The Role of the Kidney in Drug Elimination: Transport Metabolism and the Impact of Kidney Disease on Drug Clearance</p> <p>Clin Pharmacol Ther 2017 Sep;102(3):436-449</p>	<p>Anticoagulation Endpoints with Clinical Implementation of Warfarin Pharmacogenetic Dosing in a Real-World Setting: a Proposal for a New Pharmacogenetic Dosing Approach</p> <p>Clin Pharmacol Ther 2017 May;101(5):675-683</p>
<p>G</p> <p>BIOLOGICS/BIOSIMILARS</p>	<p>H</p> <p>DRUG APPROVAL SUMMARIES</p>	<p>I</p> <p>DDIs</p>
<p>Perspectives on the Current State of the Biosimilar Regulatory Pathway in the United States</p> <p>Clin Pharmacol Ther 2017 Nov 20 [Epub ahead of print]</p>	<p>Osimertinib for the Treatment of Metastatic Epidermal Growth Factor T970M Positive Non-Small Cell Lung Cancer</p> <p>Clin Cancer Res 2017 May 1;23(9):2131-2135</p>	<p>Clinical Drug-Drug Interaction Evaluations to Inform Drug Use and Enable Drug Access</p> <p>J Pharm Sci 2017 Sep;106(9):2214-2218</p>

RESEARCH & COMMUNICATION

— Presentations & Workshops

2017 OCP Scientific Rounds

This year's OCP Scientific Rounds hosted by OCP units offered a forum for presentation, discussion, and debate of timely and complex scientific and regulatory topics.

OCP Scientific Rounds Topics

Is Demonstration of PK Comparability Needed to Support Presentation Change for Biological Products?

Confidence Interval Criteria: Should it Include 1?

The Section 12 Guidance

Optimization of Short-Term Schizophrenia Trials

How Easily Can One Precisely Aim at Moving Targets? Myths and Challenges of Pharmacogenomics and Precision Medicine

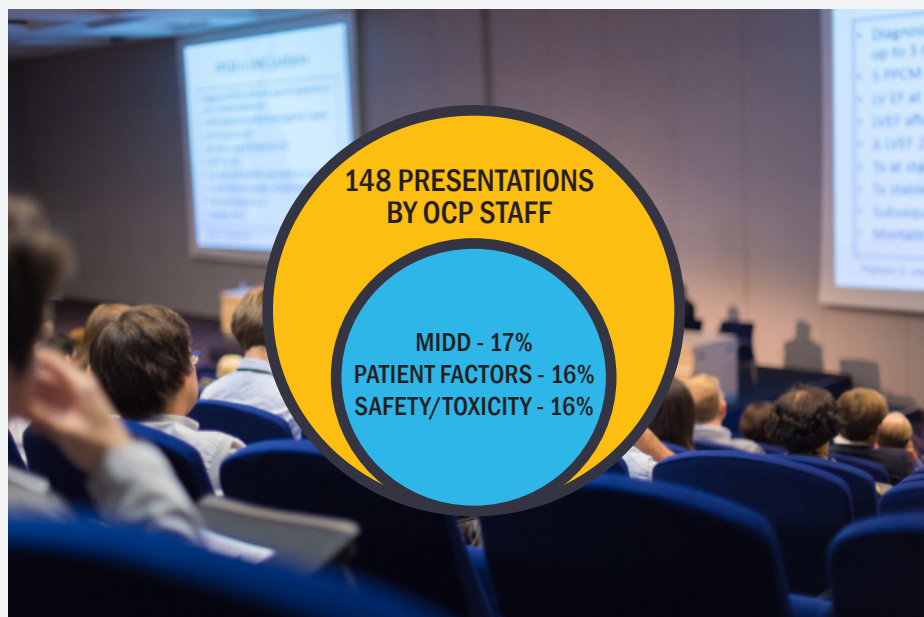
A Translational Pharmacology Approach for Predicting Abuse Potential Based on Chemical Structure

Balance Between Empirical and Mechanistic Analyses

Presentations

- Areas of Focus

All the divisions and units across OCP presented at internal, national, and international scientific and regulatory meetings in 2017. Nearly 50% of the 148 presentations were focused primarily on model-informed drug development (including modeling/simulation and physiologically-based pharmacokinetics), intrinsic patient factors, or safety/toxicity.



Communication Spotlight

WORKSHOPS

OCP staff planned, organized, and participated in a variety of workshops in 2017. Workshop themes ranged from general drug development and clinical pharmacology-related topics to targeted product-, class-, and therapeutic-specific focuses, as highlighted below.

- Clinical Pharmacology of HIV and Hepatitis Therapy Workshop
- Clinical Pharmacology of Tuberculosis (TB) Drug Development
- PK/PD for Development of Therapeutics Against Bacterial Pathogens
- Model-based Approaches to Assist Clinical Development of Psychiatric Products
- Pediatric Trial Design and Modeling: Moving into the Next Decade
- Long-Acting Extended-Release Antiretroviral Formulations for HIV Treatment and Prevention in Children, Adolescents, and Pregnant Women: Knowledge Gaps and Approaches for Development

RESEARCH & COMMUNICATION

— *Communication, Collaboration, & Engagement*

Our role in advancing drug development, promoting state-of-the-art review, and informing health care providers and patients relies on effective communication. Recognizing the importance of communication from OCP staff to both internal and external stakeholders, the OCP Communication Initiative was rolled out in 2017.



COLLABORATION & OUTREACH

GUIDANCE ROLLOUT STRATEGY FOR EXTERNAL STAKEHOLDERS

OCP partnered with OTS and CDER'S Office of Communications to standardize a guidance rollout strategy using multiple communication and outreach methods, including:

- **Direct communications**
- **Direct stakeholder engagement**
- **Trade media outreach**
- **Social media outreach**
- **Web-based tools**
- **Stakeholder training**



Communication Spotlight

COMMUNICATION-RELATED IQPS FINALIZED IN 2017

- 1 ***Procedure for Clinical Pharmacology Burst Communications (aka Burst IQP)***
 - The objective of bursts is to provide early notification of public information pertaining to newly approved therapies, important labeling updates, upcoming events, new regulatory and scholarly publications, and other items of interest. The Burst IQP ensures consistent presentation of this information by providing procedures for preparing, revising, clearing, and disseminating OCP bursts.
- 2 ***OCP Integrated Labeling Review Process for NME NDAs and Original BLAs***
 - The purpose of this integrated review process (also known as the NME Labeling IQP) is to integrate OCP's Labeling and Health Communication (LHC) staff into OCP's labeling review. It covers the initiation of the LHC review, meetings, and documentation of the LHC review.

RESEARCH & COMMUNICATION

— Stakeholder Engagement & Outreach

Engagement Spotlight

OCP LABELING INITIATIVE OUTREACH

CDER Labeling Conference 2017: “Cracking the Code for Clinical Pharmacology-Related Prescription Drug Labeling”

- FDA and industry labeling specialists shared their unique perspectives pertinent to prescription drug labeling development. OCP LHC staff participated in this interactive 2-day conference in which over 2000 registrants across 40 different countries participated. LHC presented actionable labeling tips for Section 12 of product labeling (12 CLINICAL PHARMACOLOGY) regarding content, organization, alternative displays, and unique clinical pharmacology situations under the PD and PK subsections, and the Specific Populations and Drug Interaction Studies headings.

Section 12 Guidance Webinar: “The Ins and Outs of Presenting Clinical Pharmacology Information in Prescription Drug Labeling”

- Highlights of the 2016 final FDA guidance Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products—Content and Format were presented in an OCP-led webinar. The goals of the webinar were to provide key regulations that impact clinical pharmacology content in labeling, where clinical pharmacology content is found, the content structure of the Clinical Pharmacology section, and alternative methods of communicating complex clinical pharmacology content. This webinar included over 1400 international registrants and received 99 percent positive feedback.

EXAMPLES OF OCP EXTERNAL ENGAGEMENT IN 2017

AMERICAN ASSOCIATION OF PHARMACEUTICAL SCIENTISTS (AAPS)

AAPS MICRODIALYSIS FOCUS GROUP

AMERICAN SOCIETY OF CLINICAL PHARMACOLOGY AND THERAPEUTICS (ASCPT)

ASCPT INFECTIOUS DISEASES COMMUNITY STEERING COMMITTEE

CLINICAL AND LABORATORY STANDARDS INSTITUTE

CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM

CLINICAL TRIALS TRANSFORMATION INITIATIVE

CRITICAL PATH TO TB MEDICINES

EUROPEAN MEDICINES UNION

HEALTH AND ENVIRONMENTAL SCIENCES INSTITUTE

INTERNATIONAL CONFERENCE ON HARMONISATION

INTERNATIONAL PHARMACEUTICAL FEDERATION

ONCOLOGY HEXALATERAL DISCUSSIONS

SOCIETY OF TOXICOLOGY

US COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

INTERNATIONAL OUTREACH

Section 12 Guidance Webinar



OUTLOOK AND PRIORITIES

2018

This coming year will be one marked by exciting scientific, regulatory, and organizational developments.

REGULATORY SCIENCE

OCP's multidisciplinary scientific staff is uniquely positioned in 2018 to leverage advances in basic, biomedical and clinical science into useful tools for drug development and evaluation. With the recent passage of PDUFA VI, OCP will have a key role in advancing the science of Model-Informed Drug Development (MIDD) and translating it into regulatory practice. Other focus areas include expanding the biosimilars research program, evaluating biomarkers and innovative approaches to drug safety, including for opioids, and investigating human-based alternative methods to animal research that will be more predictive of drug safety and efficacy. As CDER develops new Center-wide research priorities and goals, OCP will evaluate and align research priorities with the Center's mission, leveraging collaborations within and outside of OCP.

GUIDANCE & POLICY

The coming year will mark a transition from the publication of the remaining guidances under the Guidance Modernization Initiative to a focus on the development of de novo guidances and policies addressing policy gaps and new, emerging scientific and regulatory issues. We will fully implement our end-to-end process for guidance/policy initiation, development, implementation, and evaluation in 2018. These activities will be supplemented with timely training, support, and review resources to ensure consistent implementation. We will continue to consolidate all policy development activities and establish standards of practices and procedures. We will expand our communication activities through publications and presentations as well as extend our stakeholder engagement within the FDA and with professional societies and other regulatory agencies.

ORGANIZATIONAL EFFECTIVENESS & EFFICIENCY

OCP continues to experience tremendous growth as it migrates to a more dynamic and process-focused organization. In the coming year, we will enhance processes by which individuals and teams are empowered and accountable at every level of the organization to continuously improve and achieve Office goals. The continued integration of our Executive Program and Project Management (EPPM) staff and their broad oversight will increase transparency, optimize communication, and build relationships within and beyond the Office. EPPM will identify policy, process, and scientific gaps and lead initiatives to address these unmet needs. Process enhancements in workshop planning, review issue identification, and regulatory science research will strengthen current knowledge management systems and facilitate information sharing to meet our unique needs.

ADVANCING DRUG DEVELOPMENT UNDER THE USER FEE PROGRAMS

The reauthorization of the user fee programs in 2017 will have a significant impact on the Office, most notably, in approaches to MIDD. The Office will play a pivotal role in facilitating and applying MIDD approaches in medical product development. This exciting work will enable further collaboration between CDER and the Center for Biologics Evaluation and Research partners through the launch of the MIDD meeting pilot program, and engagement in workshop discussions that focus on current and emerging scientific approaches. These combined efforts will expand our expertise and leadership in approaches to regulatory science and review of MIDD. The biosimilars strategic planning initiative within the Office will ensure Office-wide scientific and policy readiness for the increasing regulatory activity in biosimilar product development. Finally, we will continue to facilitate and support the generic drugs program through lifecycle management of the drug products we review, and look forward to additional collaborations with Office of Generic Drugs, Office of Product Quality, and Center for Devices and Radiological Health on the scientific and regulatory issues of complex generic drug products and development of product-specific guidances.



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