U.S. FOOD & DRUG ADMINISTRATION

OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF CLINICAL PHARMACOLOGY

2019 Annual Report

January 2020

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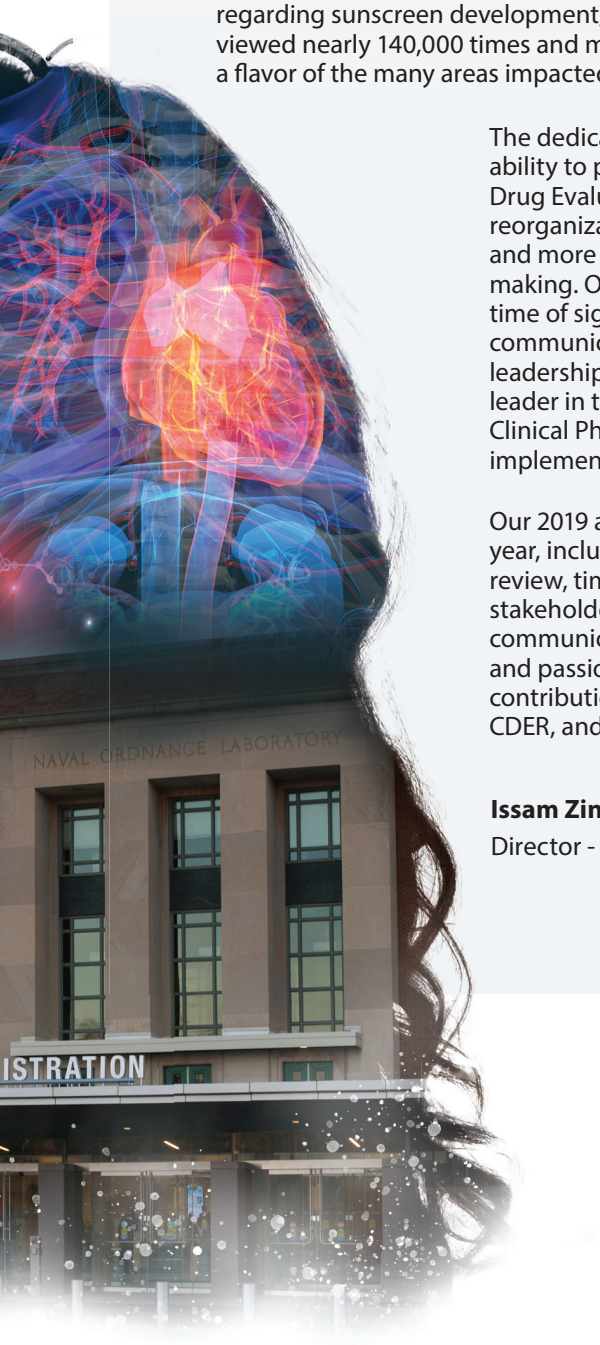
DIRECTOR'S MESSAGE

This year was an exciting one for the U.S. Food and Drug Administration (FDA) Office of Clinical Pharmacology (OCP). We faced a variety of scientific and regulatory issues that required our exceptional staff to leverage diverse knowledge, skills, and abilities for the benefit of public health, all during a time of significant organizational change. Our staff efforts in research, regulatory review, guidance and policy development, program and project management, and labeling and communications were critical in advancing Model-Informed Drug Development (MIDD). The MIDD regulatory meeting pilot program offered an opportunity for interdisciplinary FDA staff engagement to foster the science and improve outcomes in drug development through early and focused discussions on modeling and simulation (M/S) (see page 7 for details). Public workshops on Precision Dosing and Physiologically Based Pharmacokinetic Analyses (PBPK) brought together thought leaders to help inform next steps for research and regulatory policy in these contemporary areas. These efforts successfully fulfilled our Prescription Drug User Fee Act VI (PDUFA VI) commitments to advancing MIDD for the year. OCP was also instrumental in establishing the validity of studies to determine the extent of absorption of sunscreen components and publishing guidance for industry regarding sunscreen development, with our seminal research article in the area being viewed nearly 140,000 times and mentioned by nearly 200 news outlets. These are only a flavor of the many areas impacted by our dedicated staff.



The dedication and resilience of our staff were evident in their ability to promote the mission of the FDA during the Center for Drug Evaluation and Research's (CDER's) reorganization. Our reorganization was designed to better align therapeutic areas and more clearly articulate regulatory review and decision making. OCP ensured continuity of operations during this time of significant change by developing a transition plan, communicating changes to staff in real time, and providing leadership development training opportunities. A recognized leader in team-based collaborative review through the Clinical Pharmacology Integrated Review, OCP is fully ready to implement CDER's new issue-based, integrated review process.

Our 2019 annual report provides highlights of an outstanding year, including innovations in research and regulatory review, timely issuance of guidances and policies, proactive stakeholder outreach and engagement, and effective communication. I am honored to be part of this committed and passionate group of individuals, and proud of our staff's contributions to the Office of Translational Sciences (OTS), CDER, and the Agency in advancing OCP's vision and mission.

Issam Zineh, PharmD, MPH, FCP, FCCP
Director - Office of Clinical Pharmacology

Who We Are

OCP is a dynamic, purpose-driven organization dedicated to promoting and protecting global public health through the application of clinical pharmacology and translational medicine principles. OCP, an office within CDER's OTS super-office, is made up of over 220 pharmacologists, pharmacists, chemists, physicians, nurses, project and program managers, and administrative professionals. Our shared vision is to improve public health by building and translating knowledge of drug-response into patient-centered regulatory decisions of the highest quality.

Our mission is two-fold: 1) play a pivotal role in advancing the development of innovative new medicines by applying state-of-the-art scientific principles; and 2) promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product lifecycle. OCP fulfills its mission through its core functions of regulatory review, policy development and implementation, and research. Outcomes in these functional areas are enhanced by our expansive communication, stakeholder engagement, and outreach on national and international levels. We embrace our core values, stewardship, leadership, excellence, connectedness, diversity and respect, which foster a culture that empowers staff to translate knowledge for the benefit of patients (Figure 1).

Figure 1

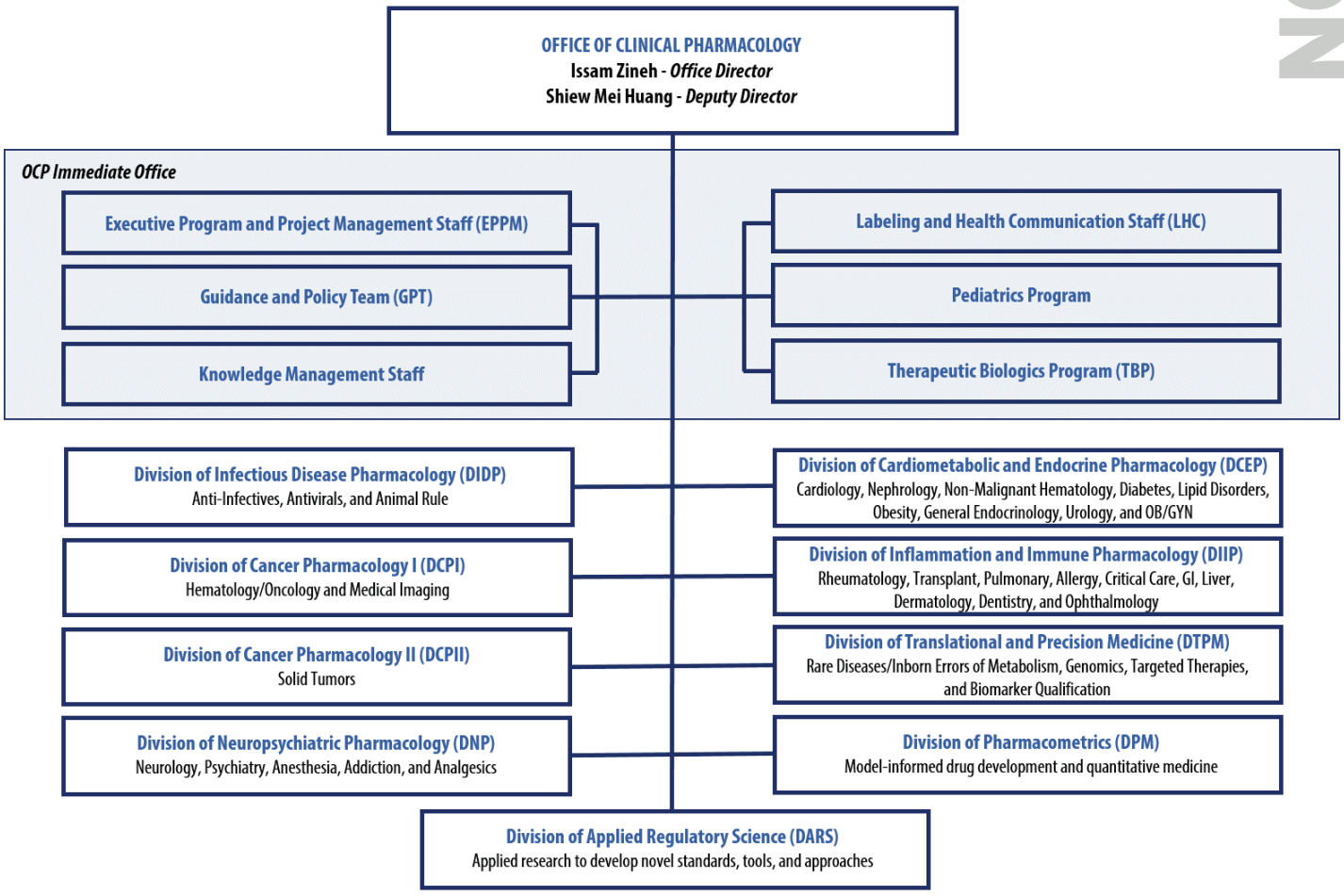
OCP Core Values

On September 26, 2019, CDER announced the approval of a major reorganization of offices within the New Drugs Regulatory Program (NDRP). This reorganization is part of CDER's modernization effort, first announced in June 2018, which is an ongoing, multi-phase regulatory improvement initiative comprised of structural changes, process and documentation improvements, and enhancements to administrative and regulatory operations.

OCP has embraced this period of organizational change with optimism. We have newly organized into therapeutically aligned divisions, consolidating cross-cutting functions and areas of drug assessment for better review quality and process efficiency (Figure 2). Through thoughtful realignment of our organization and a vision towards serving patients in the current health care landscape, we continue our commitment to CDER's mission and ensure that safe, effective, high-quality drugs are available for the public.

Figure 2

New Office of Clinical Pharmacology Organizational Structure



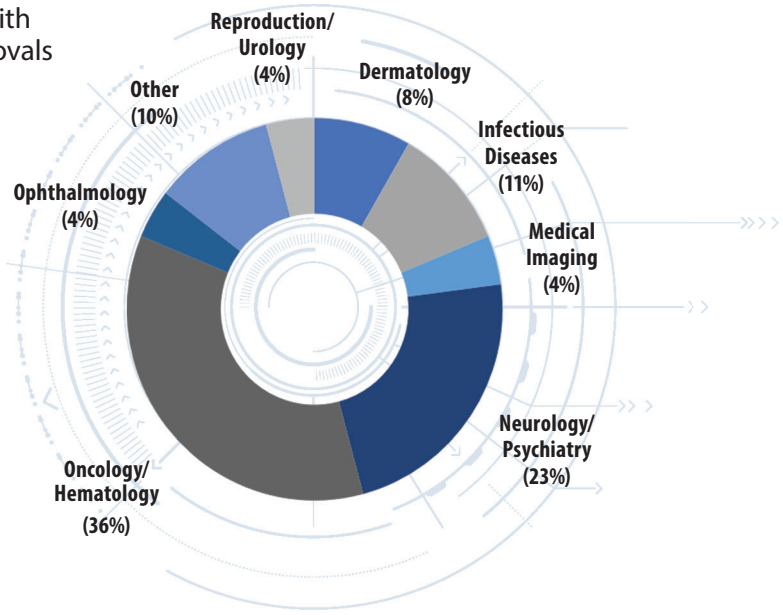
REVIEW

OCP REGULATORY REVIEW IN 2019

Fostering innovation and promoting optimized therapies - OCP regulatory review is central to accomplishing these goals. In 2019, OCP implemented regulatory initiatives to modernize review functions to support PDUFA VI, the Biosimilar User Fee Act II (BsUFA II), and the Generic Drug User Fee Act II (GDUFA II) programs. Our multi-disciplinary, issue-based review strategy resulted in the cohesive, streamlined review of clinical pharmacology information in new drug applications (NDAs), biologics license applications (BLAs), including 351(k) applications (i.e., biosimilars), and investigational new drug applications (INDs). OCP review findings were integrated into the benefit-risk assessment framework for these applications, ultimately bringing 48 safe and effective new drugs and biological products to patients (Figure 3).

Figure 3

Therapeutic Areas with Novel Product Approvals in 2019 (N=48)



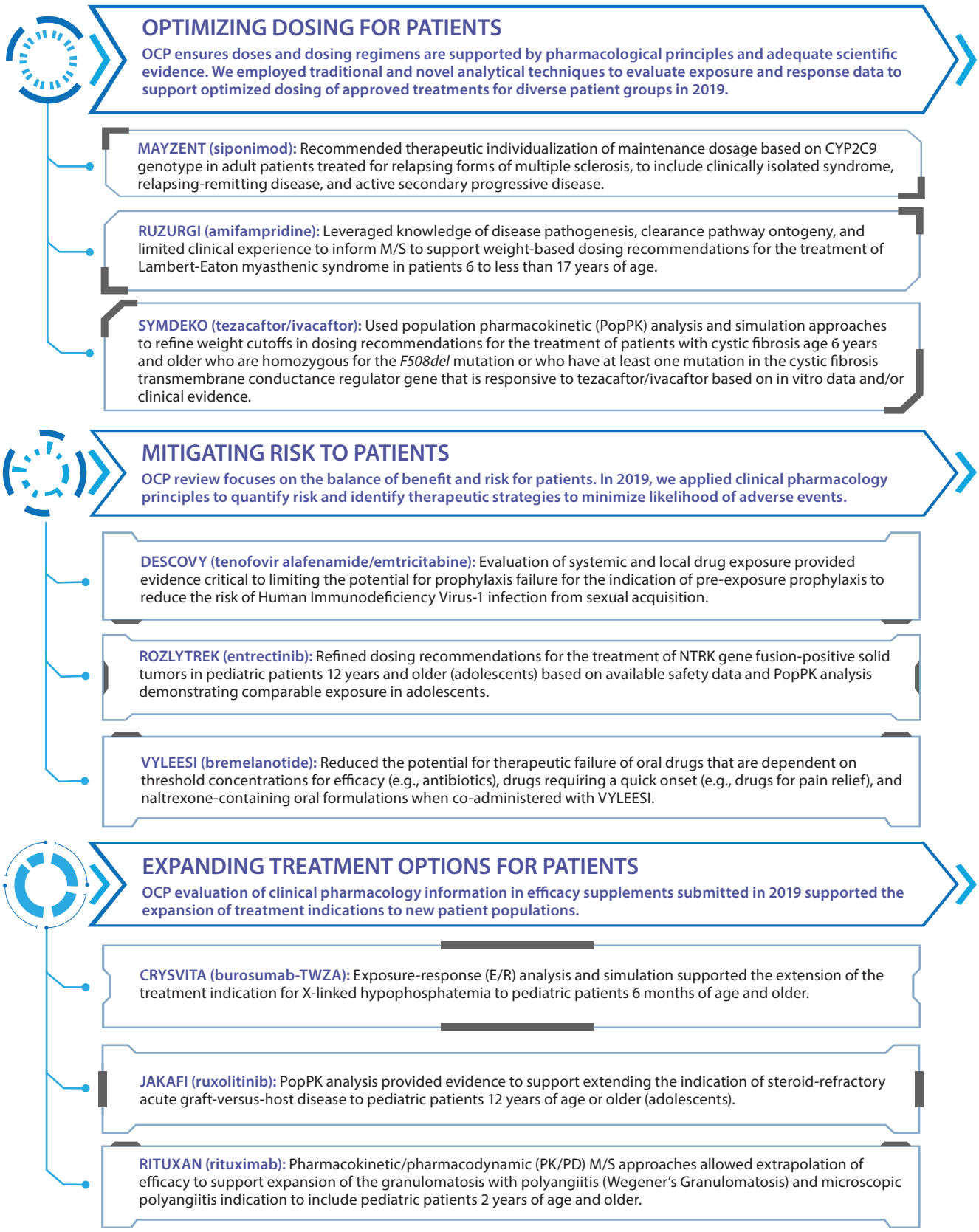
Review Achievements in 2019

OCP staff conducted approximately 2400 reviews for NDA, BLA and IND submissions throughout 2019. Our staff engaged sponsors in over 2100 IND meetings in 2019, including crucial end-of-phase meetings to refine development strategies, and through a variety of communication formats (face-to-face meetings, written responses as requested, etc.). Scientific exchange on global and emerging disease-focused topics impacting public health, drug development challenges, and product-specific portfolios was encouraged by OCP involvement in 12 FDA advisory committee forums. Thoughtful analysis and integration of clinical pharmacology knowledge of the products we review allows us to optimize dosing recommendations for patient groups, quantify risk for the products we approve, develop management strategies to mitigate those risks, and expand treatment options for patients (Figure 4).

In addition to application-focused review, FDA colleagues from offices outside OCP and across FDA centers sought clinical pharmacology guidance from our staff on 53 review-related consults in areas such as general clinical pharmacology development plan considerations, labeling claims for drugs and devices, promotional material content, lactation and maternal health issues, bioanalysis, assessment of safety signals, and toxicity evaluation. OCP's Chemical Informatics Program conducted structure-based safety assessments of non-clinical and clinical endpoints to inform regulatory decision-making, including genetic toxicity, carcinogenicity, hepatotoxicity, and cardiotoxicity, in response to 211 consults for 633 chemicals analyzed in 2019.

Figure 4

Impact of OCP Reviews - Select NDA and BLA Approvals in 2019



Model-Informed Drug Development

MIDD is defined as the use of exposure-based, biological, and statistical models derived from preclinical and clinical data to facilitate decision-making. MIDD tools include a variety of quantitative M/S approaches that enable the prediction of drug PK and PD for broad applications, including dose optimization, supportive evidence for efficacy, clinical trial design, and informing policy (Figure 5). The added value of these approaches is that they have the potential to accelerate and de-risk drug development.

The importance of MIDD in OCP this year has been reflected in many efforts under CDER's MIDD initiative, established under recent amendments to PDUFA VI. These efforts include policy development, stakeholder engagement, education, and research to advance the use and potential of model-based approaches to accelerate the development of safe and effective medicines. Strong leadership from OCP and partnership across CDER and the Center for Biologics Evaluation and Research (CBER) has been critical for success. The MIDD pilot program is a great example (https://go.usa.gov/xdjek). This multidisciplinary program, including OCP, the Office of New Drugs (OND), the Office of Biostatistics (OB) and others, provides sponsors an opportunity to engage with regulators on MIDD strategy issues during pre-IND and IND phases. Examples of our shared success under the MIDD initiative in 2019 are described in Table 1.

Figure 5

MIDD - an Overview

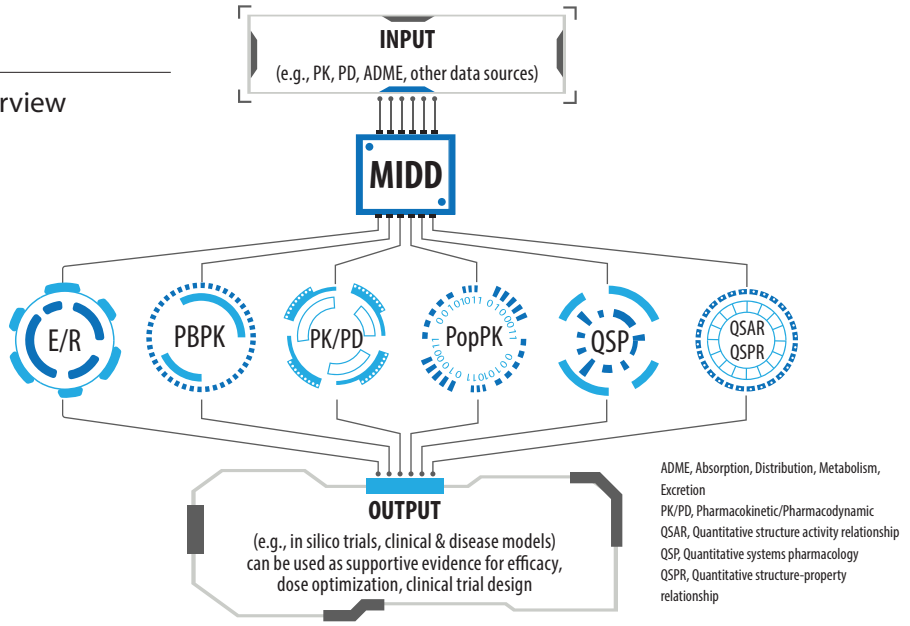


Table 1

MIDD Milestones in 2019

GUIDANCE AND POLICY	Published a revised draft guidance on PopPK (https://go.usa.gov/xdjen) to better guide drug development and inform recommendations on therapeutic individualization
MIDD PILOT PROGRAM	Accumulated over one year of experience leading the MIDD Meeting Pilot Program • Granted 34 sponsor meetings to date (two meetings granted per submission accepted); submission topics included dose determination and clinical trial optimization across various therapeutic areas • Program impact included early alignment between sponsors and FDA on regulatory pathways (see PMID:31081932)
REGULATORY SCIENCE AND REVIEW EXPERTISE	• Created an MIDD Training Committee to identify staff training needs and provided continuing education hours on MIDD • Developed an intranet website to consolidate staff resources and enable knowledge sharing related to MIDD
WORKSHOPS/ STAKEHOLDER ENGAGEMENT	Co-hosted two public workshops on MIDD-related topics: • Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making (https://go.usa.gov/xp7YJ) • Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting (https://go.usa.gov/xp7gx)

OCP POLICY INITIATIVES

OCP policy initiatives in 2019 emphasize our commitment to communicating the most up-to-date scientific and regulatory information on clinical pharmacology issues critical in drug development. OCP instituted a lifecycle process for guidances and policies, providing mechanisms not only to modernize existing guidances, but also to facilitate the development of Agency guidance on contemporary topics (Figure 6). OCP published six guidance and policy documents in 2019, providing modernized recommendations for clinical pharmacology studies involving food effect, bioavailability, bioanalytics, and PopPK as well as the first Agency guidance on maximal usage trials (MUsT) for topical products such as sunscreens, and considerations for clinical pharmacology studies in neonates. OCP staff were also instrumental in the development of 24 other FDA guidances, highlighting the role of clinical pharmacology in every aspect of drug development, including but not limited to, clinical trial design, drug delivery systems, lactation studies, and appropriate uses of M/S to assess safety and efficacy.

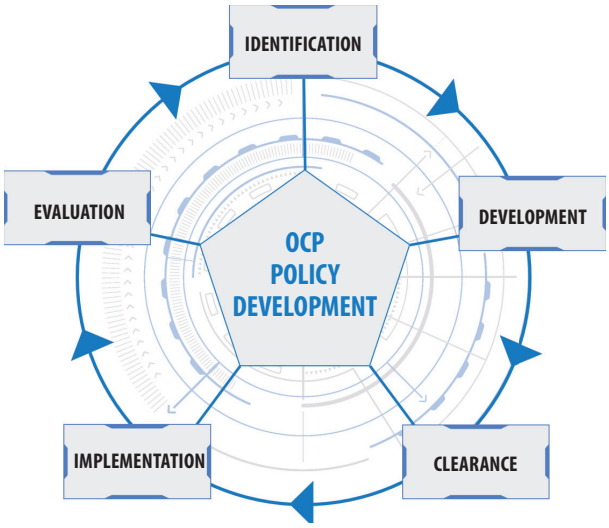


Figure 6

End-to-End Guidance and Policy Development and Implementation in OCP

LEADING DRUG DEVELOPMENT THROUGH POLICY

6

Clinical pharmacology guidances issued in 2019

24

Multidisciplinary guidances on broad development topics to which OCP contributed

OCP-LED GUIDANCES PUBLISHED IN 2019

- **Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations (Draft):** Considerations for food effect studies to determine the impact of food on the rate and extent to which an active ingredient becomes available (https://go.usa.gov/xdjem)
- **Bioavailability Studies Submitted in NDAs or INDs – General Considerations (Draft):** Recommendations to sponsors on the conduct of bioavailability studies for orally administered and certain non-orally administered drug products (https://go.usa.gov/xdjep)
- **General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products (Draft):** The first regulatory guidance on the PK, PD, and pharmacogenomic considerations in the planning and conduct of neonatal clinical pharmacology studies (https://go.usa.gov/xdjef)
- **Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in the Over-The-Counter Monograph (Final):** Recommendations for the conduct of in vivo absorption trials for topical active ingredients that are under consideration for inclusion in an over-the-counter (OTC) drug monograph (https://go.usa.gov/xdjeA)
- **Population Pharmacokinetics (Revised Draft):** Common applications of PopPK analysis to inform drug development and drug use, data and model requirements to inform regulatory decisions, and expectations regarding the content and format of PopPK reports submitted to the Agency (https://go.usa.gov/xdjen)
- **Bioanalytical Methods Templates (Technical Specifications Document):** Ready-to-use templates for sponsors to submit summaries of bioanalytical methods used in clinical pharmacology studies that require PK concentration evaluation (https://go.usa.gov/xdjeh)

OCP RESEARCH & PUBLICATIONS

Advancing regulatory science for maximal impact on public health is predicated on innovative, hypothesis-driven research. Our research activities provide a foundation for clinical pharmacology policy and review, respond to urgent public health needs, and aid in the successful development of new drug products for patients. We share our research findings and contemporary regulatory thinking through publications to foster transparency and successful drug development. In 2019, OCP engaged in 138 research projects and published 155 manuscripts that focused on a wide range of clinical pharmacology and translational medicine regulatory science topics (Figures 7 and 8). Our dedicated research group, the Division of Applied Regulatory Science (DARS), applies translational approaches, such as in vitro and in vivo laboratory methods, in silico computational modeling and informatics, and experimental medicine, to address challenges encountered during all phases of drug development and regulatory review.

Figure 7

OCP Research Focus in 2019 (N = 138)

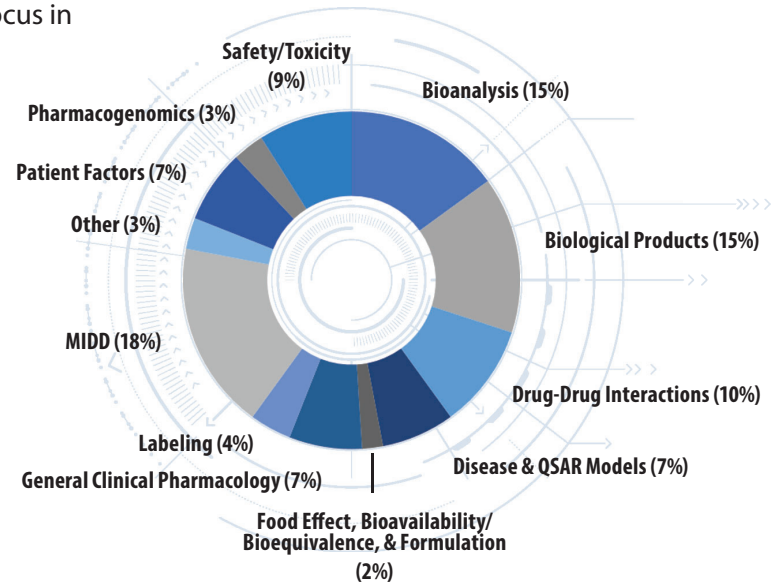
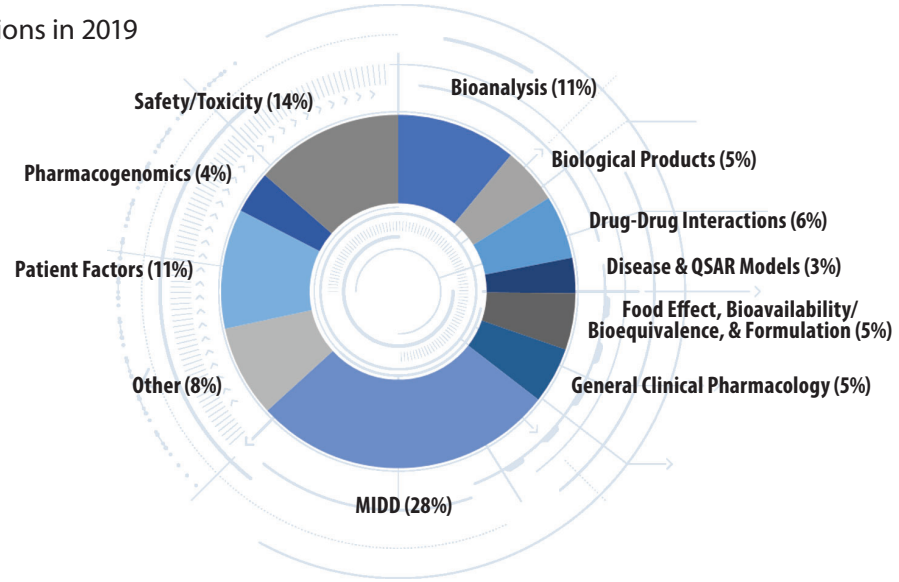


Figure 8

OCP Publications in 2019 (N = 155)



INFORMING REGULATORY ACTIONS, PRESCRIBING, AND PATIENT USE

- Employed an in vitro cell permeation model and drug classification system for the prediction of drug transfer and excretion into human breast milk
- Investigated the systemic absorption and safety of sunscreen ingredients in commonly used OTC sunscreen products
- Improved efficiency of biosimilar development and review through an expanded understanding of PD biomarkers, application of an in silico-based modeling tool to describe bioanalytical variability, exploration of a communication framework for labeling, and a novel immunogenicity review tool

EXPLORING INNOVATIVE TECHNOLOGIES

- Applied machine learning/artificial intelligence (AI) to read patient imaging data to facilitate diagnosis and precision treatment with immune checkpoint inhibitors for a variety of cancer types
- Assessed dosing modification recommendations in patients with impaired organ function receiving anticancer target therapies using real-world data (RWD)
- Developed a machine learning algorithm and tool for evaluating dose-dependent adverse events from Integrated Summary of Safety data in NDAs and BLAs coupled with data from the FDA Adverse Event Reporting System (FAERS)

UNDERSTANDING DRIVERS OF PATIENT RESPONSE

- Assessed how patient-reported outcome (PRO) data can be used to improve characterization of E/R for safety and early dose optimization in oncology drug development and inform drug specific dose adjustment strategies
- Used novel methods to predict adverse drug events including a bioinformatics approach to aggregate data from disparate public resources to develop biological networks around drug targets and their related clinical phenotypes

GENERATING KNOWLEDGE TO ADVANCE REGULATORY SCIENCE AND TRANSFORM PUBLIC HEALTH

25%

Projects leveraging MIDD approaches in 2019

13

Average number of OCP publications per month in 2019

31%

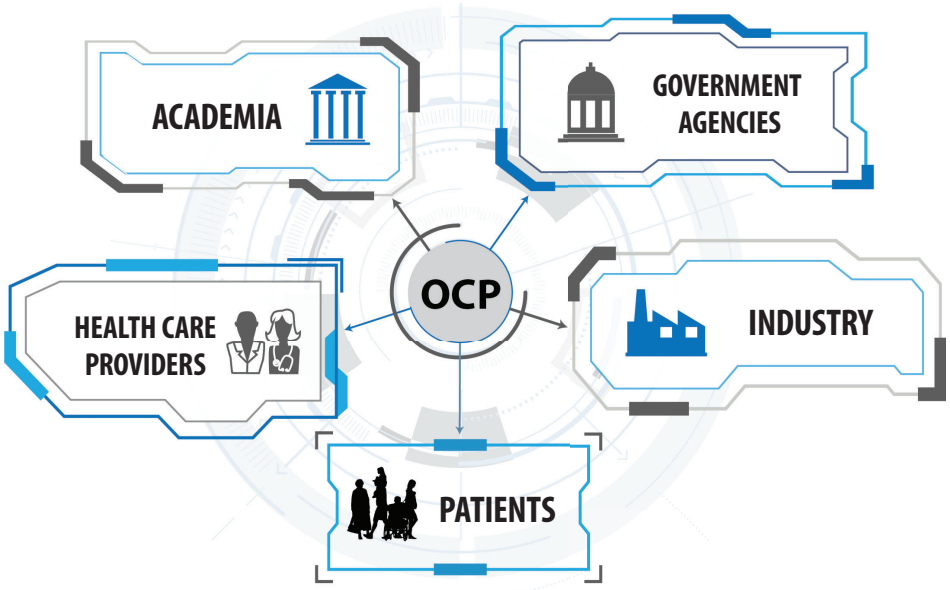
Publications aimed at mitigating risk in patients

STRATEGIC COMMUNICATION, OUTREACH, AND ENGAGEMENT IN 2019

Connectedness with our stakeholders is essential to OCP's charge of promoting and protecting global public health through the application of clinical pharmacology (Figure 9). In 2019, our communication strategies, outreach efforts, and engagement opportunities were designed to maximize reach to stakeholders while sharing our evolving regulatory science. OCP informs and engages stakeholders domestically and internationally, through several mechanisms, including workshops, working groups and consortia, scientific presentations to diverse audiences, and direct information distribution via email and web-based media.

Figure 9

OCP Communications: Fostering Connectedness and Community



OCP uses workshops to engage stakeholders, foster collaboration, and further clinical pharmacology innovation. In 2019, OCP was involved in planning, organizing, and participating in 34 workshops and symposia highlighting the application of novel technologies and transforming drug development paradigms. In addition to workshops, our collaborative efforts with fellow regulators, academia, and industry through over 50 internal and external working groups, committees, and consortia further promoted productive dialogue to inform regulatory science and review.

Motivated by our goals of transparency and positively impacting successful drug development, OCP staff gave 180 presentations at internal, national, and international scientific and regulatory venues in 2019 (Figure 10). To address challenging regulatory topics, OCP engaged domestic and international thought leaders and promoted exchange of ideas. We cultivated our partnerships with academic stakeholders by hosting visiting faculty to enhance student learning experiences, as well as multiple Doctor of Pharmacy students on rotation, policy fellows, and visiting scientists to offer diverse professional development opportunities. OCP actively promoted the role of clinical pharmacology through thoughtful communication strategies leveraging email, web, and social media resources, to enhance OCP's many engagement and outreach efforts.

34

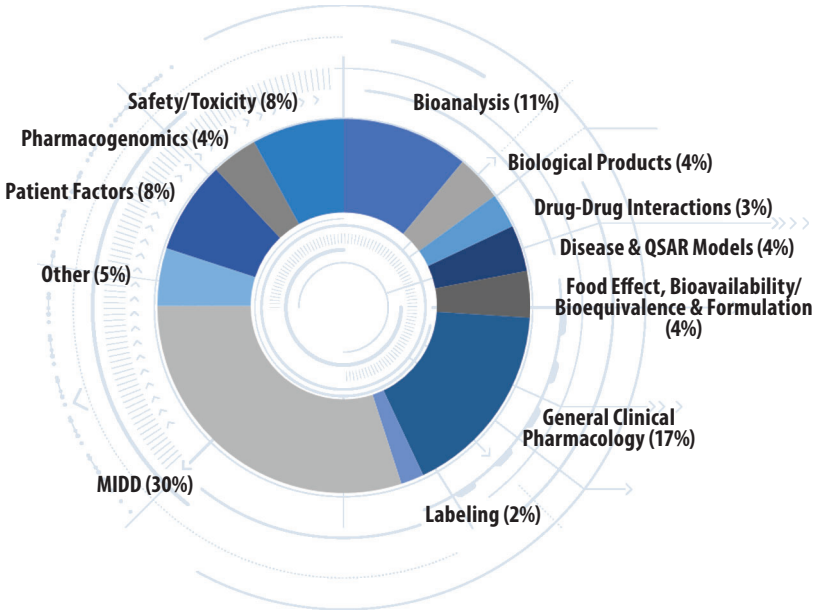
OCP engagement events in 2019, including workshops, seminars, symposia, lecture series, and webinars

TRANSFORMING DRUG DEVELOPMENT THROUGH WORKSHOPS IN 2019

- Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)
- Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making
- Enhancing the Accessibility and Utility of Drug Interaction Information in Labeling
- Implementing FDA's Predictive Toxicology Roadmap: An Update of FDA Activities
- Leveraging Clinical Pharmacology to Optimize Drug Development for Nonalcoholic Steato-hepatitis (NASH) and Cholestatic Liver Diseases
- Pediatric Ontogeny: Ready for Incorporation into Modeling in Pediatric Drug Development?
- Precision Dosing: Defining the Need and Approach to Deliver Individualized Drug Dosing in the Real-World Setting
- Topical Drug Development - Evolution of Science and Regulatory Policy

Figure 10

OCP Presentations in 2019
(N = 180)



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WORKING GROUPS/COMMITTEES

Technology & Tools (18%)
Biological Products/Biosimilars (14%)
General Policy (14%)
Pharmacogenomics (13%)
Regulatory Review (13%)
Biopharmaceutics (7%)
MIDD (5%)
Research Topics (5%)
Specific Products/Therapeutics (5%)
Labeling (4%)
Professional Development (2%)

MAXIMIZING COMMUNICATION REACH IN 2019

- FDA Drug-Drug Interaction (DDI) websites maintained by OCP offer a general overview of DDIs in drug development, current guidances and policies related to DDIs, and development and educational resources, including useful tables of substrates, inhibitors and inducers. These websites averaged approximately **92,000** unique page views in 2019.
- OCP's Clinical Pharmacology Corner free newsletter subscription service disseminates concise and timely information on new drug and biological product approvals, policy updates, event announcements, and notable scientific topics to over **78,700** stakeholders.
- OCP hosted faculty from the University of Georgia College of Pharmacy to present and assist with the development of high-quality PharmD student learning experiences.
- OCP fostered international partnerships with European Medicines Agency (EMA), Health Canada (HC), Pharmaceuticals and Medical Devices Agency (PMDA), and Therapeutic Goods Administration (TGA).
- OCP promoted harmonization through involvement in multiple forums, such as the Comprehensive in Vitro Proarrhythmia Assay (CiPA) Steering Committee, EMA-FDA Pharma-cogenomics and Pharmacometrics Clusters, Global Bioequivalence Harmonization Initiative (GBHI) meeting, In Silico Toxicology Protocols Consortium, and International Council for Harmonisation (ICH) meetings and working groups on M7 Option 4 (evaluation of mutagenic impurities), S7B/E14 (evaluation of proarrhythmic potential), M9 (Biopharmaceutics Classification System (BCS)-based biowaivers), M10 (bioanalytical method validation), M12 (drug interaction studies), and generic drugs.

2020 OUTLOOK AND PRIORITIES

The prominent role of applied clinical pharmacology in drug development, regulatory assessment and policy, and the individualization of pharmacotherapies has been instrumental to improving the health of individuals worldwide. Maximizing the use of clinical pharmacology and translational medicine principles throughout drug discovery, development, regulation, and therapeutic use is no small feat, requiring extensive partnership with academia, industry, the clinical practice community, not-for-profit organizations, and other global health organizations. OCP plans to continue its leadership in this global enterprise by facilitating the development of promising new therapies as well as refining optimal use in real-world settings. A major focus of our efforts in 2020 will be the continued development and strategic positioning of highly skilled scientific and regulatory experts in regulatory review, applied research, program management, guidance and policy, and communications.

In 2020, we will continue to advance the cutting-edge science of MIDD as well as its application during regulatory evaluation of therapeutic products. This upcoming year provides OCP with the opportunity to refine and enhance the Agency's MIDD program through collaboration with our partners across CDER, CBER, and the Center Devices and Radiological Health (CDRH). We will also broaden and deepen our efforts in areas of both emerging science (e.g., machine learning/AI; biomarker qualification; drug-disease-trial M/S) and perennial public health challenges (e.g., antimicrobial resistance, opioid use disorder). Finally, we plan to set our priorities and strategic plan for the next five years with our OCP 2025 Initiative.

OCP staff are passionate about science, dedicated to public health, and committed to engaging our colleagues within the Agency and throughout the world. We look forward to improving the human condition by making a positive impact on patients wherever they may be.

OUTLOOK

Examples presented in this Annual Report are illustrative and are not a comprehensive representation of 2019 information. For detailed information on the content of this report or our Office's other activities, please contact *ocp@fda.hhs.gov*.

Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
AI	Artificial Intelligence
ANDA	Abbreviated New Drug Application
BCS	Biopharmaceutics Classification System
BLA	Biologics License Application
BsUFA II	Biosimilar User Fee Act II
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CiPA	Comprehensive In Vitro Proarrhythmia Assay
DARS	Division of Applied Regulatory Science
DCEP	Division of Cardiometabolic and Endocrine Pharmacology
DCPI	Division of Cancer Pharmacology I
DCPII	Division of Cancer Pharmacology II
DDI	Drug-Drug Interactions
DIDP	Division of Infectious Disease Pharmacology
DIIP	Division of Inflammation and Immune Pharmacology
DNP	Division of Neuropsychiatric Pharmacology
DPM	Division of Pharmacometrics
DTPM	Division of Translational and Precision Medicine
EMA	European Medicines Agency
EPPM	Executive Program and Project Management
E/R	Exposure/Response
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GBHI	Global Bioequivalence Harmonization Initiative
GDUFA II	Generic Drug User Fee Act II
GPT	Guidance and Policy Team
HC	Health Canada
ICH	International Council on Harmonisation
IND	Investigational New Drug
LHC	Labeling and Health Communication
M/S	Modeling and Simulation
MIDD	Model-Informed Drug Development
MUsT	Maximal Usage Trial
NASH	Nonalcoholic Steatohepatitis
NDA	New Drug Application
OB	Office of Biostatistics
OCP	Office of Clinical Pharmacology
OND	Office of New Drugs
OTC	Over-the-Counter
OTS	Office of Translational Sciences
PBPK	Physiologically Based Pharmacokinetic
PDUFA VI	Prescription Drug User Fee Act VI
PD	Pharmacodynamic
pJIA	Polyarticular Juvenile Idiopathic Arthritis
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PMDA	Pharmaceuticals and Medical Devices Agency
PopPK	Population Pharmacokinetics
PRO	Patient-Reported Outcome
QSAR	Quantitative Structure-Activity Relationship
QSPR	Quantitative Structure-Property Relationship
QSP	Quantitative Systems Pharmacology
RWD	Real-World Data
TGA	Therapeutic Goods Administration
TBP	Therapeutic Biologics Program

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