U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

2023 OND Annual Report

Breaking Barriers to Advance Public Health

April 2024

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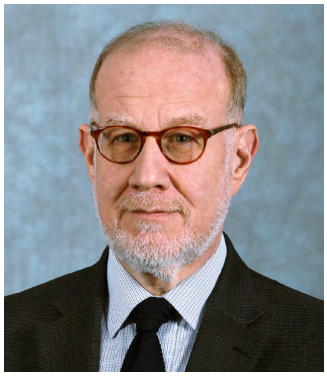
Director's Message



Peter Stein, MD
Director, Office of New Drugs

As you read this annual report on the Office of New Drugs' (OND) activities and accomplishments for 2023, I think you will see an incredibly wide range of efforts, from across the organization, that advance the health of the American public. You will find numerous important approval actions—new drugs for rare diseases that previously had no approved therapies, drugs that advance the management of patients with common, chronic disorders providing greater effectiveness or improved safety, drugs for important infectious diseases—including for COVID-19 and for RSV infections—and drugs for a range of oncological diseases, among many other approval actions.

This report documents the diverse efforts of OND staff, beyond the regulatory actions to approve important drugs. These efforts include holding many public meetings both to inform our OND staff of cutting edge science, and for OND staff to contribute to the knowledge of those in the pharmaceutical industry, in academics, and for patients and other stakeholder groups about advances in regulatory science, the biology of disease, and advances in clinical drug development; publishing numerous guidances that give insight to drug developers about the pathways and approaches to development that can provide the data FDA needs to support the effectiveness and safety of new drugs; the careful monitoring of drug safety post-approval to assure that drug's prescribing information is kept updated with the safety information that health care practitioners and patients need.

These, and many other efforts, are highlighted in this comprehensive review of the work of OND during 2023. In a larger sense, however, the efforts on improving the care of patients with a wide range of disorders highlights the incredible expertise—and dedication—of OND staff. Over the past several years, OND has increased in size by about 25%, bringing many new staff on-board. We've welcomed individuals who just completed training, those with long-standing academic, industry, or clinical practice careers, those with experience in pharmacy practice, and from many other settings—and this diversity of backgrounds and experiences has further enriched our organization with important skillsets and knowledge. They have joined our deeply experienced staff who have brought incredible knowledge and expertise to our work and who are essential in guiding and training new staff, and in helping to make the most informed and thoughtful regulatory decisions. Each month at our OND Town Hall, we celebrate those staff who have contributed years of dedicated service to FDA, CDER, and OND.

As I meet with our OND staff, one thing stands out above all—their intense dedication to our mission of advancing the health of the American public, and of making decisions that can best meet the unmet needs of patients. As you read this report, I think you will see this dedication and their commitment reflected in every paragraph and page.

OND's Senior Leadership Team

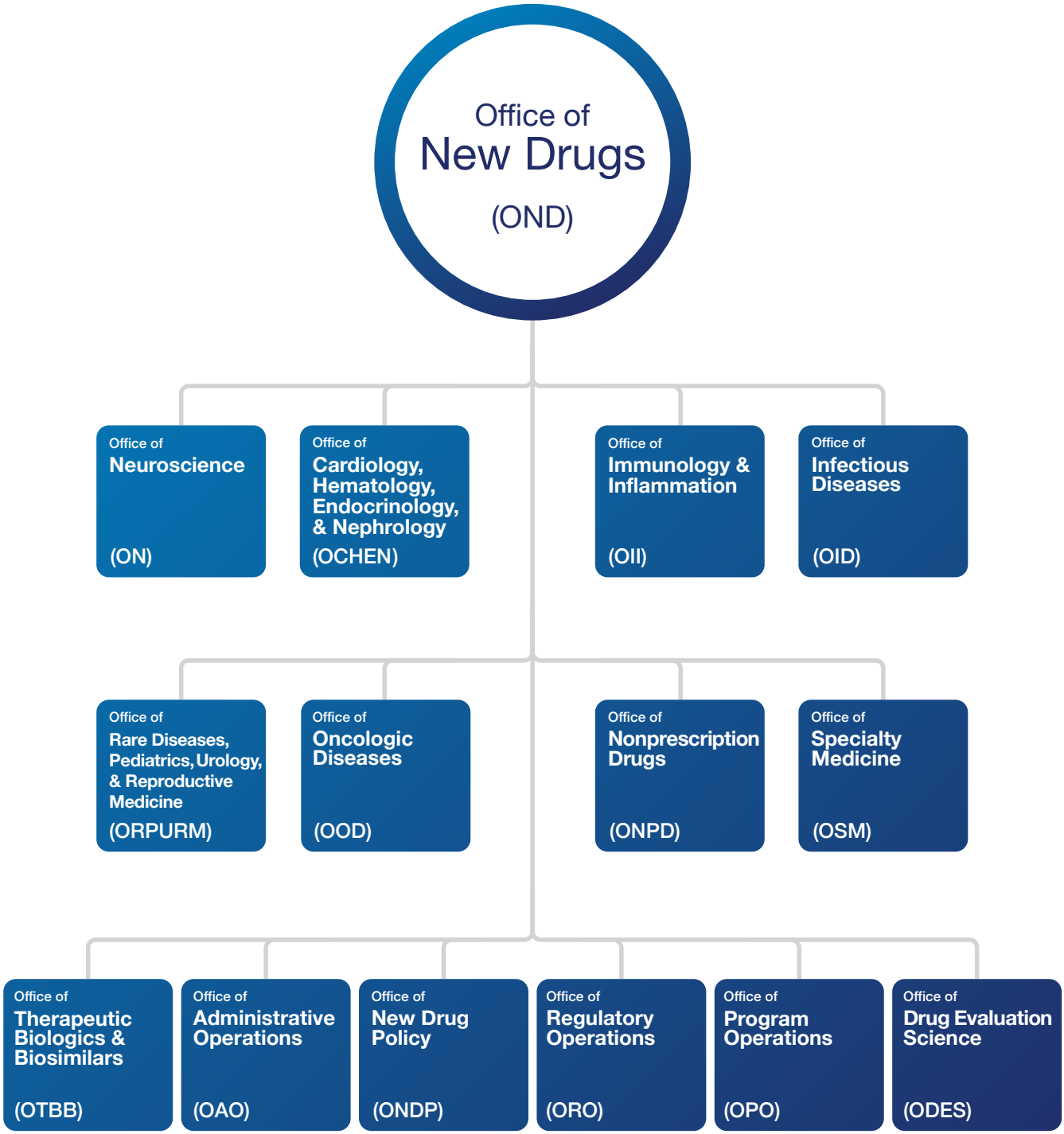
Peter Stein, MD
Director, Office of New Drugs

Kevin Bugin, PhD
Deputy Director for Operations

Mary Thanh Hai, MD
Deputy Director for Clinical

Helen Edelberg, MD, MPH
Deputy Director for Drug Safety

Organizational Chart



OND by the Numbers (CY2023)

The Office of New Drugs (OND), working hand-in-hand with other Center for Drug Evaluation and Research (CDER) super-offices, had a successful year for novel drug approvals and other drug development activities; including industry meetings and guidances published during the calendar year 2023. Please see below for more information.

- Investigational new drugs (INDs) received and INDs with activity
- Novel Drug Approvals (new molecular entity [NME] new drug applications [NDAs]/biologics license applications [BLAs])
- Efficacy Supplement Approvals
- Breakthrough Therapy Requests
- Fast Track Requests
- Expanded Access INDs Received and Expanded Access INDs Safe to Proceed

34 **Published Guidances**

5 **Critical Path Innovation Meeting** with OND representation

13 **Patient-Focused Drug Development meetings** with OND representation

18 **Patient Listening Sessions** organized by the Office of the Commissioner (OC)/the Office of Patient Affairs with OND representation

3 **Patient Listening Sessions** organized by Professional Affairs and Stakeholder Engagement with OND representation

651 **OND speaking engagements**

Non-Clinical Offices

OND Operations

In 2023, OND achieved a net hiring gain of 152 staff members. This important progress facilitated by OND operations helped OND manage increasing workload and public health priorities. In addition, to help maintain OND's internationally recognized standard of excellence for drug review and regulation, OND operations delivered 102 internal staff training courses for the equivalent of 14,422 attendees, to strengthen staff's scientific, regulatory, operational, and leadership skills and abilities. OND operations facilitated interactions with sponsors of new drug development programs via more than 3,400 formal meetings, and protected patient safety by overseeing the management of safety reviews for over 3,500 new INDs. OND operations also established a new internal advisory committee (AC) support team that provided review teams with necessary resources to enable better preparation and presentation for 25 public AC meetings during 2023, resulting in a more consistent and effective AC experience for the Agency, industry, and public. Finally, OND operations kept stakeholders such as Agency leadership, the public, media, and Congress informed of important New Drug Review program information by triaging and facilitating responses to more than 950 internal and external inquiries.

950+

internal and external inquiry responses managed

Office of New Drug Policy

The Office of New Drug Policy, formed in 2019, works to support OND by generating and applying clinical and regulatory policy to promote the advancement of new drugs and biologics based on sound scientific principles and consistent with applicable legal and regulatory requirements. In addition to developing new drug policy, which includes identifying and prioritizing current and future policy needs, the office supports OND's implementation of existing FDA and OND policies in a principled and supportable manner by advising, training, and

assisting OND staff in review and regulatory decision-making efforts. OND Policy manages CDER's review and clearance process for all 505(b)(2) NDAs, directs and manages the clearance process on behalf of OND for policy documents, and represents OND's interests with other FDA offices, policy-related councils and committees, and other governmental entities.

In 2023, OND Policy fielded more than 1750 individual inquiries from OND review divisions and offices, as well as others across the Agency. Routinely, OND Policy staff are involved in providing advice for some of the most complex applications under review by OND, often requiring the intersection of regulatory, legal, and clinical expertise. The Regulatory Policy Advisors Team of the Division of Regulatory Policy (DRP) not only fields such application-specific inquiries, but also provides regulatory advice in areas such as expanded access, expedited programs, clinical holds, Part 3 combination products, fixed-combination drug regulatory requirements, formal dispute resolution requests, 505(b)(2)-related development programs, and priority review vouchers. The team also has played a substantial role during 2023 in the implementation of various new statutory provisions such as, but not limited to, critical contributions to the development of new policy related to accelerated approval and therapeutic equivalence requests for certain products approved pursuant to the 505(b)(2) regulatory pathway.

1750+

individual inquiries fielded

OND Policy's guidance team had a very busy 2023 as well, leading the clearance efforts within OND for more than 170 distinct policy-related documents, including guidances, federal register notices, and rules. This activity facilitated the publication of 34 OND-authored documents this year, including 21 guidances on wide-ranging topics important to drug development in specific therapeutic areas such as diabetes mellitus and its complications, infectious diseases, and rare diseases (e.g., acromegaly and endogenous Cushing's syndrome).

170+

policy-related documents cleared

DRP's 505(b)(2) team reviews 505(b)(2) original NDAs, efficacy supplements, and CMC new strength supplements before regulatory action with the 505(b)(2) committee. During fiscal year 2023, this amounted to an average of 13.5 actions per month. This fiscal year included 162 total actions for the team, including 100 approvals, which is the second highest of all time. The number of 505(b)(2) supplement approvals (44) was a historic high, and the original 505(b)(2) approvals accounted for nearly half (43%) of all original NDA approvals in FY23. The team's unwavering dedication to provide regulatory oversight and consistency to 505(b)(2) NDAs, therefore, is essential to a substantial proportion of new drug approvals.

44

505(b)(2) supplement approvals

The office's Division of Clinical Policy (DCP) continues to lead the development and publication of cross-cutting guidance documents as well as training related to clinical and labeling policy. In September 2023, the DCP-led draft guidance *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* published. This pivotal guidance supplements and expands the recommendations in the draft 2019 guidance *Demonstrating Substantial Evidence of Effectiveness for*

Human Drug and Biological Products by providing further detail on the use of data drawn from one or more sources to support the results of one adequate and well controlled clinical investigation. It also provides examples on types of data that could considered confirmatory evidence. Given the broad reaching impact of this topic, DCP provided several widely attended training events for FDA staff related to this guidance. The division's Clinical Advisors Team is often called upon by OND staff and leadership to provide advice on a range of clinical policy topics, including those related to foundational issues such as substantial evidence of effectiveness and benefit/risk assessment.

Led by DCP's Labeling Policy Team, the draft guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* also published this year. The Labeling Policy Team continues to not only provide substantial input during the drafting and publication of many labeling-related guidance documents but also is instrumental in developing and delivering labeling-related training internal and external to FDA. In 2023, the team conducted 16 different training sessions for FDA staff and 4 external presentations, including a presentation at the 2023 FDA Regulatory Education for Industry conference, reaching more than 2300 participants. The team also continues to mentor and support the Associate Directors of Labeling in OND's clinical review divisions and helps to maintain labeling review resources for CDER and the pharmaceutical industry.

OND Policy aims to be trusted advisors and thought leaders within FDA that ensure new drug clinical and regulatory policy strategically transforms with, and inspires, scientific innovation. Our staff is committed to OND's mission, and we will continue to work collaboratively with colleagues throughout OND, CDER, and FDA to ensure that we continue to help OND offices and divisions best serve the American public.

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Office of Cardiology, Hematology, Endocrinology, and Nephrology

The Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) oversees the development, review, and regulation of applications for drug and biologic products reviewed in the following five divisions:

- Division of Cardiology and Nephrology (DCN)
- Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
- Division of General Endocrinology (DGE)
- Division of Non-Malignant Hematology (DNH)
- Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology and Nephrology (DPT-OCHEN)

Notable Drug Approvals

In February, FDA approved Jesduvroq (daprodustat) for the treatment of anemia (low numbers of red blood cells) in adults with chronic kidney disease who have been receiving dialysis for at least four months. Patients with chronic kidney disease often develop anemia because they do not make enough erythropoietin, the hormone that stimulates red blood cell formation. Jesduvroq, the first approved hypoxia-inducible factor propyl hydroxylase inhibitor, increases erythropoietin production. It is taken orally once per day, which some patients may prefer over the erythropoietin stimulating agents that are administered less frequently either intravenously (e.g., during a dialysis session) or subcutaneously (injected under the skin).

Also in February, FDA granted accelerated approval for Filspari (sparsentan), an endothelin and angiotensin II receptor antagonist, to reduce proteinuria (protein

in the urine) in adults with primary immunoglobulin A (IgA) nephropathy at risk of rapid disease progression, generally a urine protein-to-creatinine ratio ≥1.5 g/g. It is the first and only non-immunosuppressive therapy approved for the treatment of this condition. IgA nephropathy, also known as Berger's disease, is a rare kidney disease that occurs when immune complexes containing IgA (a type of antibody) deposits build up in the kidneys. These immune complexes lead to kidney inflammation, hematuria (blood in the urine), varying degrees of proteinuria, and in some patients, progressive loss of kidney function and kidney failure.

In June, FDA approved Lodoco (colchicine) to reduce the risk of heart attack, stroke, coronary revascularization, and cardiovascular death in adults with established atherosclerotic disease or with multiple risk factors for cardiovascular disease. Other colchicine formulations are approved for gout and a rare condition called Familial Mediterranean fever. This is the first approval of colchicine for cardiovascular disease.

In August, FDA expanded the approved uses of Reblozyl (luspatercept) to include treatment of anemia without previous erythropoiesis stimulating agent use in adults with very low- to intermediate myelodysplastic syndrome who may require regular red blood cell transfusions. Myelodysplastic syndrome is a bone marrow failure disorder, where the body no longer makes enough healthy, normal blood cells in the bone marrow.

Also in August, FDA approved Sohonos (palovarotene), a retinoid, for reducing the volume of new bone formation outside the skeleton (heterotopic ossification) in females eight years and older and in males ten years and older with fibrodysplasia ossificans progressiva; making it the first approved treatment for fibrodysplasia ossificans progressiva, a rare disease that progressively restricts motion and shortens lifespan due to accumulating bone formation outside the skeleton.

In September, FDA approved Ojjaara (momelotinib), the first and only treatment of intermediate- or high risk myelofibrosis in adults with anemia. Patients with myelofibrosis develop extensive scarring of the bone marrow (the site of blood cell production), which can lead to anemia.

In November, FDA approved Zepbound (tirzepatide) as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of 30 kg/m2 or greater (obesity) or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease). Zepbound is the first glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist approved for chronic weight management.

In December, FDA approved Fabhalta (iptacopan), the first oral medication and the first complement Factor B inhibitor, for the treatment of adults with paroxysmal nocturnal hemoglobinuria. This rare disease is caused by a mutation in the PIG-A gene that leads to anemia from red blood cell destruction by the complement system and various other health effects.

Guidances, Reports, and Notices

DGE published Acromegaly: Developing Drugs for Treatment; Draft; January 2023, which provides recommendations to sponsors on the clinical development of drugs for the treatment of acromegaly. Acromegaly is a rare disease (50-70 cases per million people) most commonly caused by a growth hormone secreting tumor of the pituitary gland.

DDLO published Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products; Draft; May 2023, to help sponsors develop antidiabetic drugs for adults and children with type 1 diabetes mellitus and/or type 2 diabetes mellitus.

DGE published Endogenous Cushing's Syndrome: Developing Drugs for Treatment; Draft; September 2023, to provide clinical trial design recommendations for drugs intended to treat Endogenous Cushing's Syndrome, a rare condition that causes inappropriately high levels of cortisol, leading to signs and symptoms such as easy bruising, muscle weakness, fatigue, depression, osteoporosis, high blood pressure, weight gain, and type 2 diabetes mellitus.

Public Meetings

- Endocrinologic and Metabolic Drugs Advisory Committee; June 2023. The Committee discussed palovarotene capsules, submitted by Ispen Pharmaceuticals, for the treatment of fibrodysplasia ossificans progressiva.
- Cardiovascular and Renal Drugs Advisory Committee; September 2023. The committee discussed Onpattro (patisiran) lipid complex for injection, submitted by Alnylam Pharmaceuticals, Inc. for the proposed treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults.
- Endocrinologic and Metabolic Drugs Advisory Committee; September 2023. The Committee discussed the safety and efficacy of ITCA 650 (exenatide in DUROS device), a drug-device combination product that is the subject of a new drug application submitted by Intarcia Therapeutics, Inc. to improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise.

Presentations and Conferences

NephCure Kidney International Membranous Nephropathy Scientific Workshop; January 2023. This global workshop aimed to bring together various stakeholders to advance membranous nephropathy science and clinical trials.

"Toward Consensus on Best Practices for the Design and Conduct of Pediatric Obesity Pharmacotherapy Clinical Trials"; 30th European Congress on Obesity; May 2023.

Pathway to SGLT2i [sodium-glucose cotransporter-2 inhibitors] for Renoprotection in Pediatric Chronic Kidney Disease [CKD] Workshop; July 2023. This workshop aimed to discuss what is known about SGLT2i and pediatric CKD, what knowledge gaps remain, and to identify the next steps to evaluate this class of drugs in children and adolescents with CKD.

The Global CardioVascular Clinical Trialists Forum; December 2023. This forum examined cardiovascular trial issues relating to methodology, interpretation, approval, and implementation in specific cardiovascular therapeutic areas.

Office of Drug Evaluation Sciences

The Office of Drug Evaluation Sciences (ODES) promotes innovative approaches to drug evaluation through the promotion of novel drug development tools, standardized drug evaluation approaches, and regulatory science research, focusing on: Clinical Outcome Assessment (COA), Biomedical Informatics and Regulatory Review Science, research, biomarkers, and innovative technologies.

Notable Drug Approvals

Throughout the year, ODES served in the role of consultant throughout the approval process for multiple drugs that eventually received approval from the Agency.

In May, Rinvoq (upadacitinib) became the first oral product approved by the Agency to treat moderately to severely active Crohn's disease (CD), a chronic inflammatory bowel disease which is characterized by focal asymmetric, transmural inflammation. In September, Ojjaara (momelotinib) became the first and only treatment indicated for myelofibrosis patients with anemia. Nearly all myelofibrosis patients are estimated to develop anemia over the course of the disease, and over 30% will discontinue treatment due to anemia.

In November, Adzynma (ADAMTS13, recombinant-krhn) became the first genetically engineered protein product indicated for prophylactic or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP), a rare and life-threatening blood clotting disorder. Also approved, Ogsiveo (nirogacestat) is the first drug to be approved for the treatment of patients with desmoid tumors, a rare subtype of soft tissue sarcomas.

Guidances, Reports, and Notices

ODES provides an ongoing review of draft updates to FDA Patient-Focused Drug Development Guidance 3(G3) Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments; Draft; June 2022.

Other reports published by ODES include:

- PHUSE Safety Analytics Webinar Series: "Overall Safety Assessment – Standard Safety Tables and Figures"; July 2023
- Drug Development Tools Research Grants Reviewer (U01) (PAR-21-178 BMQ grant proposal solicitation); August 2023
- 2023 Drug Trials Snapshots Summary Report

The OND Research Program (OND-RP) published two externally shared FY21 OND research outcomes reports:

1. FY21 Extramural Research Outcomes Report
2. FY21 Oak Ridge Institute for Science and Education (ORISE) Fellowship Research Outcomes Report

OND-RP published the 2023 edition of *"OND ORISE on the Move"* an externally shared newsletter. The theme for this year's edition was DEIA. This annual newsletter summarizes selected research projects from 2023 summer students. Links are also provided for students interested in applying to the 2024 summer program.

Notable Accomplishments

- ODES completed the Standard Safety Tables and Figures Follow-On Guides for Hyperglycemia, Hypoglycemia, and Drug-Induced Muscle Injury. This is typically used by OND clinical reviewers during marketing application review and provided trainings for these products.
- ODES has been actively engaging students in research endeavors and in providing professional experience. This year, ODES participated in the FDA's student engagement initiative, FDA Student Volunteer Service Program. An ODES staff member and student explored the use of imaging biomarkers in clinical development programs for rare diseases, specifically concerning their application in pivotal trials of enzyme replacement therapies and other established pharmacological classes indicated for rare diseases (from 2000-2023).
- OND's Research Program onboarded 27 fellows for its ORISE summer student program. This was the largest cohort since the summer program was launched in 2020.

- ODES and DTS continues to support and advocate on behalf of OND's mission and regulatory processes to promote dialogue on the appropriate representation of different subgroups in clinical trials. ODES continues to build DTS, publishing over 50 summaries online, and a 2022 Drug Trials Snapshots Summary Annual Report.

Public Meetings

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M11 - guideline, clinical study protocol template and technical specifications - Scientific guideline - Harmonised Guideline and Protocol Template Webinar; January 2023.
- "FDA Safety Regulatory Updates"; Drug Information Association (DIA) 2023 Global Pharmacovigilance and Risk Management Strategies Conference; February 2023. In this session, FDA representatives provided updates on Risk Evaluation and Mitigation Strategies from the Office of Surveillance and Epidemiology, draft guidances on the Benefit-Risk Assessment for New Drug and Biological Products for Industry; September 2021, and on Sponsor Responsibilities-Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies; June 2021, and updates from the FDA's Premarketing Safety Assessment Working Group on FDA Medical Queries.
- "FDA Technical Specification for Implementing E2B R3"; DIA 2023 Global Pharmacovigilance and Risk Management Strategies Conference; February 2023. This session reviewed requirements for submitting safety reports for INDs, IND-exempt bioequivalence/bioavailability studies, and approved drug products using the ICH E2B(R3) - guideline for Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports - format while also highlighting variations between the core and regional data elements.
- Electronic Submission of Adverse Event Reports to FDA Adverse Event Reporting System (FAERS) using ICH E2B(R3) Standards; April & November 2023. The purpose of these public meetings is to provide the pharmaceutical industry and other interested parties with updated information on the plans, progress, and technical specifications to upgrade electronic submission standards for the Premarket and Postmarket Safety surveillance programs managed by CDER & CBER. These meetings focus on enhancements to electronic submission of Individual Case Safety Reports in FAERS using ICH E2B(R3) standards.
- Use of Biomarkers for Diagnosing and Assessing Treatment Response in Noncirrhotic Nonalcoholic Steatohepatitis (NASH) Trials; September 2023. The virtual workshop was attended by about 1,000 drug developers, clinical trial investigators, and biomarker developers. Through the discussion and

presentations, the workshop accomplished moving forward biomarkers as reasonable likely surrogate endpoints for NASH drug trials.

- Digital Endpoints: Why Language Matters, Digital Medicine Society; September 2023. ODES serves as a panelist, providing a regulator perspective on the importance of common terminology across digital health stakeholders, their potential impact on regulatory programs, and using digital health technologies to support drug development.
- Wittek Research Foundation's Hypertrophic Cardiomyopathy (HCM) PRO Meeting; November 2023. This meeting was held during the 2023 American Heart Association Meeting to discuss the clinical unmet needs for PROs in HCM and to share patient, regulatory, clinical, and industry perspectives on the utility of PROs in clinical practice and drug development.

Presentations and Conferences

ODES made multiple presentations throughout the year:

- ODES presented "FDA Medical Queries and Standard Safety Tables and Figures"; Drug Information Association Pharmacovigilance and Risk Management Strategies Conference; February 2023.
- ODES gave an external presentation on OND's ORISE Program at the Department of Education's annual Title III Historically Black Colleges and Universities Project Directors Meeting Registration; March 2023.
- ODES presented at the Rare Disease Clinical Research Training Program, Rare Disease Clinical Research Network; May 2023.
- ODES presented "Newcastle Mitochondrial Disease Scale for Adults (NMDAS) as an adequate tool in mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)"; European Medicines Agency-FDA Rare Disease Cluster Meeting; July 2023.
- ODES presented "Elements of Guidances 1-3 of Particular Interest to Statisticians and Constructing/Analyzing Endpoints"; FDASA Training Session – Patient-Focused Drug Development Guidance Series; September 2023.
- ODES presented "Adverse Event Groupings in the Assessment of Safety Topics of Interest"; PHUSE Safety Analytics Webinar Series; September 2023.
- ODES presented FDA Medical Queries and Standard Tables and Figures; PHUSE CSS; September 2023.
- ODES presented "Overview of Qualification and Application to CIVM" at the Critical Path Institute-sponsored workshop, Complex In Vitro Models (CIVM) Qualification Framework Public Workshop; September 2023.
- ODES submitted an abstract and poster entitled, "Biomarkers Used for Dose Selection in Rare Disease Clinical Development Programs" for the National

Organization for Rare Disorders (NORD) Summit; October 2023. Both were accepted.

- ODES presented "Clinical Outcome Assessments in Rare Disease Clinical Trials: Key Considerations for Reviewers"; Office of Biostatistics Science Day; October 2023.
- ODES provided a review of good sponsor COA submissions in rare disease indications from CBER and CDER at DRDMG's Think Tank presentation; October 2023.
- ODES served as a panelist for "AE groupings in safety (AEGiS): Operationalizing the FDA medical queries (FMQs)"; World Drug Safety Congress Americas 2023; October 2023.
- ODES presented "FDA Perspective on the Use of Biomarkers in Drug Development" at the NIMH-sponsored workshop on Blood-Based Biomarkers in Alzheimer's and Related Dementias; October 2023.
- ODES presented "Surrogate Endpoints and Biomarkers" at the FDA-sponsored public workshop, Endpoints and Trial Designs to Advance Drug Development in Kidney Transplantation; November 2023.
- ODES served as a respondent for "Meeting of the Pulmonary-Allergy Drugs Advisory Committee"; November 2023.
- ODES presented an abstract and poster entitled, "Effect of Variation In Alanine Aminotransferase (ALT) and Total Bilirubin (TB) Upper Limits of Normal (ULN) on the Evaluation of Hepatocellular Drug Induced Liver Injury (DILI) in Clinical Trials"; American Association for the Study of Liver Disease (AASLD) The Liver Meeting; November 2023.
- ODES organized and moderated, "Use of WHODrug and Other Pharmaceutical Classification Systems"; December 2023.

ODES participated in the following conferences:

- The National Academy of Sciences, Engineering and Medicine with speaker representation in the workshop entitled, Multimodal Biomarkers for Central Nervous System Disorders: Development, Integration, and Clinical Utility; March 2023. This workshop discussed key steps toward reducing the burden of central nervous system disorders by identifying disease-specific biomarkers that can help predict, monitor, and guide treatment development. Multimodal biomarkers, in particular, offer the potential for improved diagnosis and more accurate disease assessments.
- The 14th Annual Patient-Reported Outcome Consortium Workshop; April 19-20, 2023. At the opening session, FDA colleagues provided updates on:

    - The COA Qualification Program, Medical Device Development Tools Program
    - A Patient-Focused Drug Development Update
    - The "Accelerating Access to Critical Therapies for Amyotrophic Lateral Sclerosis (ALS)" Act
    - A few, brief methodological topics of interest, including:
        - Computerized Adaptive Testing
        - Collection of Patient-Reported Outcome Data from People Who Have Visual Impairments or are Unable to Read
        - Social Media Data as an Input for Generating COAs
- The Fluid & Imaging Biomarkers in Neuroscience Summit; August 2023. ODES gave a presentation on "Regulatory Considerations for Fluid & Imaging Biomarkers of Neurodegeneration & Neuroinflammation."

ODES provides ongoing support as a reviewer for the Rare Disease Endpoint Advancement (RDEA) Program Selection Committee triage committee/review team and an FDA CDER Liaison for the C-Path Rare Disease COA Consortium (RD-COAC).

Office of Immunology and Inflammation

The Office of Immunology and Inflammation (OII) oversees the development, review, and regulation of applications for drug and biologic products reviewed in the following six divisions:

- Division of Dermatology and Dentistry (DDD)
- Division of Gastroenterology (DG)
- Division of Hepatology and Nutrition (DHN)
- Division of Pulmonology, Allergy, and Critical Care (DPACC)
- Division of Pharmacology/Toxicology for Immunology and Inflammation (DPT-II)
- Division of Rheumatology and Transplant Medicine (DRTM)

Notable Drug Approvals

In February, Kevzara (sarilumab) received approval for treatment of the novel indication of adult patients with polymyalgia rheumatica who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper. In March 2023, Joenja (leniolisib) received approval for treating activated phosphoinositide-3 kinase delta syndrome, a rare immunodeficiency disorder; making this NME the first FDA-approved drug for the condition. In April 2023, FDA issued an Emergency Use Authorization (EUA) for the use of Gohibic (vilobelimab) injection for the treatment of COVID-19 in hospitalized adults, when initiated within 48 hours of receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (artificial life support). With this approval, Gohibic becomes the first drug authorized to control complement factor C5a, a protein in the immune system associated with the inflammatory response that exacerbates COVID-19 disease progression.

In May, Rinovq (upadacitinib) became the first approved oral product available to treat moderately to severely active CD in adults who have had an inadequate response or intolerance to one or more tumor necrosis factor blockers. In June 2023, FDA approved Litfulo (ritlecitinib), the first and only treatment for severe alopecia areata in patients as young as 12 years old. FDA also approved Linzess (linaclotide) for pediatric functional constipation; making it the first therapy to be approved for this indication.

In May, the labeling supplements for each of the five intravenous lipid emulsions (IVLE) also received approval. The following issues were aligned in the various IVLE products:

- New "Warning/Precautions" statement for parenteral nutrition-associated liver disease/intestinal failure-associated liver disease
- New "Warning/Precautions" statement for clinical decompensation with rapid infusion of intravenous lipid emulsion in neonates and infants
- Removal of antiquated boxed warning about deaths in preterm infants
- Alignment of labeling language for the class "Warning/Precautions" statements for IVLEs

In August, Veopoz (pozelimab-bbfg) injection received approval for its treatment of adult and pediatric patients 1 year of age and older with CD55-deficient protein-losing enteropathy, also known as CHAPLE disease. Veopoz is the first and only treatment indicated specifically for CHAPLE. Ilaris (canakinumab) also received approval for the treatment of gout flares in adults in whom non-steroidal anti-inflammatory drugs and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate. Ilaris provides significant advantages over existing competitive therapies, including bimonthly administration and approved use in children.

In October, Bimzelx (bimekizumab-bkzx) injection, received approval for the treatment of moderate to severe plaque psoriasis in adults. It is the first and only Interleukin-17A (IL-17A) and IL-17F inhibitor approved for the treatment of adults with moderate to severe plaque psoriasis. Velsipity (etrasimod) and Omvoh (mirikizumab-mrkz) injection, the first and only interleukin-23p19 (IL-23p19) antagonist, also received approval for the treatment of moderately to severely active ulcerative colitis in adults. In December, Filsuvez (birch triterpenes), a topical gel received approval for the treatment of partial thickness wounds in patients 6 months and older with junctional epidermolysis bullosa (JEB) and dystrophic epidermolysis bullosa (EB). Filsuvez is the first approved treatment for wounds associated with JEB, a rare, moderate-to-severe form of EB with blisters beginning in infancy.

Guidances, Reports, and Notices

Chronic Rhinosinusitis with Nasal Polyps: Developing Drugs for Treatment; Final; June 2023. This guidance aimed to assist sponsors in the development of drugs or biological products for the treatment of chronic rhinosinusitis with nasal polyps. Specifically, this guidance addresses FDA's current thinking regarding trial population and design, effectiveness, statistical analysis, and safety for drugs being developed for the treatment of chronic rhinosinusitis with nasal polyps.

Public Meetings

- FDA-led Patient Listening Session on Bronchopulmonary Dysplasia (BPD); March 2023, where individuals who had BPD, and caregivers of individuals with BPD, shared first-hand with FDA staff their experiences with this condition.
- Joint meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee; March 2023, to discuss revisions to the iPLEDGE Risk Evaluation and Mitigation Strategy for isotretinoin.
- Several OND divisions, including three from OII (DRTM, DPACC, DDD), participated in a public workshop on Outcome Measures in Systemic Sclerosis, June 2023.
- DDD participated in the 2023 International Dermatology Outcome Measures Annual Meeting; June 2023.
- DG co-organized a Patient Listening Session: Carcinoid Syndrome; April 2023, with the Office of Patient Affairs.
- DG organized and held the FDA Town Hall session at the Digestive Disease Week; May 2023, an annual scientific meeting organized by the American Gastroenterological Association.
- DHN and the Biomarker Qualification Program conducted a two-day workshop, Use of Biomarkers for Diagnosing and Assessing Treatment Response in Noncirrhotic NASH Trials; September 2023 on the use of Non-Invasive Tests to gauge effectiveness in assessing new drugs for the treatment of metabolic-associated steatohepatitis (MASH).
- DPACC participated in the Summit and a Symposium for Endpoints for Idiopathic Pulmonary Fibrosis; June 2023.
- DRTM established a PPP: Lupus ABC Inaugural Meeting; April 2023. The PPP works on expediting drug development in lupus with the first objective of optimizing existing and developing new, patient-oriented endpoints.
- DRTM sponsored Endpoints and Trial Designs to Advance Drug Development in Kidney Transplantation; November 2023.

Presentations and Conferences

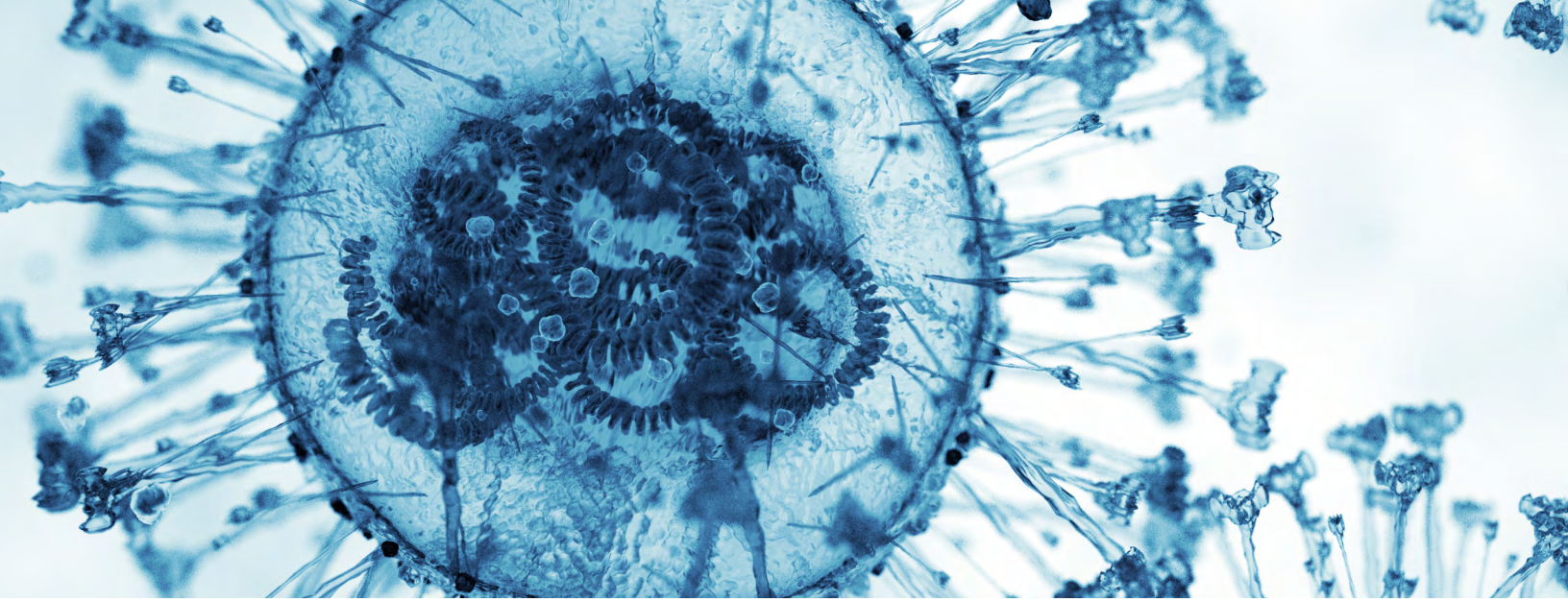
- DG presented "Assessment of Endoscopic and Histologic Findings in IBD Clinical Development: FDA Perspective"; and served as panelists at Inflammatory Bowel Disease Innovate; April 2023, a conference organized by the Crohn's and Colitis Foundation.
- DG presented "Developing Guidance to Facilitate Drug Development in Celiac Disease: A Regulatory Perspective"; and served as panelists at the Celiac Disease: On the Horizon Biennial Symposium; April 2023.
- DG presented "Patient Experience Data: Use in Regulatory Decision-making and Labeling"; and participated as panelists at the 14th Annual Patient-Reported Outcome Consortium Workshop; April 2023.
- DG presented four presentations "Assessment of a Clinically Meaningful Change in a Patient-Reported Outcome. A Case Example: FDA Review of Dupixent (Dupilumab) for the Treatment of Eosinophilic Esophagitis", "FDA Review of Skyrizi (risankizumab) for Treatment of Crohn's Disease", "FDA Review of Rebyota for Recurrent C. Difficile Infection", and "FDA's Current Thinking on the Regulation of Artificial Intelligence/Machine Learning for Medical Devices"; Digestive Disease Week; May 2023, an annual scientific meeting organized by the American Gastroenterological Association.
- DG presented at the annual PancreasFest; July 2023.
- DHN presented, "Assessing Clinical Effectiveness for Treating Liver Diseases at the Food and Drug Administration: Translating Law into Medical Therapy"; Sitaraman Lecture Series; April 2023, as a part of an endowed lectureship that is given annually by invitation from the Division of Digestive Diseases at Emory University School of Medicine.
- DHN participated in the 19th Annual Patient & Caregiver Conference; September 2023. DHN gave a talk during the meeting to patients about patient-focused drug development in the rare disease space for which primary sclerosing cholangitis is rare.
- DHN gave a remote European Lecture "Use of Liver Histology as a Validated Surrogate Endpoint in Evaluation of Treatments for Alpha-one Anti-trypsin Deficiency-related Liver Disease"; AATD 2023 Meeting; September 2023, presented in Naples, Italy.
- DHN presented "FDA Perspective on Nomenclature Change"; Liver Meeting; November 2023.
- DHN presented at the MOSAIC Annual Meeting; October 2023.
- DPACC presented four presentations: "Regulatory Consideration in Severe Cand Critical COVID-19", "FDA Updates: Highlights from Recent Asthma Approvals – Pediatric Considerations in the Review of an Albuterol/Budesonide

Combination Product", "Pulmonary Update from the US FDA", and "Regulatory Considerations for Development of Novel OSA Drugs"; Annual American Thoracic Society Conference; May 2023.

- DPACC participated in "It Takes A Village – The Critical Role of Federal Agencies in Pulmonary Fibrosis Research and Care" and "FDA perspective: Regulatory Considerations for Developing New Treatments While Maintaining Clinical Trial Safety"; Pulmonary Fibrosis Foundation Summit; November 2023.
- DRTM participated in "Update from the FDA", "FDA Year in Review: Update on Safety Issues", "Update and Safety Issues on Recently Approved Agents for Rheumatic Disease", "Study of Pediatric Rheumatic Diseases: FDA Perspective", and "FDA Update on Biosimilar and Interchangeable Products"; American College of Rheumatology Annual Meeting; November 2023.

Publications

- Therapeutics Development in Polyarticular Course Juvenile Idiopathic Arthritis (pcJIA): Extrapolation, Dose Selection and Clinical Trial Design, Arthritis Rheumatol; Wiley Online library; April 2023.
- Reflections from the Osteoarthritis Research Society International (OARSI) 2022 clinical trials symposium: The pain of Osteoarthritis (OA)—Deconstruction of pain and patient-reported outcome measures for the benefit of patients and clinical trial design; Osteoarthritis Cartilage; June 2023.
- Thermal Ablation Compared to Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: A Multi-Center Retrospective Comparative Study; Hepatology Communications; July 2023.
- Vancomycin-Induced Liver Injury, drug-reaction with eosinophilia and systemic symptoms (DRESS), and human leukocyte antigen (HLA)-A*32:01; The Journal of Allergy and Clinical Immunology; September 2023.



Office of Infectious Diseases

The Office of Infectious Diseases (OID) is responsible for making available safe and effective drugs to treat or prevent infectious diseases to the American public. OID consists of three review divisions:

- Division of Anti-Infectives (DAI)
- Division of Antivirals (DAV)
- Division of Pharm/Tox for Infectious Diseases (DPT-ID)

Notable Drug Approvals

In March, FDA approved Rezzayo (rezafungin for injection) for the treatment of candidemia and invasive candidiasis, serious conditions often affecting immunosuppressed patients and associated with substantial mortality risks. Compared to existing parenteral treatment options requiring daily infusions, administration occurs once weekly which allows avoiding placement of central lines to complete treatment, especially in outpatient settings.

In April, FDA tentatively approved Tivicay (dolutegravir), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg. This innovative formulation of dolutegravir is a fast-dissolving oral film that is placed on top of the tongue, where it adheres and dissolves, on an empty stomach or after food for children unable to swallow tablets.

In May, FDA approved Xacduro (sulbactam for injection; durlobactam for injection), the first and only treatment for patients 18 years of age and older with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible isolates of Acinetobacter baumannii-calcoaceticus complex.

Also in May, Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) was approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. This was the first oral antiviral approved by the FDA to treat COVID-19 in adults. Zinplava (bezlotoxumab) also received approval in May. The use of Zinplava was expanded to include the reduction of the recurrence of Clostridioides difficile infection in pediatric patients 1 year to less than 18 years of age who are receiving antibacterial drug treatment and are at a high risk for Clostridioides difficile infection recurrence.

In June, FDA converted accelerated approval to full approval for the use of Lampit (nifurtimox) in pediatric patients from birth to less than 18 years of age for the treatment of Chagas disease (American trypanosomiasis), caused by Trypanosoma cruzi. Prevymis (letermovir) tablets and injections were also approved for prophylaxis of cytomegalovirus (CMV) disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]). This indication provides an important new option for patients at risk for CMV infection following a kidney transplant. Later in the month, FDA approved two supplements, Triumeq (abacavir, dolutegravir, and lamivudine) and Triumeq PD (abacavir, dolutegravir, and lamivudine). With these approvals, three components of labeling were updated; the U.S. Prescribing Information, Instructions for Use, and Medication Guide with data to support the use of Triumeq PD tablets for oral suspension for the treatment of HIV-infection in pediatric patients aged at least three months and weighing at least six kg, and to include long-term safety, pharmacokinetics, and antiviral activity data.

In July, Beyfortus (nirsevimab-alip) was approved for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants born during or entering their first RSV season; and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. This is the first product approved to prevent RSV disease in all infants, including neonates, during their first RSV season.

In November, FDA approved Defencath (taurolidine and heparin) catheter lock solution to reduce the incidence of catheter-related bloodstream infections in adult patients with kidney failure receiving chronic hemodialysis through a central venous catheter. Defencath is indicated in this limited and specific patient population. Of note, this application is the third drug approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs.

Guidances, Reports, and Notices

OID published the following guidances:

- Early Lyme Disease as Manifested by Erythema Migrans: Developing Drugs for Treatment; Draft; January 2023.

- Mpox: Development of Drugs and Biological Products; Guidance for Industry; Draft; January 2023.
- Nontuberculous Mycobacterial Pulmonary Disease Caused by Mycobacterium avium Complex: Developing Drugs for Treatment; Final; September 2023.
- Diabetic Foot Infections: Developing Drugs for Treatment; Draft; October 2023.
- Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment or Prevention of HIV-1 Under PEPFAR; Draft; August 2023.

Notable Accomplishments

Antimicrobial Resistance Regulatory Science Research Studies:

The goal of the Combating Antibiotic-Resistant Bacteria (CARB) research program is to stimulate the development of new antibacterial and antifungal drugs that are active against pathogens associated with antimicrobial drug resistance and poor clinical outcomes to improve patient health.

OID awarded the following regulatory research studies through the CARB research program.

- Characterizing beta-lactam efficacy against metallo-beta lactamase producing bacteria in zinc-limited culture media. Awarded to the University of Southern California.
- Characterizing azithromycin efficacy against carbapenem-resistant Gram-negative bacteria in bicarbonate containing culture media. Awarded to the University of Southern California.
- Development of Modernized Susceptibility Guidance for Ampicillin and Vancomycin for Enterococcus Species Using Pharmacometric Approaches. Awarded to the Institute for Clinical Pharmacodynamics.
- Bridging the gap between urinary tract infection pharmacokinetic/pharmacodynamic in vitro models and the optimization of antibiotic selection, dosing strategies, clinical breakpoints, and novel drug development. Awarded to Monash University.
- Development of a rabbit model to characterize antifungal drug resistance. Awarded to the University of Liverpool.
- Development of in vivo Pharmacometric Approaches to Guide Antifungal Dosing and Susceptibility Breakpoint Determination for Drug Resistant Aspergillus. Awarded to University of Wisconsin-Madison.
- Using big data to generate contemporaneous cohorts for study of novel antimicrobials targeting rare infections. Inter-Agency Agreement (IAA) between FDA and NIH.

- Identify Metabolomic Features Shared by in vitro and in vivo Human Intestinal Microbiome Disruption. IAA between FDA and CDC.
- An Electronic Approach for Post-Market Safety Monitoring for Antibiotic-Associated Adverse Events (ABX-AEs). Awarded to the Johns Hopkins Center of Excellence in Regulatory Science and Innovation (CERSI).

Additional information can be found on OID's research webpage.

Public Meetings

- The Antimicrobial Drugs Advisory Committee; January 2023, discussed rezafungin. The proposed indication was treatment of candidemia and invasive candidiasis in adults.
- World Health Organization Consensus Meeting on Target Regimen Profiles for Tuberculosis (TB) Treatment; March 2023. DAI/OID staff participated in the working group discussions related to revising the Scientific Target Regimen Profiles for TB Treatment; last revised in 2016. Due to an urgent need for safer, simpler, more efficacious, and accessible treatment regimens for TB, these Target Regimen Profiles are intended to guide the drug development process toward important regimen characteristics corresponding to the needs of patients and providers.
- The Antimicrobial Drugs Advisory Committee; March 2023, discussed Paxlovid (nirmatrelvir and ritonavir co-packaged tablets) for oral use. The proposed indication was treatment of mild-to-moderate coronavirus disease (COVID–19) in adults who are at high risk for progression to severe COVID–19, including hospitalization or death.
- The Antimicrobial Drugs Advisory Committee; April 2023, discussed sulbactam-durlobactam for injection. The proposed indication was treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible strains of Acinetobacter baumannii-calcoaceticus complex in adults.
- The Antimicrobial Drugs Advisory Committee; June 2023, discussed nirsevimab-alip, a long-acting respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody for intramuscular use. The proposed indication was prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Presentations and Conferences

- DAI participated in the Institute for Advanced Clinical Trials for Children meeting, Improving the Investigation of New Antibacterial Agents for Use in Children: Ensuring That Our Youngest Patients Also Benefit from Innovative Treatments of Infections Caused by Multi-Drug Resistant Bacteria; January & February 2023.
- DAI presented "Safety Assessment in Clinical Trials and Beyond"; FDA-Sponsor-Investigator Virtual Conference; March 2023.
- DAI served as a panelist in a session on "Pathogen Burden Reduction" during the World Antimicrobial Resistance (AMR) Congress; September 2023.
- DAI served as a panelist in a session entitled, "Are There Aspects of the Antifungal Regulatory Pathway That Could Be Applied to Antibacterial?" during the American Society of Microbiology and the European Society for Clinical Microbiology and Infectious Diseases Joint Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance; September 2023.
- DAI presented "Clinical Evidence Considerations for Orthopedic Device-Antimicrobial Drug Combination Products" during the Orthopedic Surgical Manufactures Association Meeting; October 2023.
- DAI participated at the Clinical and Laboratory Standards Institute Antimicrobial Susceptibility Testing Subcommittee meetings; January 2023 and June 2023.
- DAI presented and participated in a WHO-sponsored meeting "Accelerating Optimal Approval of Priority Formulations for Antibiotic Use in Children", December 2023.
- DAV led a session entitled, "Will an Oral Lead-In Always be a Part of Long-Acting Antiretroviral Drug Development?"; The Long-Acting Extended Release Antiretroviral Research Resource Program Investigator Meeting and Annual Workshop; February 2023.
- DAV attended the Acquired Immunodeficiency Syndrome Clinical Trial Group's Hepatitis Transformative Science Group - Scientific Retreat Session; March 2023.
- DAV attended "Regulatory Considerations for the Development of Monoclonal Antibodies Against Zika Virus"; Continuing Development of Vaccines and Monoclonal Antibodies Against Zika Virus Meeting; February 2023.
- DAV served as a panelist on the topic of "Actions and Recommendations to Improve HCV Linkage and Treatment in Pregnancy"; March 2023.
- DAV presented, "Regulatory Framework for Moving from Emergency Use Authorization (EUA) to FDA Approval for Antiviral Products"; 7th International Society for Influenza and other Respiratory Virus Diseases – Antiviral Resistance Group Conference; May 2023.

- DAV presented, “FDA Perspective: Development of Long-Acting Therapies for Chronic Hepatitis B”; HBV Forum 10 Meeting; June 2023.
- DAV presented and participated in the Forum for Collaborative Research meeting, Advancing Therapeutic Development for COVID-19 Treatment: Part One; November 2023.
- DAV presented and participated in the Forum for Collaborative Research meeting, HIV Treatment bNABs: Clinical Research Considerations; October 2023.
- DAV participated in an IAVI-sponsored international meeting on the development of broadly neutralizing monoclonal antibodies (bNAbs) for prevention perinatal/postnatal HIV transmission; October 2023.
- DAV participated in WHO-sponsored meetings on the development of antivirals for the prevention of perinatal/postnatal HIV transmission; July-November 2023.
- DPTID presented “Regulatory Considerations for Immunosafety”; CE Course; Society of Toxicology Annual Meeting 2023; March 2023.
- DPTID presented “Regulatory Toxicology: A Nonclinical Pharmacology and Toxicology Perspective”; ACT Toxicology for Pharmaceutical & Regulatory Scientist Training Course; April 2023.
- DPTID presented “IND Applications for Biologics: A Regulatory Perspective”; Preclinical Development and IND Filing for Antibody-Based Therapeutics workshop, Pharmaceutical & BioSciences Society of San Francisco, CA; May 2023.
- DPTID presented and served on the panel for the “Basic Course in Drug Development”; Pharmaceutical Education & Research Institute (PERI); May and November 2023.
- DPTID presented “Nonclinical Safety Assessment for Botanical Drug Development”; American Society of Pharmacognosy Annual Meeting 2023; July 2023.
- DPTID provided CE training entitled “Hematopoietic and Immune System Toxicology”; ACT Advanced Comprehensive Toxicology Training Course; August 2023.
- DPTID led a session entitled “Managing Nitrosamine Impurities in Pharmaceuticals: 2023 Update”; American College of Toxicology Annual Meeting 2023, November 2023.
- DPTID presented “Regulatory Considerations in Nitrosamine Assessments Update from FDA”; American College of Toxicology Annual Meeting 2023, November 2023.
- DPTID presented “NCTR Update: Assessing Nitrosamine Risk and Potency”; American College of Toxicology Annual Meeting 2023, November 2023.

- DPTID presented “Regulatory Considerations When Standard Species Used for Toxicology Assessment Are Not Considered Relevant”; American College of Toxicology Annual Meeting 2023, November 2023.
- DPTID presented “NAMS in the Regulatory Space”; American College of Toxicology Annual Meeting 2023, November 2023.
- DPTID chaired symposium session entitled “The 505(b)(2) Approval Pathway for New Drugs: Short Cut or a Long and Winding Road?”; American College of Toxicology Annual Meeting 2023, November 2023.
- DPTID presented “Bridging the divide – animal rule to clinical development”; World Vaccine Congress; November 2023.
- DPTID presented “An FDA/CDER Perspective on Nonclinical Testing Strategies Including New Approach Methodologies (NAMs); American Society for Computational and Cellular Toxicology; November 2023.
- DPTID presented “IND Applications for Biologics: A Regulatory Perspective”; Preclinical Development and IND Filing for Antibody-Based Therapeutics: Nuts, Bolts and Best Practices workshop, Pharmaceutical & BioSciences Society of San Diego, CA; December 2023.
- DPTID regularly presented in FDA training for review staff on “Regulatory Considerations in Nitrosamine Assessments Update from FDA”, Fundamental Courses for New Pharmacology/Toxicology Reviewers”, “Toxicologist for Non-Toxicologists”, “Pharm/Tox 101”, and PTCC Subcommittee training seminars; 2023.
- An ORISE Fellow within OID/DAI presented “Exploration of a Potential Desirability of Outcome Ranking (DOOR) Endpoint for Complicated Intra-Abdominal Infections” at:
  - Walter Reed Medical Rounds; January 2023
  - The 6th Annual Texas Medical Center Antimicrobial Resistance and Stewardship Conference; January 2023
  - Duke University Medical Center Grand Rounds; March 2023

Office of Neuroscience

The Office of Neuroscience (ON) oversees the development, review, and regulation of applications as well as issues related to toxicology for drug and biologic products reviewed in the following five divisions:

- Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
- Division of Neurology I (DNI)
- Division of Neurology II (DN II)
- Division of Pharmacology and Toxicology for Neuroscience (DPT-N)
- Division of Psychiatry (DP)

Notable Drug Approvals

In January, Leqembi (lecanemab), became the second drug approved under the accelerated approval pathway for the treatment of Alzheimer's disease based on reduction of amyloid plaques on positron emission tomography (PET) imaging.

In February, FDA approved Prevduo (neostigmine methylsulfate and glycopyrrolate) injection, which reverses the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery, while decreasing the peripheral muscarinic effects (e.g. bradycardia and excessive secretions) associated with cholinesterase inhibition following NMBA reversal administration. This fixed-dose combination product provides clinicians a convenient option for combined administration of neostigmine and glycopyrrolate for NMBA reversal and reduces the number of administration steps compared to those required for preparation of the individual neostigmine and glycopyrrolate products. FDA also approved Skyclarys (omaveloxolone), the first treatment approved for Friedreich's Ataxia, a rare neurodegenerative disease that affects pediatric and adult patients.

In March, FDA approved Naloxone Hydrochloride Nasal Spray, 4mg/0.25mL for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adults and pediatric patients. It is the first naloxone product approved for use without a prescription. FDA also approved Narcan (Naloxone Hydrochloride) Spray Metered. This action allowed for the full prescription to non-prescription switch that allows for over-the-counter access to Narcan for the emergency treatment of opioid overdose. Zavzpret (zavegepant) was also approved as an acute treatment of migraine with or without aura in adults. Zavegepant is the first intranasal calcitonin gene-related peptide (CGRP) antagonist and therefore provides a new route of administration to this class of highly effective therapies. FDA approved Daybue (trofinetide) to treat Rett syndrome. This is the first treatment approved for Rett Syndrome, a rare neurogenetic disease that causes severe neurodevelopmental impairment.

In April, Qalsody (tofersen) received FDA approval under the accelerated approval pathway. It is indicated for the treatment of patients with ALS caused by a mutation in the superoxide dismutase gene. Qalsody is the first targeted therapy for a rare genetic form of ALS and is also the first drug approval using neurofilament light, a novel biomarker of neuronal degeneration, as a reasonably likely surrogate endpoint. FDA also approved Uzedy (risperidone), which is a subcutaneous extended-release formulation of risperidone approved for the treatment of schizophrenia in adults. This is the first product to utilize SteadyTeq, a copolymer technology proprietary to MedinCell that controls the release of drug. FDA approved an efficacy supplement for Vimpat (lacosamide) based on a “real world evidence” database to support the use of an alternate initial dosing (loading dose) for initiation of lacosamide treatment in partial onset seizure patients ≥1 month to <17 years of age and in primary generalized tonic-clonic seizure patients ≥4 to <17 years, across all formulations.

In May, FDA approved Rexulti (brexpiprazole) tablets for agitation associated with dementia due to Alzheimer’s disease. This is the first treatment approved for this indication. FDA also approved Brixadi (buprenorphine hydrochloride) for the treatment of moderate-to-severe opioid use. Brixadi offers additional options to patients for whom Sublocade is not suitable. FDA also approved Opvee (nalmefene hydrochloride) for the emergency treatment of known or suspected overdose induced by natural or synthetic opioids in patients aged 12 years and older, as manifested by respiratory and/or central nervous depression. This is the first non-naloxone, non-opioid reversal agent in a nasal formulation.

In June, FDA approved Rystiggo (rozanolixizumab-etti) for the treatment of generalized myasthenia gravis. This is the first treatment approved for generalized myasthenia gravis patients who have muscle-specific tyrosine-kinase-antibody positive myasthenia gravis antibodies.

In July, Leqembi (lecanemab-irmb) received traditional approval for the treatment of Alzheimer’s disease after initially receiving accelerated approval in January

2023. Lecanemab is the first monoclonal antibody that targets aggregated forms of amyloid beta to receive traditional approval.

In August, both Tyruko (natalizumab-sztn) and Zurzuvae (zuranolone) received FDA approval. Tyruko is a monotherapy for relapsing forms of multiple sclerosis. It is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's Disease. Tyruko is a biosimilar to Tysabri (natalizumab), and this is the first biosimilar approved by the ON. Zurzuvae (Zuranolone) is the first oral medication approved to treat postpartum depression. Until now, treatment for postpartum depression was only available as an intravenous (IV) injection given by a health care provider in certain health care facilities.

In October 2023, FDA approved Agamree (vamorolone), a synthetic steroid for the treatment of patients 2 years of age and older with Duchenne muscular dystrophy (DMD). Vamorolone is the second steroid approved for this indication.

Guidances, Reports, and Notices

ON published Psychedelic Drugs: Considerations for Clinical Investigations; Draft; June 2023, to highlight fundamental considerations for researchers investigating the use of psychedelic drugs for potential treatment of medical conditions, including psychiatric or substance use disorders. This is the first FDA draft guidance that presents considerations to industry for designing clinical trials for psychedelic drugs. ON also published Migraine: Developing Drugs for Preventive Treatment; Draft; June 2023. This guidance is intended to assist sponsors in the clinical development of drugs for the preventive treatment of migraine.

ON published Stimulant Use Disorders: Developing Drugs for Treatment, Guidance for Industry; Draft; October 2023. The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of stimulant use disorders.

Public Meetings

- At the Peripheral and Central Nervous System Drugs Advisory Committee Meeting; June 2023, the committee discussed Leqembi (lecanemab-irmb) for treatment of Alzheimer's Disease, and the available data to confirm clinical benefit of prior accelerated approval. This is the first drug for Alzheimer's approved under the accelerated pathway with established clinical benefit based on reduction in amyloid plaque, with established clinical benefit. Discussion at the meeting focused on the data to support clinical benefit as well as the benefit-risk given the known risk of amyloid-related imaging abnormalities with this class of drugs, as well as the possibility that some patients who are homozygous for apolipoprotein E gene may be at an increased risk for these complications.

- DNI participated on a panel for the Duke-Margolis Rare Disease Endpoint Advancement Pilot Program Workshop; June 2023, discussing digital health technology-based endpoint examples.
- At the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee; April 2023, the committee discussed Rexulti (brexpiprazole) for the treatment of agitation associated with Alzheimer's disease. Considering the increased risk of death among elderly patients with dementia receiving antipsychotic treatment and the risks of other off-label medications without established evidence of efficacy, the Committee was asked to opine on the relative benefits and risks of brexpiprazole for the proposed indication of the treatment of agitation associated with AD.
- At the Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee; March 2023, the committee discussed a proposed drug for the treatment of ALS in patients with a mutation in the superoxide dismutase type 1 (SOD1 gene). The committee discussed whether reduction in the biomarker of neurofilament light chain was reasonably likely to predict clinical benefit for patients with SOD1-ALS treated with tofersen. The committee also discussed whether the clinical data from a negative double-blind placebo-controlled trial and an open-label extension study provided evidence of effectiveness of tofersen in SOD1-ALS, in addition to overall benefit-risk assessment of tofersen for SOD1-ALS.
- ON staff presented on the drug review process and challenges and key consideration in the design of rare disease trials and moderated a session at Advancing the Development of Therapeutics Through Rare Disease Patient Community- Duke Margolis; December 2023.

Presentations and Conferences

- DAAP participated in "Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose"; Reagan-Udall Foundation workshop; March 2023.
- "FDA Perspectives on Orphan Product Development"; NORD Rare Diseases and Orphan Products Breakthrough Summit; October 2023. DNI leadership participated with other FDA Center representatives in a panel discussion entitled that addressed the challenges and recent successes in rare disease drug development in DNI.
- "Regulatory Considerations"; Identifying and Addressing Challenges in the Ultrarare and N-of-Few Translational Research and Clinical Trials Workshop; November 2023. DNI leadership participated in a closed session workshop with other stakeholders from academia, clinicians, translational scientists and industry and participated in a panel.

- "The Future Pathway to Access Discussion"; N=1 Collaborative Webinar Series; November 2023. DNI joined a panel discussion/webinar on regulatory considerations in N of 1 individualized drug development with regulators from Europe.
- Federal Convening: Forum on Traumatic Brain Injury; October 2023. DN II leadership participated with CDRH representatives in a Federal Convening of USG partners to (1) identify opportunities for cross-agency collaboration and alignment and (2) discuss USG role to transform TBI care in response to recommendation 8 of the NASEM TBI Roadmap Consensus Study Report to create and promulgate a national framework and plan for improvement in TBI care.
- DP presented the "Use of existing datasets to inform regulatory decision making," and the "Use of existing data to inform and speed development of personalized medicine for central nervous system disorders"; International Society for Central Nervous System Clinical Trials and Methodology's annual scientific meeting; February 2023.
- DP participated in the following panels: "Regulatory Plenary on Pediatric Drug Development", "Enhancing Relevance for Public Health: A Focus on Diversity and Inclusion", and "Regulatory Challenges: Ask the Experts"; American Society for Clinical Psychopharmacology; May-June 2023. DP also served as a member of the Program Committee and the New Investigator Award Committee.
- "Psychedelics as Therapeutics: Research Advances and Implications for Practice"; American Academy of Child and Adolescent Psychiatry Annual Meeting; October 2023. DP provided an overview of regulatory considerations for research in psychedelics.
- "Psychedelics as Therapeutics: Research Advances and Implications for Practice"; American Academy of Child and Adolescent Psychiatry Annual Meeting; October 2023. DP provided an overview of regulatory considerations for research in psychedelics.
- "Creating a Multicomponent-Driven Biomarker Framework for Disease Staging in Psychiatric Disorders: Development, Integration, and Clinical Utility"; American College of Neuropsychopharmacology Annual Meeting; December 2023. Representatives from DP, industry (pharma and tech), NIH, and the AMP-SCZ public-private partnership participated in an interactive session discussing challenges and opportunities in multimodal biomarker development.
- DPT-N presented and served as a panelist for a session on "New approach methodologies (NAMs) in the regulatory space"; American College of Toxicology Annual Meeting; November 2023. The presentation was on nonclinical testing strategies comparing standard toxicology approach and New Approach Methodologies (NAMs) from an FDA/CDER perspective. There is great interest in evaluating NAMs to enhance or replace certain aspects of nonclinical testing to support discovery and clinical development of human pharmaceuticals.

- ON discussed the adaptation and validation of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale and the efforts to increase diversity and inclusion of ALS patients in this study, in an ON led session for FDA Rare Disease Day; February 2023.
- ON participated in the Critical Path for Rare Neurological Diseases (CP-RND): An Introduction to the Patient Community Webinar; March 2023. ON provided thoughts on the CP-RND public-private partnership (PPP), conveyed ON's support of the PPP, and described how the PPP can advance regulatory science and accelerate rare neurodegenerative drug development.
- ON presented, "Therapies in Alzheimer's Disease – The Approval Process and Implementing Scientific Discoveries and Advances into Patient Health"; Advisory Council on Alzheimer's Research, Care, and Services Meetings; May 2023.
- ON served as a moderator and DNI served as a panelist for Considerations in Developing Rare Disease Endpoints: Digital Health Technology (DHT); Duke-Margolis Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development; June 2023.
- ON served as a panelist for NIA-AA (National Institute on Alcohol Abuse and Alcoholism) Working Group, and Patient Access to Treatments for Alzheimer's Disease in the U.S. and EU: Perspectives on Clinical Meaningfulness; Alzheimer's Association International Conference; July 2023.
- ON served as a panelist for the Frontotemporal Degeneration Research Roundtable Meeting; September 2023. This was a roundtable meeting sponsored by the Association for Frontotemporal Degeneration including patients, industry, academic partners, and FDA discussed efficiency and power in frontotemporal degeneration clinical trial design, including development of novel biomarkers in this area.
- ON served as a panelist for the LGS (Lennox-Gastaut Syndrome) Meeting of the Minds: Advancing Clinical Research; September 2023.
- ON presented and served as a panelist for the virtually held "Use of DHTS in Drug Development"; National Institute of Neurological Disorders and Stroke Digital Endpoints Meeting; September 2023.
- ON served as a panelist for the National Institute of Neurological Disorders and Stroke- National Institute on Aging Workshop Anti-Beta-Amyloid Passive Immunotherapy for Alzheimer's Dementia and Amyloid Related Imaging Abnormalities: What's Next?; September 2023.
- Neuroscience Forum Fall Membership Meeting, National Academies of Sciences, Engineering, and Medicine; October 2023. As a member of the Forum, ON participated in discussions on rare disease endpoints.
- "Clinical Trials in Alzheimer's Disease"; CTAD Alzheimer Congress | 16th Clinical Trials on Alzheimer's Disease; October 2023. ON attended the meeting focused on therapeutic trials in Alzheimer's disease.

- Opportunities and Challenges in the Use of Blood-based Biomarkers in Clinical Research and Population Studies on Alzheimer's Disease and AD-Related Dementias; October 2023. ON served as a panelist at this NIH meeting.
- ON participated in a task force meeting focused on the topic of "Clinical Meaningfulness and Optimizing Therapies"; Clinical Trials in Alzheimer's Disease Task Force; October 2023.
- ON presented on "Use of Performance Outcome Measures in Neurological Clinical Trials"; ISPOR Europe Meeting 2023; November 2023.
- ON presented on "Accelerating Drug Development in Neurodegenerative Diseases"; American Neurological Association Academia-Industry Workshop: Clinical Trials & Tribulations; November 2023.
- NINDS ACT for ALS and ALS Strategic Priorities Community Update (Virtual); November 2023. ON presented FDA update on the implementation of ACT for ALS.
- Accelerate Cure/Treatments for All Dementias (ACT-AD) Meeting; November 2023. ON participated as a panelist to discuss recent advances in the field of Alzheimer's disease.
- CPATH Neuroscience Annual Meeting; November 2023. ON served as panelists on various panels on drug development in Alzheimer's Disease and Parkinson Disease.
- ON presented the topic, "Regulatory Considerations for Combination Therapies in Alzheimer's disease and AD-related Dementias"; Precision Medicine Approaches for Developing Combination Therapies for the Treatment and Prevention of Alzheimer's Disease/Alzheimer's Disease-Related Dementias; December 2023.
- Parkinson's Disease Endpoints Roundtable Meeting (Virtual); December 2023. ON served as panelists and provided regulatory reflections for early Parkinson's disease endpoints.
- Alzheimer's Association Research Roundtable Meeting; December 2023. ON served as panelists to discuss implementation of proposed diagnostic and staging criteria for Alzheimer's disease based on disease biology.
- ON and DNI served as panelists for "Myotonic Dystrophy (DM) Drug Development and Approval Considerations"; Myotonic Dystrophy Foundation Meeting; September 2023. This public meeting discussed the unmet need and important considerations for drug development in the treatment of myotonic dystrophy, including patient selection, study design, and endpoints.
- ON and DNI served as panelists for the C-Path Rare and Orphan Disease Conference; September 2023. This meeting provided an opportunity to discuss the perspectives of patients, regulators and industry partners on drug development for rare diseases, particularly rare neurodegenerative diseases.

- ON and DN II presented at the Epilepsy Research Roundtable; March 2023. This annual meeting brought together academic investigators, industry leaders, and the Agency to facilitate the development and implementation of new treatments and diagnostic tools for people with epilepsy, by collectively addressing issues related to research and development. The 2023 meeting focused on the appropriate use of biomarkers in epilepsy development and a discussion of the role of remote assessments in clinical trials as a potential means to promote enrollment and capture novel outcomes. ON and DN II presentation topics included:
  - "Biomarkers in Drug Development"
  - "The Use of Neuroimaging in Multiple Sclerosis Development Programs"
  - "Remote Assessment: Understanding Implementation & Comparability Evidence"
- Amyotrophic lateral sclerosis (ALS) Association Research Roundtable; October 2023. ON and OMP served as panelists on a discussion of real-world data and real-world evidence at this roundtable meeting, which brings together various stakeholders to advance science and therapeutic development for amyotrophic lateral sclerosis.

Office of Nonprescription Drugs

The Office of Nonprescription Drugs (ONPD) oversees the development, review, and regulation of nonprescription products (marketed under over-the-counter [OTC] monographs and under NDAs) that play an increasingly vital role in America's health care system. ONPD consists of two review divisions:

- Division of Nonprescription Drugs I (DNPD I)
- Division of Nonprescription Drugs II (DNPD II)

Notable Drug Approvals

A rising numbers of opioid overdose deaths represent a public health emergency in the United States. FDA's approval of Narcan (naloxone hydrochloride) nasal spray, 4 mg/0.1 mL in March, provides a critical tool to help reduce opioid overdose deaths, broadens access to this life-saving therapy, and underpins a huge public health benefit. It is the first time FDA designed and tested a model Drug Facts Label to support switching a product to nonprescription and issued a formal preliminary evaluation that a class of products should switch to nonprescription.

In July, FDA approved Opill (norgestrel) tablet for nonprescription use to prevent pregnancy. It is the first daily oral contraceptive approved for use in the U.S. without a prescription. This approval provides an option for consumers to purchase oral contraceptive medicine without a prescription at drug stores, convenience stores and grocery stores, as well as online. FDA also approved RiVive, a naloxone hydrochloride nasal spray, for nonprescription use for the emergency treatment of known or suspected opioid overdose. This is the second nonprescription naloxone product the agency has approved, helping increase consumer access to naloxone without a prescription.

Guidances, Reports, and Notices

Over-the-Counter Monograph Order Requests (OMORs): Format and Content; Draft; April 2023. This guidance is intended to assist requestors in preparing OTC monograph order requests for submission to FDA under section 505G of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h).

Formal Dispute Resolution and Administrative Hearings of Final Administrative Orders Under Section 505G of the Federal Food, Drug, and Cosmetic Act; Draft; June 2023. This guidance provides recommendations for industry and review staff on the formal dispute resolution and administrative hearings procedures for resolving scientific and/or medical disputes between CDER and requestors and sponsors of drugs that will be subject to a final administrative order under section 505G of the FD&C Act (21 U.S.C. 355h).

Notable Accomplishments

- ONPD posted the remaining final administrative orders as deemed by the CARES Act on OTC Monographs@FDA.
- ONPD posted the third Annual Forecast for Planned Monograph Activities; September 2023; listing the planned OTC monograph activities that FDA intends to initiate over the ensuing three years.
- FDA's CDER NextGen Portal, a website for users to report information to FDA, including certain OTC monograph drug submissions, began accepting OMORs in October 2023.

Public Meetings

- A Joint Meeting of the Nonprescription Drugs Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee; February 2023, was held to discuss nonprescription use of naloxone nasal spray. The committees discussed the supplemental NDA for NARCAN nasal spray, 4 mg/0.1 mL, submitted by Emergent BioSolutions Inc. NARCAN is proposed for nonprescription treatment of known or suspected opioid overdose. Adequacy of the data supporting the nonprescription application was discussed. This product represents a potential first-in-class product in a new therapeutic category for nonprescription drugs.
- There was a Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive and Urologic Drugs Advisory Committee; May 2023, to discuss Opill (norgestrel), a first-in-class switch application for a daily oral contraceptive. The meeting received a high level of public interest and there is a great unmet medical need for prevention of pregnancy in the U.S.
- OTC Monograph Reform: OMOR Format and Content & Electronic Submissions; August 2023. In support of guidances required by section 505G of the FD&C

Act, ONPD conducted a webinar to provide an overview of two draft guidances:

  - Over-the-Counter Monograph Order Requests (OMORs): Format and Content; Draft; April 2023.
  - Over-the-Counter Monograph Submissions in Electronic Format; Draft; September 2022.

- During the Nonprescription Drugs Advisory Committee Meeting; September 2023, the Advisory Committee met to discuss new data regarding the Generally Recognized as Safe and Effective status of oral phenylephrine as a nasal decongestant that have become available since FDA last examined the issue.
- Public workshop, Defining 'Candy-Like' Nonprescription Drug Products; October 2023 discussed how alternatives to conventional solid oral tablets are becoming more prevalent in the nonprescription drug space as manufacturers seek to make drugs more palatable for consumers. Many of these products are easily confused with candy and non-drug products, resulting in misuse and inadvertent overdose, particularly among young children.

Presentations and Conferences

- ONPD presented regulatory updates on OTC monograph reform at the Consumer Healthcare Products Association's (CHPA) Regulatory, Scientific & Quality Conference; September 2023.
- ONPD presented on the proposed rule entitled "Nonprescription Drug Products with an Additional Condition of Nonprescription Use" at RAPS Convergence; October 2023.

Office of Oncologic Diseases

The Office of Oncologic Diseases (OOD) is responsible for making safe and effective drugs for cancer available to the U.S. public. OOD consists of six divisions:

- Division of Hematologic Malignancies 1 (DHM1)
- Division of Hematologic Malignancies 2 (DHM2)
- Division of Hematology Oncology Toxicology (DHOT)
- Division of Oncology 1 (DO1)
- Division of Oncology 2 (DO2)
- Division of Oncology 3 (DO3)

Notable Drug Approvals

In January, FDA granted accelerated approval to Tukysa (tucatinib) in combination with Herceptin (trastuzumab) for RAS wild-type human epidermal growth factor receptor 2 (HER2)-positive unresectable or metastatic colorectal cancer that has progressed following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. FDA also granted accelerated approval to Jaypirca (pirtobrutinib), the first and only non-covalent (reversible) btk inhibitor, for adult patients with relapsed or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a BTK inhibitor. Trodelvy (sacituzumab govitecan-hziy) also received approval to treat patients with unresectable locally advanced or metastatic hormone receptor-positive, (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

In March, Tafinlar (dabrafenib) with Mekinist (trametinib) received approval for pediatric patients one year of age and older with low-grade glioma with a B-Raf proto-oncogene codon 600 of exon 15 mutation who require systemic therapy. FDA

also approved new oral formulations of both drugs suitable for patients who cannot swallow pills. This represents the first FDA approval of a systemic therapy for the first-line treatment of pediatric patients with LGG with a BRAF V600E mutation.

In May, FDA granted accelerated approval to Epkinly (epcoritamab-bysp), the first and only T-cell engaging bispecific antibody for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy.

In June, Talzenna (talazoparib) received approval for the treatment of adult patients with metastatic castration-resistant prostate cancer with mutations in certain genes involved in DNA repair (homologous recombination repair genes). This represents the first approval of this class of drugs for patients without prior treatment for metastatic castration-resistant prostate cancer with mutations in genes other than the breast cancer susceptibility gene. The FDA also granted accelerated approval to Columvi (glofitamab-gxbm) for relapsed or refractory DLBCL, not otherwise specified, or large B-cell lymphoma arising from follicular lymphoma, after two or more lines of systemic therapy.

In August, FDA granted accelerated approval to Talvey (talquetamab-tgvs) for adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 (surface antigen of hematopoietic cells) monoclonal antibody.

Guidances, Reports, and Notices

OOD published the following guidances:

- Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics; Draft; March 2023, describes considerations for designing, conducting, and analyzing data for trials intended to support accelerated approvals of oncology therapeutics.
- Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases; Draft; January 2023, is intended to assist sponsors in identifying the optimal dosage(s) for human prescription drugs or biological products for the treatment of oncologic diseases during clinical development prior to submitting an application for approval for a new indication and usage.

The Oncology Center of Excellence (OCE) and CDRH issued the Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program; Final; June 2023. In cases where some oncology therapeutic products are approved without corresponding in vitro companion diagnostics (as per In Vitro Companion Diagnostic Devices; Final; August 2014), tests offered as laboratory developed tests (LDTs) are being used for patient treatment decisions. FDA generally does not review LDTs for safety or effectiveness. With this pilot program, FDA seeks

to improve the care of patients with cancer by providing transparency regarding performance characteristics of these LDTs should meet if tests are to be used in connection with oncology drug treatment decisions.

Public Meetings

- At the Oncologic Drugs Advisory Committee Meeting; February 2023, the committee discussed Jemperli (dostarlimab-gxly) for injection. The proposed indication (use) for this product is as a single agent for the treatment of patients with locally advanced, treatment-naïve mismatch repair deficiency/microsatellite instability-high rectal cancer. The committee voted that data from two proposed trials will provide adequate means of characterizing the risk-benefit profile of the drug for this indication.
- At the Oncologic Drugs Advisory Committee Meeting; March 2023, the committee discussed Polivy (polatuzumab vedotin-piiq) for injection. The proposed indication for this product is in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone for the treatment of adult patients with previously untreated DLBCL. The committee voted that the benefit/risk profile of the drug is favorable for the indication.
- OCE in coordination with OOD and the National Cancer Institute (NCI), hosted FDA and National Institutes of Health/NCI Center for Cancer Research: Advancing Drug Development in Myelodysplastic Syndromes; May 2023, to advance the discussion around optimal design of clinical trial for patients with myelodysplastic syndrome.
- The Foundation for the National Institutes of Health, NCI, and OCE in coordination with OOD held Creating a Public-Private Partnership to Support Development of Anti-Cancer Therapies for Ultra-Rare Tumor Indications; August 2023, to discuss plans for creating a public-private partnership to guide and support the development of new treatments for patients with ultra-rare cancers.
- At the Oncologic Drugs Advisory Committee Meeting; November 2023, the committee received updates on the accelerated approval program in oncology and two NDAs approved under Code of Federal Regulations Title 21, Volume 5, Section 314.500, Subpart H (accelerated approval regulations) that have not met their agreed-upon milestones for completion of confirmatory trial(s). Confirmatory trials consist of postmarketing studies to verify and describe the clinical benefit of a drug after it receives accelerated approval.

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

The Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM) oversees the development, review, and regulation of applications for drug and biologic products reviewed in the following four divisions:

- Division of Pharmacology/Toxicology for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM)
- Division of Pediatrics and Maternal Health (DPMH)
- Division of Rare Diseases and Medical Genetics (DRDMG)
- Division of Urology, Obstetrics and Gynecology (DUOG)

Notable Drug Approvals

In February, FDA approved Lamzede (velmanase alfa), the first enzyme replacement therapy for the treatment of non-central nervous system manifestations of alpha-mannosidosis, a rare genetic condition characterized by lack of the alpha-mannosidase enzyme in the body. Symptoms of the disorder vary, but often include mild-to-moderate intellectual disability, hearing loss, weakened immune system, distinctive facial features (e.g., a large head, prominent forehead, and protruding jaw), skeletal abnormalities, and muscle weakness. Alpha-mannosidosis affects about one in every 500,000 people worldwide.

In May, Veozah (fezolinetant) received approval for the treatment of moderate to severe vasomotor symptoms due to menopause. Veozah is the first neurokinin 3 (NK3) receptor antagonist approved by the FDA to treat moderate to severe hot flashes from menopause. It works by binding to and blocking the activities of the NK3 receptor, which plays a role in the brain's regulation of body temperature.

Although not life-threatening, menopausal symptoms, such as vasomotor symptoms, can negatively affect women's daily activities and quality of life.

In July, ONPD and ORPURM jointly approved Opill (norgestrel), the first nonprescription daily oral contraceptive tablet. This approval provides an option for consumers to purchase oral contraceptive medicine without a prescription and reduces barriers to access safe and effective contraceptives by allowing individuals to obtain an oral contraceptive without the need to first see a health care provider.

Guidances, Reports, and Notices

DPMH supported the release of two draft guidances for industry: Pediatric Drug Development: Regulatory Considerations – Complying with PREA and Qualifying for Pediatric Exclusivity Under the BPCA; Draft; May 2023, and Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations; Draft May; 2023. Once finalized, both guidances will provide recommendations to support the assessment of pediatric drugs, biological products, and vaccines under the Pediatric Research Equity Act and/or the Best Pharmaceuticals for Children Act. The guidance documents revise and replace the draft guidance for industry, How to Comply with the Pediatric Research Equity Act; Draft; September 2005.

DUOG published a revised draft guidance for industry: Interstitial Cystitis/Bladder Pain Syndrome: Establishing Drug Development Programs for Treatment; Draft; June 2023. This draft guidance provides recommendations for drug development programs for drugs intended to treat patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Currently, there are limited pharmacological treatment options for use in the syndrome.

The revised draft guidance for industry: Inborn Errors of Metabolism that Use Dietary Management: Considerations for Optimizing and Standardizing Diet in Clinical Trials for Drug Product Development; Draft; July 2023, is a revision of the draft guidance of the same name issued July 2018. This guidance describes FDA's current recommendations for optimizing and standardizing dietary management in clinical trials for the development of drug products intended to treat inborn errors of metabolism when dietary management is a key component of patients' metabolic control.

Notable Accomplishments

- The Accelerating Rare disease Cures (ARC) Program recently initiated *Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D)* to better understand the challenges in bringing rare disease drug products to market. As part of LEADER 3D, CDER is seeking input to help identify knowledge gaps and produce educational materials on fundamental topics important to our stakeholders, such as: nonclinical and clinical

pharmacology considerations, clinical trial design and interpretation, and regulatory considerations for rare disease drug development.

- The Rare Disease Endpoint Advancement pilot program was successfully implemented and launched. The program fulfills a Prescription Drug User Fee Act commitment and serves to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process. Learnings and innovations will be shared by FDA with internal and external stakeholders.
- The rare disease filters, "Original Rare Disease Application Approval" and "Novel Rare Disease Drugs Approval" were added under CDER's "Pre-Approval Safety Review: Drugs and Biologics Dashboard" to FDA-TRACK, the agency-wide performance management program that reports on performance measures and key projects for various FDA Centers and Programs. This information provides a more accessible view to the rare disease community about CDER's support for the development and approval of safe and effective drugs to treat rare diseases.
- The CDER OND ORISE Fellowship Research Outcomes Report for FY21; January 2023, highlighted DRDMG's ORISE research project on "Rare Disease Knowledge Management and Characterizing the Impact of the Rare Pediatric Disease Priority Review Voucher". The outcomes of this research informed discussions between FDA's Office of Orphan Products Development and CDER's rare disease subject matter experts.
- In May 2023, ARC celebrated its one-year anniversary. The program was launched in May 2022, and harnesses CDER's collective expertise and activities to drive scientific and regulatory innovation for rare diseases. ARC also builds upon CDER's existing capabilities by fostering collaboration within the rare disease stakeholder community. The anniversary was recognized by an Anniversary Update report and a web post entitled FDA Voices: ARC Program Emerges as a Conduit for Empowering Rare Disease Stakeholders.
- DPMH established the first Regulatory Pharmaceutical Fellowship in OND. The program is a two-year regulatory fellowship in collaboration with Rutgers University and Sanofi and is designed to expose postdoctoral scholars to drug development and regulatory science. The program includes:
  - 8 months in a clinical rotation experience at Rutgers
  - 8 months in regulatory affairs and strategy at Sanofi
  - 8 months in pediatric and maternal health regulatory science in DPMH
- The first Regulatory Pharmaceutical fellow was selected and will be onboarded in July 2024. The fellow will have the unique opportunity to work on a regulatory science project as part of the comprehensive training program.

- DPMH expanded its formal Pediatric Regulatory Science Fellowship Program to include an additional academic site: Children's Hospital of Philadelphia (CHOP). This innovative program provides practical training in regulatory science to academic pediatricians so that clinical therapeutics research in children can be conducted more efficiently, and ultimately more successfully. Through an Intergovernmental Personnel Act (IPA) that is coordinated through ORPURM, DPMH will recruit one fellow from each site (the Clinical and Translational Science Institute at Children's National and CHOP). The fellows will begin the program in July 2024.
- In September 2023, the Rare Diseases Team held the 2023 Annual Rare Disease Training Day for FDA staff. The training focused on the role of translational science and confirmatory evidence in rare disease product development. The Pediatric Review Committee (PeRC), administered and chaired by DPMH, oversees the review of submissions required under BPCA and PREA. Each week the PeRC meets for 3 hours to review these submissions.
- In 2023, the PeRC reviewed 661 submissions, including 172 initial pediatric study plans, 127 agreed initial study plans, 76 requests for deferral extensions for required PREA PMR studies, and 67 labeling changes with pediatric-specific information.

Public Meetings

- DRDMG moderated "Understanding Challenges of Clinical Trials with Small Patient Populations" and presented on ARC during "FDA Initiatives to Advance Product Development for Rare Diseases"; February 2023, at FDA Rare Disease Day.
- ORPURM and DRDMG participated in CDER and Johns Hopkins University's Center of Excellence in Regulatory Science and Innovation jointly sponsored virtual workshop, Addressing Challenges in the Design and Analysis of Rare Disease Clinical Trials: Considerations and Tools; May 2023.
- CDER, CBER, and the Duke-Margolis Center for Health Policy hosted a jointly sponsored virtual public workshop, Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development; June 2023. Participation in this workshop allowed attendees to improve their familiarity and understanding of the Rare Disease Endpoint Advancement (RDEA) Pilot Program, and the issues associated with development of efficacy endpoints for clinical trials of therapies for rare diseases.
- DPMH and DCN participated in the Steering and Planning Committee for the workshop entitled, "Pathway to SGLT2i for Renoprotection in Pediatric Chronic Kidney Disease (CKD): Consensus Meeting" convened by NephCure in July 2023. The introduction of SGLT2i has revolutionized the care of adults with CKD regardless of the underlying cause. However, there is a persistent knowledge gap about the efficacy and safety of these drugs to guide their use

in pediatric patients with CKD. This workshop allowed for an open dialogue between patients and their care providers, experts in clinical nephrology, basic science, regulatory science, and data analysis to address this knowledge gap. Participants discussed the course and treatment of CKD in pediatric patients, current experience with use of SGLT2i, and ongoing efforts by biopharmaceutical companies engaged in trials in children with CKD. The discussion provided a foundation for a general framework for evaluation of this novel class of drugs in children and adolescents with CKD.

- DPMH in collaboration with OSE, CBER, and the Duke Margolis Center for Health Policy hosted a PDUFA VII public workshop on Optimizing the Use of Post-Approval Pregnancy Safety Studies; September 2023.
- DPMH hosted a public workshop entitled "Advancing the Development of Pediatric Therapeutics (ADEPT 8) Workshop on Drug Dosing in Pediatric Patients with Renal Impairment"; November 2023. The workshop discussed assessment of renal function, translating adult renal impairment data to pediatric patients with renal impairment, the role of modeling and simulation as well as potential approaches to generating evidence pre- and post-market to improve the current paradigm for dosing in pediatric patients with renal impairment.

Presentations and Conferences

- ORPURM provided the keynote address at the Foundation for Sarcoidosis Research Clinical Education and Engagement Forum: Visions for Progress in Sarcoidosis in 10 Years; March 2023. This presentation highlighted CDER's rare disease programs and initiatives, research opportunities and programs, and strategies to support innovation in clinical trials.
- ORPURM spoke at the Rare Diseases and Innovation Summit; March 2023, providing updates related to their work with rare diseases.
- ORPURM presented the keynote address at the 6th Annual New England Rare Disease Statistics (NERDS) Workshop; October 2023.
- ORPURM spoke at the 20th DIA Japan Annual Meeting 2023 in Tokyo, Japan. The presentation and panel discussion focused on regulations and strategies among the different regulatory agencies on accelerating orphan drug development and opportunities for global cooperation; November 2023.
- ORPURM, DRDMG, and DPMH presented at the National Organization of Rare Disorders (NORD) Annual Rare Diseases & Orphan Products Breakthrough Summit; October 2023.
- ORPURM, DRDMG, and DPMH presented at the Critical Path Institute's Scientific Breakthrough Summit; October 2023. This workshop focused on advancing medical product development for Lysosomal Diseases, Type-1 Diabetes, Alpha-1 Antitrypsin Deficiency, and neonatal indications.

- DPMH spoke at an Institute for Advanced Clinical Trials for Children (I-ACT) for Children Meeting on improving the investigation of new antibacterial agents for use in children; January 2023.
- DPMH spoke at the Society of Clinical Research Associates (SOCRA) Annual Conference; September 2023.
- DPMH participated in the Treatment in Pregnancy for Hepatitis C (Tip-HepC) Webinar on optimizing treatment options for pregnant persons diagnosed with Hepatitis C; January 2023.
- DPMH participated in the Pediatric Academic Societies (PAS) meeting; April 2023.
- DPMH spoke at the 2023 ASCP (American Society of Clinical Psychopharmacology) Annual Meeting; June 2023, providing a perspective on pediatric drug development.
- DPMH presented "FDA initiatives to advance data collection in pregnancy and lactation"; Canadian Mother-Child Active Surveillance Conference; May 2023.
- DPMH participated as a panelist for the in the National Academies of Sciences, Engineering, and Medicine meeting, Developing a Framework to Address Legal, Ethical, Regulatory, and Policy Issues for Research Specific to Pregnant and Lactating Persons; June 2023. The panel discussed the implications of using real-world evidence to study medical products in the pregnant and lactating population.
- DPMH participated in ICH E21 Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials Guideline Working Group (WG) meetings. This newly formed ICH guideline WG's goal is to provide a globally accepted framework and best practices to enable inclusion and/or retention of pregnant and breastfeeding individuals in clinical trials; June and October 2023.
- DPMH led a discussion on advancing pregnancy and lactation data collection through collaboration at the Society for Birth Defects Research and Prevention 63rd Annual Meeting; June 2023.
- DPMH and ORPURM spoke at the DIA 2023 Annual Meeting; June 2023.
- DPMH presented at the Pharmaceuticals and Medical Devices Agency-Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) and US FDA Pediatric Drug Review Seminar in Japan; July 2023.
- DPMH moderated a session called "Risky Business" on the safety of medications used in pregnancy at the International Conference on Pharmacoepidemiology; August 2023.
- DPMH spoke and served as a panelist at the Consumer Healthcare Products Association's Regulatory, Scientific & Quality Conference; September 2023.
- DPMH participated in the World Health Organization (WHO) Pediatric Regulatory Network Meeting in Nairobi, Kenya; September 2023.

- DPMH presented at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) NCE Seminar on Model-Informed Drug Development in Lifecycle Management: Focus on Pediatrics; October 2023.
- DPMH participated in the EFGCP (European Forum for Good Clinical Practice) Better Medicines for Children Pre-Conference Workshop: Pediatric Dose Optimization; October 2023.
- DPMH presented at EFGCP (European Forum for Good Clinical Practice) Better Medicines for Children Conference on pediatric extrapolation and the value of multistakeholder collaboration for pediatric drug development at the global level; October 2023.
- DPMH was a panelist for the American College of Cardiology Heart House Roundtable on Reproductive Maternal Care for the Cardiovascular Patient; October 2023.
- DPMH presented at the CERSI Program Showcase on evaluation of the application of machine learning algorithms to the management of postpartum hemorrhage; October 2023.
- DPMH presented at the American Academy of Pediatrics Committee on Drugs (AAP COD) meeting to provide an overview of BPCA and PREA; November 2023.
- DPMH spoke at World Children's Day held by ICON on diversity in pediatric drug development; November 2023.
- DPMH presented at the Task force on Research Specific to Pregnant Women and Lactating Women meeting on recommendations regarding optimizing pregnancy registries; November 2023.
- DPMH presented on real world evidence for regulation of treatments during pregnancy at the Harvard School of Public Health at the 16th Kolokotrones Symposium; December 2023.
- DRDMG gave a presentation on regulatory review at the pre-conference session, "Emerging Trends 2023: State-of-the-Art for Experts"; 19th Annual WORLD*Symposium* 2023 Scientific Meeting; February 2023.
- DRDMG presented "FDA's Center for Drug Evaluation and Research: Considerations in Rare Disease Drug Development" and "How CDER is Accelerating Rare Disease Treatments" at the (RE(ACT)) Congress and the International Rare Diseases Research Consortium Conference; March 2023, for the inaugural meeting of the International Rare Diseases Research Consortium's new Regulatory Science Committee.
- DRDMG presented at FDA's Division of Drug Information Rare Diseases - Challenges and Progress in Drug Development; April 2023.
- DRDMG spoke at Creating a Roadmap to Quantitative Systems Pharmacology-Informed Rare Disease Drug Development; May 2023. The

purpose of this workshop was to discuss the potential utility of quantitative systems pharmacology in rare disease drug development and brainstorm the potential path to address the challenges and facilitate its use.

- DRDMG participated on the panel titled "Clinical Development & Regulatory Panel Session: Patient focused drug development - best practices on patient group and drug developer interaction with FDA"; World Orphan Drug Congress; May 2023.
- DRDMG spoke at the WCG MAGI Clinical Research Conference; May 2023, on considerations in rare disease clinical trials.
- DRDMG presented "How CDER is Accelerating Rare Disease Cures and the PDUFA VII Rare Disease Endpoint Advancement Pilot Program"; Regulatory Education for Industry Annual Conference 2023; June 2023.
- DRDMG presented at the Biotechnology Innovation Organization International Convention: 40 years of the Orphan Drug Act, the Rare Disease Endpoint Advancement Pilot Program, and Transforming Rare Disease Development; June 2023.
- DRDMG participated in "How Will Shifts in the Stage of Patients with ATTR-CA Affect Ongoing and Future Clinical Trials?"; Advancing Drug Development in ATTR in an Evolving Treatment Landscape; June 2023.
- DRDMG discussed the Accelerating Rare disease Cures Program at the Ladders to Cures Symposium: Achieving escape velocity in rare genetic diseases; July 2023.
- DRDMG presented at The Critical Path's 2023 Rare and Orphan Disease Conference; September 2023.
- DRDMG spoke at the Externally-Led Patient Focused Drug Development meeting on Classical Homocystinuria; October 2023.
- DRDMG spoke at the Regulatory Affairs Professional Society Convergence 2023 on the Rare Disease Endpoint Advancement (RDEA) pilot program; October 2023.
- DRDMG spoke at the International Porphyrias Symposium 2023: Advancing the Science & Art, discussing what's new in rare diseases at the FDA Center for Drug Evaluation and Research; October 2023.
- DRDMG presented at the National Academies of Sciences, Engineering, and Medicine Forum on Neuroscience and Nervous System Disorders; October 2023.
- DRDMG participated in a National Academies of Sciences, Engineering, and Medicine FDA briefing; November 2023. In response to a congressional request, an ad hoc committee of the National Academies of Sciences,

Engineering, and Medicine is conducting a study on processes for evaluating the safety and efficacy of drugs for rare diseases or conditions in the United States and the European Union.

- DRDMG participated in the virtual public meeting titled "Advancing the Development of Therapeutics Through Rare Disease Patient Community Engagement"; December 2023. This meeting was hosted by FDA in collaboration with Duke-Robert J. Margolis, MD Center for Health Policy (Duke-Margolis) and supported by a cooperative agreement between FDA and Duke-Margolis. The purpose of this public meeting was to highlight and build upon existing actionable approaches for engaging patients, patient groups, and related experts when developing necessary evidence to support rare disease drug approvals. This meeting also fulfilled the requirement for a public meeting as discussed in Section 3202 of the Food and Drug Omnibus Reform Act of 2022 (FDORA).
- DUOG served as a moderator at the Princeton IV symposium; March 2023. The symposium used a multi-disciplinary approach where 15 participants led scientific presentations/discussions on cardiovascular risk associated with erectile dysfunction as well as various safety aspects of phosphodiesterase 5 inhibitors. Conclusions at the Princeton IV symposium are intended to update the Princeton Guidelines that were generated at the three prior Princeton symposia (1999, 2004, and 2010).
- DUOG participated in a panel discussion to commemorate the 25th Anniversary of FDA's approval of Viagra; "Sildenafil: 25 Years Later"; May 2023. The discussion was organized by Grand Rounds in Urology.
- DUOG, Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive medicine, the Office of Pharmaceutical Quality's and the Division of Pharmacology/Toxicology for Infectious Diseases presented at the American Society of Pharmacognosy Annual Meeting; July 2023.
- DUOG presented at CDER Small Business and Industry Assistance meeting; September 2023. This workshop focused on biomarkers and surrogate endpoints, which have been used to support clinical programs for non-alcoholic steatohepatitis (NASH). DUOG presented "Lesson Learned from Makena Drug Development" in Session 1.
- DUOG presented at FDA's Office of Women's Health (OWH) and CDER's Office of Clinical Pharmacology's virtual public workshop— Menopause: Potential Impact on Clinical Pharmacology and Opportunities for Future Research; October 2023. The workshop discussed the current understanding of the impact of menopause on drug pharmacology and highlighted the areas with the greatest need for further research and exploration.
- DUOG spoke at the Borne International Collaborative Meeting at University of California, Los Angeles on novel treatment strategies in human preterm labor;

November 2023. The talk was on considerations for development of medical products for prevention of preterm birth.

- DUOG provided opening remarks at the Externally-Lead Patient-Focused Drug Development Meeting on Polycystic Ovary Syndrome (PCOS), convened by the National Polycystic Ovary Syndrome Association; November 2023.
- DPT-RPURM/SM spoke at the 11th Juvenile Toxicology Symposium; April 2023, discussing a variety of topics, including the challenges associated with conducting nonclinical studies in juvenile non-human primates.
- DPT-RPURM/SM spoke at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Annual Meeting; June 2023.
- DPT-RPURM/SM spoke at the American College of Toxicology Annual Meeting in a session on adversity in intraocular toxicity studies: scientific and regulatory considerations and clinical translation; November 2023.
- DPT-RPURM/SM presented at the Positron Emission Tomography: Product Quality Regulatory Submissions, Facility Inspections, and Benefit-Risk Considerations workshop and participated in a panel discussion; November 2023.

Office of Specialty Medicine

The Office of Specialty Medicine (OSM) oversees the development, review, and regulation of applications for drug and biologic products reviewed in its divisions. OSM consists of the Pharmacy Compounding Review Team and two review divisions:

- Division of Imaging and Radiation Medicine (DIRM)
- Division of Ophthalmology (DO)

Notable Drug Approvals

In February, FDA approved Syfovre (pegcetacoplan injection), 150 mg/mL for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD); making it the first product approved for this indication. GA secondary to AMD is characterized by progressive and irreversible atrophy of retinal cells. Individuals affected by GA experience decreases in quality of life, including difficulty reading and recognizing faces and loss of independence. In August, FDA approved Izervay (avacincaptad pegol intravitreal solution) as the second drug product for the treatment of GA secondary to age-related macular degeneration.

Later in February, FDA approved Eylea (aflibercept) injection for the treatment of retinopathy of prematurity (ROP); making it the first product approved for this indication. ROP is a vision-threatening, vasoproliferative disease of the incompletely vascularized, immature retina of preterm infants (born <37 weeks of gestational age).

In May, FDA authorized Mydcombi (tropicamide and phenylephrine hydrochloride ophthalmic spray), 1%/2.5%. It induces mydriasis for diagnostic procedures and in conditions that desire short-term pupil dilation. The fixed combination provides an alternative dosage form (spray) for the dilation of pupils. Later in

May, FDA approved Miebo (perfluorohexyloctane ophthalmic solution), a sterile, single-component drug product consisting of 100% perfluorohexyloctane, a linear semifluorinated alkane. This drug product treated the signs and symptoms of dry eye disease. When placed topically on the cornea, Miebo spreads across the ocular surface and interacts with the lipophilic part of the tear-film, decreasing the rate of evaporation of the aqueous tear-film component.

Starting in June and continuing through the year, FDA approved multiple biosimilars to Humira (adalimumab) for the treatment of non-infectious intermediate, posterior, and panuveitis in adult patients. Biosimilars approved for this new indication included Abrilada (adalimumab-afzb), Cyltezo (adalimumab-adbm), Amjevita (adalimumab-atto), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimioz (adalimumab-adaz), Idacio (adalimumab-aacf), and Yusimry (adalimumab-aqvh). Although not a first-line treatment for adult uveitis, these biosimilars provide an alternative treatment for a vision-threatening condition.

In July, FDA approved Xdemvy (lotilaner ophthalmic solution); making it the first drug approved for the treatment of Demodex blepharitis, an ocular disease characterized by eyelid margin inflammation, redness, and general eye irritation. It is caused by an infestation of Demodex mites that live on humans.

In August, FDA approved Eylea HD (aflibercept) injection. Eylea HD provides a higher strength treatment for patients with neovascular (wet) AMD allowing dosing to be less frequent.

In September, FDA approved Technegas (kit for the preparation of technetium Tc 99m-labeled carbon inhalation aerosol) as a radioactive diagnostic agent for use in adults and pediatric patients aged six years and older for visualization of pulmonary ventilation and evaluation of pulmonary embolism when paired with perfusion imaging. Technegas has imaging advantages compared to currently marketed alternatives, namely increased retention that allows acquisition of images in more positions than Xenon-133 gas and improved image quality through less central airway deposition than Technetium-99m diethylene triamine pentaacetic acid aerosol. FDA also approved Ryzumvi (phentolamine ophthalmic solution); making it the second drug product approved for the treatment of pharmacologically induced mydriasis.

Guidances, Reports, and Notices

OSM published multiple guidances and notices throughout the year:

- Neovascular Age-Related Macular Degeneration: Developing Drugs for Treatment; Draft; February 2023, discusses age-related macular degeneration, a chronic eye disease characterized by progressive degeneration in the central retina (macula) and is a leading cause of severe vision loss worldwide.
- DIRM published a draft guidance for industry, Acute Radiation Syndrome: Developing Drugs for Prevention and Treatment; Draft; April 2023. This

guidance will assist sponsors in the development of certain medical countermeasure drugs that DIRM regulates.

- The Pharmacy Compounding Review Team assisted in the publishing of the 503B Bulks List Decisional Federal Register Notice; April 2023, and Quinacrine Hydrochloride Compounding Safety Information Sheet; April 2023, to provide patients with better understanding of risks of using a product containing quinacrine.
- List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act Decisional Federal Register Notice; August 2023. This notice identifies two bulk drug substances that FDA has considered and is not including on the list at this time: ephedrine sulfate and hydroxychloroquine sulfate.

Presentations and Conferences

OSM hosted FDA Drug Topics: Regulatory Framework for Human Drug Compounding; September 2023. This presentation provided an overview of human drug compounding and its regulatory framework, differentiated drug compounding from the FDA new drug approval process, described the bulk drug substance evaluation process, and provided examples.

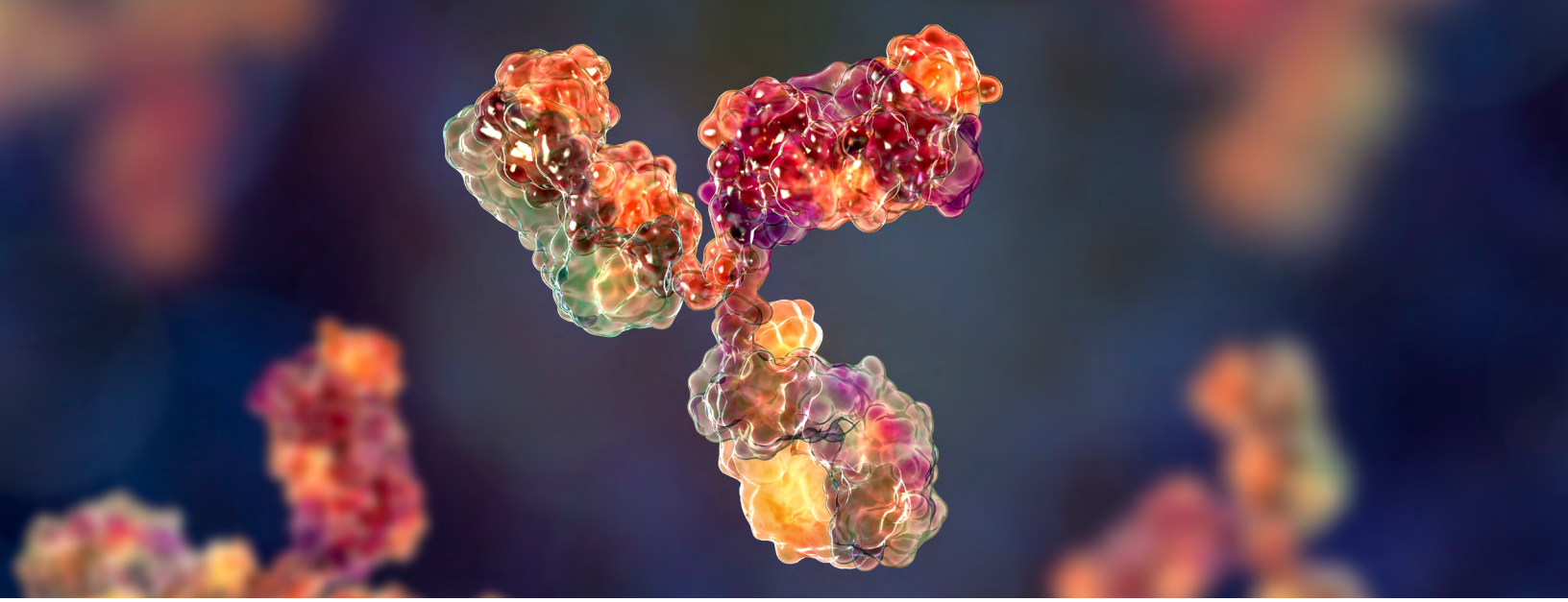
DIRM held a dedicated FDA session at the annual meeting of the Society of Nuclear Medicine and Molecular Imaging 2023 Annual Meeting; June 2023, a major gathering of stakeholders for the imaging drugs that DIRM regulates. DIRM management, clinical, Radioactive Drug Research Committee, statistical, chemistry manufacturing and controls team, and nonclinical staff gave in-person presentations, followed by a panel discussion.

DIRM hosted the Medical Imaging Drugs Advisory Committee Meeting; August 2023, to discuss dosimetry data needed to support the initial clinical study of certain new diagnostic PET drugs in an IND. The committee supported an FDA proposal to allow first-in-human studies for new PET drugs containing certain radionuclides based on existing dosimetry data from animal or human studies with other PET drugs containing the same radionuclides. Through this flexible approach, collection of animal dosimetry data with many new PET drugs would not be required. The outcome of this meeting is expected to streamline PET drug development and will be further described in a leading nuclear medicine journal and a draft FDA guidance document.

DIRM co-sponsored the workshop, Positron Emission Tomography Drugs: Product Quality Regulatory Submission, Facility Inspections, and Benefit-Risk Considerations; November 2023, to discuss a range of issues related to development and manufacturing of PET drugs with academic and commercial stakeholders.

DO participated in:

- 2023 Glaucoma 360 Meeting; February 2023. The Glaucoma Research Foundation, a national non-profit organization dedicated to finding a cure for glaucoma, hosted this meeting.
- The American Glaucoma Society Annual Meeting; March 2023. Glaucoma Specialists dedicated to sharing clinical and scientific information for the benefit of patients, colleagues, fellows and residents make up the AGS.
- The 22nd Duke Advanced Vitreous Surgery Course; March 2023. This course showcased the latest in vitreoretinal surgical techniques, use of novel instrumentation and intraoperative visualization technology, as well as an orientation to FDA organization and function regarding the field of Ophthalmology.
- Dermatologic and Ophthalmic Advisory Committee Meeting; January 2023. The committee discussed aflibercept solution for intravitreal injection, submitted by Regeneron Pharmaceuticals, Inc. for the treatment of ROP. The Agency was interested in hearing from the committee their comments on how the studied use of aflibercept in the treatment of retinopathy of prematurity could best be communicated to physicians and the caregivers of these premature infants.
- The Ophthalmic Business Council's Spring Symposium in association with the American Academy of Ophthalmology's Mid-Year Forum; April 2023.
- Regulatory Endpoints and Trial Design for IRDs; June 2023. The theme for this year's Innovation Summit was "Defining the Preclinical to Clinical Roadmap" with several presentations emphasizing design of clinical trials for emerging therapies.
- The 2023 Leber Congenital Amaurosis Family Conference; June 2023. The conference allowed for the exploration of new connections in the Leber congenital amaurosis and rare inherited retinal disease community.
- The Amyloidosis Forum: Advancing Drug Development in Transthyretin Amyloidosis (ATTR) in an Evolving Treatment Landscape; June 2023. This forum explored the current amyloidosis research landscape, its advancements, impact, and the unmet needs that currently exist by identifying key initiatives with the aim of leveraging cross-stakeholder resources to collaboratively act on field-shaping priorities.
- Future Vision Forum Rare Diseases; September 2023. This forum is comprised of visionary leaders in ophthalmology, visual science, and allied fields who meet annually to foster ideas and programs that accelerate the pace of innovation and discoveries that improve the lives of people with eye disease and visual disability.
- The Eyecelerator and the American Academy of Ophthalmology Annual Meeting; November 2023.
- Mary Tyler Moore Vision Initiative; November 2023.



Office of Therapeutic Biologics and Biosimilars

The Office of Therapeutic Biologics and Biosimilars (OTBB) coordinates and supports all biosimilar and interchangeable product activities in CDER. OTBB provides infrastructure and specialized resources to enhance the Biosimilar User Fee Amendments (BsUFA) program and support the objectives included in the Biosimilars Action Plan (BAP), as well as addressing any additional biosimilar or biological product issues

Notable Drug Approvals

In March, FDA approved a new single-dose prefilled auto-injector presentation of Udenyca (pegfilgrastim-cbqv), a biosimilar to Neulasta, which increases survival of adult and pediatric patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome, or H-ARS).

In August, FDA approved Tyruko (natalizumab-sztn). Tyruko is the first approved biosimilar for the treatment of relapsing forms of multiple sclerosis and was approved for the following indications currently approved for U.S.-licensed Tysabri: relapsing forms of multiple sclerosis which includes clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. Tyruko is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active CD who have had an inadequate response to or are unable to tolerate conventional CD therapies and inhibitors of tumor necrosis factor.

In September, FDA approved Tofidence (tocilizumab-bavi). This product is an interleukin-6 receptor antagonist that targets specific inflammatory proteins to suppress the immune system. Tofidence is approved for the following indications: rheumatoid arthritis, polyarticular juvenile idiopathic arthritis for two years of age

and older, and systemic juvenile idiopathic arthritis for two years of age and older. This is the first biosimilar approved to treat systemic juvenile idiopathic arthritis.

In October, FDA approved Wezlana (ustekinumab-auub) as a biosimilar and interchangeable to Stelara (ustekinumab) for multiple inflammatory diseases. Wezlana, is approved to treat adult patients with moderate to severe plaque psoriasis, active psoriatic arthritis; moderately to severely active Crohn's disease; and moderately to severely active ulcerative colitis. It is also approved for pediatric patients six years of age and older with moderate to severe plaque psoriasis and active psoriatic arthritis.

FDA also approved two existing approved biosimilars as interchangeable biosimilars: Byoovis (ranibizumab-nuna) and Abrilada (adalimumab-afzb). FDA currently has approved 45 biosimilar products with seven of those as interchangeable biosimilars.

Guidances, Reports, and Notices

FDA issued two draft guidances for industry: Classification Categories for Certain Supplements Under Biosimilar User Fee Act (BsUFA III); Draft; August 2023, and Formal Meetings Between the Food and Drug Administration and Sponsors or Applicants of Biosimilar User Fee Act Products; Draft; August 2023.The guidance for industry Classification Categories for Certain Supplements Under BsUFA III; Draft; August 2023 provides recommendations for applicants and FDA review staff on classification categories A, B, C, D, E, and F for original and resubmitted prior approval supplements submitted to approved applications under section 351(K) of the Public Health Service Act. This draft guidance is intended to help applicants identify the appropriate classification category and review goal date of the supplement being submitted.

The guidance for industry Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products; Draft; August 2023 provides recommendations to industry on formal meetings between FDA and sponsors or applicants relating to the development and review of biosimilar or interchangeable biosimilar products regulated by CDER or CBER. This draft guidance for industry revises and replaces the draft guidance of the same name issued in June 2018. Both draft guidances fulfill deliverables outlined in the BsUFA III commitment letter and help maintain a predictable and efficient review process for biosimilars.

FDA issued, Labeling for Biosimilar and Interchangeable Biosimilar Products; Draft; September 2023, and a corresponding Notice of Availability. In this draft guidance, FDA outlines its recommendations for biosimilar and interchangeable biosimilar product labeling. FDA has now approved 42 biosimilar products, including four interchangeable biosimilars, and has gained valuable experience about labeling considerations for biosimilar and interchangeable biosimilar products. This guidance considers that experience and includes additional recommendations on labeling for interchangeable biosimilar products and

other topics. FDA is no longer recommending that labeling for interchangeable biosimilar products include an "interchangeability statement." Instead, FDA recommends that labeling for interchangeable biosimilars and biosimilars both include a "biosimilarity statement." When finalized, this draft guidance will replace the guidance for industry: Labeling for Biosimilar Products; Final; July 2018. This draft guidance also satisfies a BsUFA III commitment that FDA publish a draft guidance on labeling for interchangeable biological products on or before September 30, 2023.

Notable Accomplishments

FDA released the BsUFA III Regulatory Science Pilot Program: Research Roadmap; January 2023, which clarifies the intent of the regulatory science program and provides more granularity on the type of research projects FDA is expecting to receive.

In September 2023, OTBB, with their OCOMM partners, conducted outreach to the general public about biosimilars through a MAT release (an article placed in newspapers and other online and print publications) and the distribution data to date is surpassing expectations. There have been 939 placements since the release, including the ten largest designated market areas in the U.S.: N.Y.C., L.A., Chicago, Philadelphia, Dallas - Ft. Worth, San Francisco-Oakland-San Jose, Washington, D.C., Houston, Boston, and Atlanta; reaching a total audience of 53,499,698. This content also performed very well across the Midwest including St. Louis, Chicago, Columbus, and Madison. The total Midwest audience has reached 22,624,669 people.

In addition, OTBB launched Google Search and Display ads as well as YouTube ads to target both health care providers and patients using our existing video assets. These continue to garner great results with over 6 million impressions as of November.

Public Meetings

- OTBB held a Reddit Ask Me Anything forum "Let's talk about biosimilars" with Pharmacists; June 2023, where the public asked questions about biosimilars and interchangeable products.
- FDA and the International Pharmaceutical Regulators Program Biosimilars Working Group hosted a virtual workshop, Increasing the Efficiency of Biosimilar Development Programs—Reevaluating the Need for Comparative Clinical Efficacy Studies; September 2023. The public sessions of the workshop included discussion of the experience accrued with comparative clinical efficacy studies to date and stakeholder perspectives on the question of whether these studies are needed.

Presentations and Conferences

OTBB held a webinar through FDA's Division of Drug Information's Health Care Providers' Continuing Education Webinar Series, Biosimilars: A Review of Scientific, Regulatory, and Clinical Considerations for Health Care Providers; June 2023. This webinar discussed the science of biological products, including size, complexity, and variation. It also described commonalities between biosimilars and referenced biological products and differences in the approval pathways, with an in-depth explanation of the scientific and regulatory concepts for biosimilars and interchangeable biosimilars. This webinar also demonstrated the functionality of The Purple Book: Database of Licensed Biological Products, an easy-to-use resource for pharmacists, other health care providers, and the public to identify approved biosimilar and interchangeable biosimilar products.

OTBB staff members conducted outreach and education in various venues and formats including:

- Serving as the keynote speaker for the Biosimilar track of the Festival of Biologics Annual Conference; March 2023.
- Speaking about biosimilar products at a meeting of the States Lieutenant Governors.
- Presenting at the Medicines for Europe 28th Annual Conference; June 2023, and visiting the European Medicines Agency (EMA) where they discussed scientific, regulatory and educational topics with EMA colleagues.
- Presenting at the 14th SUMMIT ON Biosimilars & Innovator Biologics; June 2023, Multiple Sclerosis Symposium Patient Education Program; July 2023, the Securities and Exchange Presentation: An Overview of Biosimilar Products; September 2023.
- Providing the biosimilars keynote address at the GRx+Biosims 2023 conference; October 2023.
- Presenting to The Indian Health Service National Pharmacy & Therapeutics Committee; October 2023 for its Fall meeting.
- Presented at ACR Convergence 2023; November 2023.

Publications

Office of Cardiology, Hematology, Endocrinology, and Nephrology

- Innovations in Pediatric Therapeutics Development: Principles for the Use of Bridging Biomarkers in Pediatric Extrapolation; *Therapeutic Innovation & Regulatory Science*; January 2023.
- Utility of islet autoantibodies as enrichment biomarkers in type 1 diabetes clinical studies: a viewpoint from the FDA; *Diabetologia*; March 2023.
- Patient-reported outcome measures and patient engagement in heart failure clinical trials: multi-stakeholder perspectives; *European Journal of Heart Failure*; April 2023.
- End point considerations for clinical trials in enteric hyperoxaluria; *Clinical Journal of the American Society of Nephrology*; June 2023.
- Overcoming Barriers to Drug Development in Children with CKD; *Clinical Journal of the American Society of Nephrology*; August 2023.
- ICH S7B In Vitro Assays Do Not Address Mechanisms of QTc Prolongation for Peptides and Proteins – Data in Support of Not Needing Dedicated QTc Studies; *Clinical Pharmacology & Therapeutics*; September 2023.
- Assessing the use of observational methods and real-world data to emulate ongoing randomized controlled trials; *Clinical Trials*; December 2023.

Office of Drug Evaluation Sciences

- U.S. FDA public meeting: identification of concepts and terminology for multicomponent biomarkers; *Biomarkers in Medicine*; September 2023.

Office of Infectious Diseases

- Participation of HIV-1 infected treatment-naive females in clinical trials and sex differences in efficacy and safety outcomes; *Wolters Kluwer Health, Inc.; epub* January 2023.
- Discordant Clinical and Microbiological Outcomes are Associated with Late Clinical Relapse in Clinical Trials for Complicated Urinary Tract Infections; *Clinical Infectious Diseases*; January 2023.
- Considerations and Challenges in the Remdesivir COVID-19 Pediatric Development Program; *Journal of Clinical Pharmacology*; February 2023.
- Gaps and Challenges in Nonclinical Assessments of Pharmaceutics: An FDA/CDER perspective on considerations for development of new approach Methodologies; Regulatory Toxicology and Pharmacology; February 2023.
- Book Chapter: Toxicology and Drug Development; *Handbook of Medicinal Chemistry, 4th edition*; March 2023.
- Antigenic diversity of type 1 polioviruses and its implications for the efficacy of polio vaccines; *Elsevier Ltd.*; March 2023.
- Exploration of a Potential DOOR Endpoint for Complicated Intra-Abdominal Infections Using 9 Registrational Trials for Antibacterial Drugs; *Clinical Infectious Diseases*; April 2023.
- Food and Drug Administration Public Workshop Summary—Development Considerations of Antifungal Drugs to Address Unmet Medical Need; *Clinical Infectious Diseases*; April 2023.
- Reappraisal of Idiopathic CD4 Lymphocytopenia at 30 Years; *The New England Journal of Medicine*; May 2023.
- Participation of HIV-1 infected treatment-naive females in clinical trials and sex differences in efficacy and safety outcomes; *Wolters Kluwer Health, Inc.*; May 2023.
- Uses and Challenges of Antiviral Polyclonal and Monoclonal Antibody Therapies; *Pharmaceutics*; May 2023.
- HIV-1 usurps transcription start site heterogeneity of host RNA polymerase II to maximize replication fitness; *Proceedings of the National Academy of Sciences of the United States of America*; May 2023.
- Pharmacokinetics of Antiretroviral Agents in Pregnant Individuals Living With HIV: Current Status and Considerations for Study Design and Interpretation; *The Journal of Clinical Pharmacology*; June 2023.
- Food and Drug Administration (FDA) Public Workshop Summary—Addressing Challenges in Inhaled Antifungal Drug Development; *Clinical Infectious Diseases*; October 2023.

Office of Neuroscience

- Immune-mediated colitis associated with ocrelizumab: A new safety risk; *Multiple Sclerosis Journal*; September 2023.

Office of Oncologic Diseases

- Increasing Racial and Ethnic Equity, Diversity, and Inclusion in Cancer Treatment Trials: Evaluation of an ASCO-Association of Community Cancer Centers Site Self-Assessment; *JCO Oncology Practice*; April 2023.
- FDA regulatory considerations for the review of drugs intended to treat pediatric cancers and rare tumors; *Current Opinions in Pediatrics*; February 2023.
- Recommendations on the use of item libraries for patient-reported outcome measurement in oncology trials: findings from an international, multidisciplinary working group; *Lancet Oncology*; February 2023.
- Regulatory implications of circulating tumor DNA (ctDNA) in immuno-oncology for solid tumors; *Journal for Immunotherapy of Cancer*; February 2023.
- Evaluating Pneumonitis Incidence in Patients with Non-small Cell Lung Cancer Treated with Immunotherapy and/or Chemotherapy Using Real-world and Clinical Trial Data; *Cancer Research Communications*; February 2023.
- Continuation of Third-Generation Tyrosine Kinase Inhibitors in Second-Line Trials for Epidermal Growth Factor Receptor (EGFR)-Mutated Non–Small-Cell Lung Cancer: Regulatory Considerations; *Journal of Clinical Oncology*; June 2023.
- Irreconcilable Differences: The Divorce Between Response Rates, Progression-Free Survival, and Overall Survival; *Journal of Clinical Oncology*; March 2023.
- Approvals in 2022: overall survival, dose optimization, new approvals and beyond; *Nature Reviews Clinical Oncology*; April 2023.
- U.S. Food and Drug Administration Approval Summary: Nivolumab Plus Platinum-Doublet Chemotherapy for the Neoadjuvant Treatment of Patients with Resectable Non-Small-Cell Lung Cancer; *Journal of Clinical Oncology*; May 2023.
- Equitable Access to Clinical Trials: How Do We Achieve It?; *American Society of Clinical Oncology Educational Book*; June 2023.
- Minimal Residual Disease Data in Hematologic Malignancy Drug Applications and Labeling: An FDA Perspective; *Clinical Cancer Research*; August 2023.
- Measuring Frailty Using Patient-Reported Outcomes (PRO) Data: A Feasibility Study in Patients with Multiple Myeloma; *Quality of Life Research*; August 2023.

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

- CDER Continues to Advance Rare Disease Drug Development with New Efforts, Including the ARC Program; February 2023.
- Co-authored chapter entitled, "Clinical Development of Pediatric Program within Rare Diseases"; *Drug Development for Rare Diseases*; Chapman & Hall; February 2023.
- FDA approval summary for lonafarnib (Zokinvy) for the treatment of Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies; *Genetics in Medicine*; February 2023.
- Model-Informed Approach Supporting Approval of Nexviazyme (Avalglucosidase Alfa-ngpt) in Pediatric Patients with Late-Onset Pompe Disease; *American Association of Pharmaceutical Scientists (AAPS) Journal*; January 2023.
- Pediatric Efficacy Extrapolation in Drug Development Submitted to the US Food and Drug Administration 2015–2020; *Journal of Clinical Pharmacology*; March 2023.
- Clinical Lactation Studies of Neuropsychiatric Medications: Clinical Pharmacology and Labeling Considerations; *Journal of Clinical Pharmacology*; June 2023.
- A Comparison of FDA and EMA Pregnancy and Lactation Labeling; *Clinical Pharmacology & Therapeutics*; June 2023.
- Pharmacokinetic Evaluation in Pregnancy—Current Status and Future Considerations: Workshop Summary; *Journal of Clinical Pharmacology*; June 2023.
- Evaluation of FDA Labeling Changes Related to PREA Safety–Waivers; *Therapeutic Innovation & Regulatory Science*; June 2023.
- Overcoming Barriers to Drug Development in Children with CKD; *Clinical Journal of the American Society of Nephrology*; August 2023.
- Considerations and Challenges in the Remdesivir COVID-19 Pediatric Development Program. *Journal of Clinical Pharmacology*; February 2023.
- Therapeutic Development in Polyarticular Course Juvenile Idiopathic Arthritis: Extrapolation, Dose Selection, and Clinical Trial Design; *Arthritis Rheumatology*; April 2023.
- US FDA public meeting: identification of concepts and terminology for multicomponent biomarkers; *Biomarkers in Medicine*; September 2023.
- Risk of severe COVID-19 in prevalent users of α-1 adrenergic receptor antagonists: a national case-control study of Medicare beneficiaries; *The American Journal of Medicine*; October 2023.

- Measuring ovarian toxicity in clinical trials: an American Society of Clinical Oncology research statement; *The Lancet Oncology*; October 2023.
- Alternatives to Monkey Reproductive Toxicity Testing for Biotherapeutics; *International Journal of Toxicology*; December 2023.

Office of Therapeutic Biologics and Biosimilars

- CDER's Office of Communications wrote a spotlight article, April 2023, highlighting the importance of biomarkers in streamlining biosimilar products development after OTBB published the following articles:

  1. Considerations for Use of Pharmacodynamic Biomarkers to Support Biosimilar Development - (I) A Randomized Trial with Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors; *Clinical Pharmacology & Therapeutics*; October 2022.
  2. Considerations for Use of Pharmacodynamic Biomarkers to Support Biosimilar Development - (II) A Randomized Trial with Interleukin 5 (IL-5) Antagonists; *Clinical Pharmacology & Therapeutics*; October 2022.
  3. Considerations for Use of Pharmacodynamic Biomarkers to Support Biosimilar Development - (III) A Randomized Trial with Interferon Beta-1a Products; *Clinical Pharmacology & Therapeutics*; November 2022.

Acronyms and Key Terms

Acronym/Term	Description
ALS	amyotrophic lateral sclerosis
AMD	age-related macular degeneration
ANTI-CD38	surface antigen of hematopoietic cells
ARC	Accelerating Rare disease Cures
ATTR	transthyretin amyloidosis
BLA	biologics license applications
BPD	bronchopulmonary dysplasia
BSUFA	Biosimilar User Fee Act
CBER	Center for Biologics Evaluation and Research
CD	Crohn's disease
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CMV	cytomegalovirus
COA	clinical outcome assessment
DAAP	Division of Anesthesiology, Addiction Medicine, and Pain Medicine
DAI	Division of Anti-Infectives
DAV	Division of Antivirals
DCN	Division of Cardiology and Nephrology
DCOA	Division of Clinical Outcome Assessments
DCP	Division of Clinical Policy

Acronym/Term	Description
DDD	Division of Dermatology and Dentistry
DDLO	Division of Diabetes, Lipid Disorders, and Obesity
DG	Division of Gastroenterology
DHN	Division of Hepatology and Nutrition
DHT	digital health technology
DIA	Drug Information Association
DIRM	Division of Imaging and Radiation Medicine
DLBCL	diffuse large B-cell lymphoma
DNI	Division of Neurology I
DN II	Division of Neurology II
DNPD I	Division of Nonprescription Drugs I
DNPD II	Division of Nonprescription Drugs II
DO	Division of Ophthalmology
DO1	Division of Oncology 1
DO2	Division of Oncology 2
DO3	Division of Oncology 3
DOOR	desirability of outcome ranking
DPACC	Division of Pulmonology, Allergy and Critical Care
DPMH	Division of Pediatrics and Maternal Health
DPT-II	Division of Pharmacology and Toxicology for Immunology and Inflammation
DPT-N	Division of Pharmacology and Toxicology for Neuroscience

Acronym/Term	Description
DPT-OCHEN	Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology and Nephrology
DPT-RPURM/SM	Division of Pharmacology/Toxicology for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/Specialty Medicine
DRESS	drug-reaction with eosinophilia and systemic symptoms
DRDMG	Division of Rare Diseases and Medical Genetics
DRP	Division of Regulatory Policy
DRTM	Division of Rheumatology and Transplant Medicine
DUOG	Division of Urology, Obstetrics, and Gynecology
EB	Epidermolysis Bullosa
EUA	emergency use authorization
FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
FD&C ACT	Food, Drug, and Cosmetic Act
GA	geographic atrophy
HER2	human epidermal growth factor receptor 2
HLA	human leukocyte antigen
HIV-1	human immunodeficiency virus type 1
IBD	inflammatory bowel disease
IC/BPS	Interstitial Cystitis/Bladder Pain Syndrome
ICH	International Conference for Harmonisation
IGA	immunoglobulin A

Acronym/Term	Description
IL-17A & IL-17F	interleukin-17A & and 17F
IND	investigational new drug application
IV	intravenous
IVLE	intravenous lipid emulsions
JEB	Junctional Epidermolysis Bullosa
LDTS	laboratory developed tests
MASH	metabolic-associated steatohepatitis
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
NDA	new drug application
NMBA	non-nondepolarizing neuromuscular blocking agent
NME	new molecular entity
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
OC	Office of the Commissioner
OCE	Oncology Center of Excellence
OCHEN	Office of Cardiology, Hematology, Endocrinology, and Nephrology
ODES	Office of Drug Evaluation Sciences
OID	Office of Infectious Diseases
OII	Office of Immunology and Inflammation
OMOR	over-the-counter monograph order requests

Acronym/Term	Description
ON	Office of Neuroscience
OND	Office of New Drugs
OND-RP	OND Research Program
ONPD	Office of Nonprescription Drugs
OOD	Office of Oncologic Diseases
ORISE	Oak Ridge Institute for Science and Education
ORPURM	Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
OSM	Office of Specialty Medicine
OTBB	Office of Therapeutic Biologics and Biosimilars
OTC	over-the counter
OMOR	Over-the-Counter Monograph Order Requests
PET	positron emission tomography
PPP	public-private partnership
PREA	Pediatric Research Equity Act
ROP	retinopathy of prematurity
RSV	respiratory syncytial virus
SOD1-ALS	superoxide dismutase type 1
TB	tuberculosis
TBI	traumatic brain injury

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