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Director's Message

In this Annual Report, we have focused on the importance of scientific leadership — in the era of COVID-19, that seems timely.

Over the past two decades, the types of diseases for which drugs are developed, the drug platforms used, the development tools employed, and the trial sites included have all been evolving. We've gone from an era where most drugs were small molecules developed for common diseases to one where we have seen many more biological drugs — and new approaches such as antisense oligonucleotides or siRNAs — treating rare diseases or disease subsets, often defined by biomarkers. At the same time, unmet needs in many common diseases remain, and our growing understanding of disease pathogenesis, for example in many immune-mediated inflammatory disorders, have led to exciting and novel new treatments for these conditions.

With COVID-19, changes in drug development have accelerated, with use of master protocols, decentralized trial components, application of digital technology based-endpoints, and use of real-world evidence, especially in understanding the disease natural history, outcomes, and risk factors. In this rapidly evolving landscape of drug development, drug regulation cannot be static, but also must progress to assure that we can apply our statutes and regulations to novel issues and challenges. OND staff, working with many other CDER offices, must keep up with the evolving science, and find ways that novel challenges in drug regulation can be addressed.

Indeed, to assure that we foster advances in drug development to meet unmet needs, we must often provide direction to developers at very early stages so that they can move forward in designing and implementing their development programs. As is often the case, when these programs are in areas without available guidance or clear precedent, OND staff must collaborate across CDER offices to figure out how best to provide direction. Often, this may require staff to hold workshops with external experts, conduct research to address unknowns, or foster innovative strategies.

In this report, we focus on such efforts across our organization, discussing the many ways in which OND staff have advanced programs directed at unmet needs.

Peter Stein, M.D.
Director, Office of New Drugs

OND Exemplifies Scientific Leadership

The Office of New Drugs (OND) regulates the development and approval of new drugs (including therapeutic biological products), new uses (indications) for already approved drugs, biosimilar and interchangeable products, and over-the-counter (OTC) products. OND also monitors drug safety both during IND development and post-approval. The ecosystem in which OND fulfills this role is rapidly evolving, with unprecedented scale and investment in drug development, increasing complexity in clinical trial designs, and expanding availability of drug development tools.

To adapt to these rapid changes, the Center for Drug Evaluation and Research (CDER) began an initiative in 2017 to modernize the New Drugs Regulatory Program (NDRP) and enhance its core review processes to assure the safety and effectiveness of treatments meeting the medical needs of the American public most effectively and efficiently. The NDRP involves multiple super-offices within the CDER, including OND. As a part of the NDRP effort, OND underwent a reorganization starting late in 2019 and finishing in early 2020 to therapeutically align divisions and offices with modern standards and practices. In 2021, OND continued to advance regulatory science and the regulation of new drugs through the NDRP modernization. OND's 2021 Annual Report focuses on scientific leadership as one of the six core strategic objectives that guide the NDRP modernization.

The aims of the scientific leadership objective are to grow the scientific expertise of NDRP staff and foster drug development and approval, particularly in areas of unmet medical need (disease areas that lack approved treatment options). Through scientific leadership we hope to:

- Develop strategic approaches to address substantive issues in drug development, particularly in areas of unmet medical need
- Deepen review staff's scientific expertise and support staff's professional development to continually enhance efficient and effective regulatory decisions, informed by the most current science in drug development
- To support the most efficient and effective drug development approaches to support safe and effective therapeutic options for patients, increase competition, and expand access.

In the long term, OND's scientific leadership should contribute to the approval of new treatments to address unmet medical needs, expanding drug approvals to other indications and patient populations, and expanding the number of available products with favorable benefit-risk profiles.

In the long term, OND's scientific leadership should contribute to the approval of new treatments to address unmet medical needs, expanding drug approvals to other indications and patient populations, and expanding the number of available products with favorable benefit-risk profiles. Additional outcomes associated with this strategic objective focus on innovations in trial design, sustained progress in product development through continued evolution in regulatory policy and pathways, and increased recognition of FDA's role in the scientific community.

The following sections of this report highlight OND's scientific leadership, in driving innovation in drug trial designs, progression in product development, and collaboration and information sharing, through scientific leadership. The report also highlights OND's scientific leadership efforts during the second year of the COVID-19 pandemic.

OND by the Numbers in Calendar Year 2021

Despite the challenges of working virtually during the COVID-19 pandemic and the intense focus on developing responsive therapeutics, OND, working hand-in-hand with other CDER super-offices, had a successful year for novel drug approvals and other drug development activities, such as industry meetings and guidances published during the calendar year 2021. Please click on the links for more information.

Investigational New Drugs (INDs) Received and INDs with Activity

New Drug Approvals (NME NDAs/BLAs)

Non-New Molecular Entity (NME) New Drug Application (NDA) Approvals

Efficacy Supplement Approvals

Breakthrough Therapy Requests

Fast Track Requests

Expanded Access INDs Received and Expanded Access INDs Safe to Proceed

20
Published Guidances

6
Critical Path Innovation Meeting (CPIM) meetings with OND representation

14
Patient-Focused Drug Development (PFDD) meetings with OND representation

18
Patient Listening Sessions organized by OC/Office of Patient Affairs with OND representation

11
Patient Listening Sessions organized by Professional Affairs and Stakeholder Engagement (PASE) with OND representation

594
OND speaking engagements

Scientific Leadership in Response to COVID-19

In the second year of the COVID-19 pandemic, OND's staff continued to exemplify scientific leadership in the areas of innovative trial design, progression in product development, and collaboration with partners to advance promising COVID-19 therapies.

Innovative Trial Design for COVID-19 Therapies

OND offices worked collaboratively across OND, with other CDER offices, with other FDA Centers, with other US government agencies, and with other regulatory agencies to support innovative approaches to the development of COVID-19 therapies. Staff from the Office of Infectious Diseases (OID) and the Office of Biostatistics (OB) (in the Office of Translational Sciences (OTS)) worked closely with a range of sponsors, including those from industry, academics, National Institutes of Health (NIH) and other government agencies, and with consortia, to evaluate and advise on the most efficient approaches to development of therapeutics that would lead to the information FDA needs to issue Emergency Use Authorizations (EUAs) and eventually approvals for treatments for COVID-19. OND staff, working with staff from other CDER offices, worked to develop new endpoints, such as clinical outcome assessment (COA) instruments, and to evaluate surrogate endpoints that might be useful to evaluate COVID-19 therapeutics.

An important approach to developing therapeutics is the use of master protocols or platform trials; staff from OID, OB, and the Office of Immunology and Immunization (OII) combined their expertise to provide regulatory guidance on such trial approaches to evaluate the potential benefits of COVID-19 therapies quickly. Staff from OID and OB collaborated on the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership (PPP), working with NIH staff, industry, and academic groups. As part of this PPP, the contributing FDA offices provided important input on design of the adaptive master protocols for clinical trials (the ACTIV trials). In collaboration with other FDA Centers and CDER offices, OND staff also prepared guidance, published in May 2021, providing recommendations to sponsors of master protocols evaluating drugs for the treatment of COVID-19.

Progression in Product Development

Building on 2020 activities, OND divisions continued to work with sponsors on drug development programs to progress therapies for COVID-19, starting in the Pre-Investigational New Drug application

stage and continuing to submissions for EUAs or for NDA/BLA or supplement approval. The emerging COVID-19 variants required adjustments to authorizations to ensure the benefits of treatments continued to outweigh any risks.

In collaboration with other FDA Centers and CDER offices, OND staff also prepared guidance, published in February 2021, to address the impact of emerging variants of SARS-CoV-2 on the development of monoclonal antibody products targeting the virus. The guidance recommends efficient approaches to the generation of non-clinical, clinical, and chemistry, manufacturing and controls data that could potentially support an EUA for monoclonal antibody products that may be effective against emerging variants. In connection with this effort, OND working with other CDER staff also revised a second guidance regarding phase 2 and phase 3 clinical trials for drugs and biological products under development to treat or prevent COVID-19 more broadly, including the patient population, trial design, efficacy endpoints, safety considerations and the statistical considerations for such trials, among other issues. This revision updated the guidance to address the evolving landscape of COVID-19 drug development, including the emergence of SARS-CoV-2 variants and the availability of authorized COVID-19 vaccines.

With the intense efforts of OND staff and staff from other CDER offices, FDA issued EUAs for several promising therapies for COVID-19. For example, in November 2020, FDA, on recommendation of OII's Division of Rheumatology and Transplant Medicine (DRTM), issued an EUA for baricitinib in combination with remdesivir to treat hospitalized patients with severe COVID-19 infection. In July 2021, FDA revised and reissued the EUA to no longer require that baricitinib be used in combination with remdesivir.

In June 2021, FDA, on recommendation of the Office of Immunology and Inflammation (OII)'s Division of Pulmonology, Allergy and Critical Care (DPACC), issued an EUA for the monoclonal antibody tocilizumab for the treatment of severe COVID 19 in hospitalized patients.

On recommendation of OID's Division of Antivirals (DAV) and a number of other CDER offices, FDA issued an EUA for the neutralizing monoclonal antibody sotrovimab for the treatment of COVID-19 in May 2021 and a revised EUA for the monoclonal antibody product REGEN-COV (casirivimab and imdevimab, administered together) for post-exposure prophylaxis (PEP, prevention) of COVID-19 in August 2021. DAV, working closely with staff from a number of other US government agencies, assessed the potential impact of virologic (relating to the study of viruses and the diseases they cause) and real-time variant epidemiology (the study of the frequency and causes of disease variants) data on the effectiveness of COVID-19 products. These

collaborative efforts between OND staff and outside agencies facilitated knowledge sharing and resulted in regulatory decision-making based on the best available science.

In 2021, OND offices continued to work jointly with partners within and outside of FDA to expand upon the shared understanding of COVID-19, further develop effective COVID-19 therapies, and promote the safety of products used to treat or prevent the virus.

OII's DRTM and DPACC worked with internal and external stakeholders to share novel regulatory questions, novel trial designs, and data from promising therapies to treat COVID-19. Through these collaborations, DPACC and DRTM developed recommendations for therapeutic development programs for COVID-19 that would meet FDA's regulatory standards. These collaborations also ensured that OND provided timely advice on COVID-19 to sponsors, standardized regulatory actions across OND, and modified trial designs to best evaluate potential therapies within the current standard of care treatment paradigm. The OND review teams also worked closely with internal and external stakeholders to address drug shortages of products to treat COVID-19, including tocilizumab and baricitinib.

To help ensure the safety of products in high demand in the second year of the pandemic, Office of Nonprescription Drugs (ONPD) continued to evaluate and promote hand sanitizer safety.

To help ensure the safety of products in high demand in the second year of the pandemic, Office of Nonprescription Drugs (ONPD) continued to evaluate and promote hand sanitizer safety. For example, ONPD helped update hand sanitizer guidances for industry, provided communications on hand sanitizers that consumers should not use, and working with other CDER offices, issued a Drug Safety Communication that alcohol-based hand sanitizer vapors can have side effects. Through these communications, ONPD supported FDA in encouraging the safe production and use of hand sanitizers. ONPD worked with a CDER Task Force to issue an import alert on all alcohol-based hand sanitizers from Mexico to stop products that appeared to be contaminated with methanol from entering the United States until FDA was able to review the products' safety. This was a novel regulatory action, as it marked the first time that FDA issued a countrywide import alert for any drug product category.

As part of a CDER Task Force and in collaboration with the United States Pharmacopeia (USP), ONPD also developed guidance outlining the Agency's policy for testing alcohol or isopropyl alcohol for methanol contamination before using the alcohol to produce drugs, including hand sanitizer products. This guidance helps pharmaceutical manufacturers and pharmacists who engage in drug compounding avoid using pharmaceutical alcohol contaminated or substituted with methanol in drug products. These actions will ensure the safety of alcohol-based hand sanitizers and other drug products using pharmaceutical alcohol in the United States and protect consumers.

The collaboration with USP demonstrates ONPD's commitment to ensuring that FDA appropriately balances risk and benefit in developing policies to facilitate the production and continued availability of hand sanitizers during the public health emergency.

Innovations in Drug Trial Design

During the past year, OND staff worked with sponsors to advance innovative clinical trial designs to address previously unmet medical needs. These innovations enabled the launch of new drug development programs, the inclusion of previously under-represented patient populations in clinical trials that might otherwise have been impracticable, the use of real-world data to inform new trial designs and support the approval of treatments, guidance on clinical trials for transdermal delivery of drugs, and guidance on consumer behavior studies to expand the nonprescription drug market, to name a few. The sections below highlight these activities.

New Drug Development Programs for Innovative Trial Design

In 2021, OND offices collaborated with OB in OTS on several Complex Innovative Trial Design (CID) Program meetings.

Through these CID meetings, OND and other Agency components provided leadership and guidance that shaped innovative trial designs to develop safe and effective therapies for serious diseases like systemic lupus erythematosus (SLE), an autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs. There is a lack of safe and effective therapies to treat SLE, and through the CID program, OII's DRTM encouraged drug development by actively advising sponsors on developing both master protocols and platform clinical trials for SLE. Master protocol trials have multiple sub-studies that may have different objectives and evaluate one or more drugs or diseases. Platform trials are clinical trials with a single master protocol that evaluates multiple treatments simultaneously. These trial designs are innovative because they can streamline clinical trial operations, enable early decision-making about promising therapeutic candidates for further development, and reduce drug development time and cost.

Another example of advances with innovative trial designs through the CID Program in 2021 was a two-day virtual public workshop co-led by the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine's (ORPURM's) Division of Pediatrics and Maternal Health (DPMH), the CID pilot meeting program, and the

University of Maryland Center of Excellence in Regulatory Science and Innovation (CERSI). Workshop participants discussed opportunities to leverage complex and innovative trial designs, the challenges with their applications, and potential solutions to overcome challenges, specifically the considerations for bridging biomarkers in pediatric extrapolation and Bayesian techniques in pediatric studies. These trial designs expand the ability to correctly predict relevant clinical outcomes given the challenges with pediatric clinical trials, which include smaller sample sizes and the fact that it is not feasible to use placebos in certain pediatric trial designs because this would be unethical. FDA and CERSI have planned a follow-up mini seminar to discuss additional trial design elements for a pediatric study that relies on a bridging biomarker.

Innovative Trial Designs for New Patient Populations

OND worked with other CDER offices and stakeholders to discuss expanding clinical trials to include previously underrepresented patient populations, such as those who are pregnant.

OND also worked with other CDER offices and with stakeholders to discuss expanding clinical trials to include previously under-represented patient populations, such as those who are pregnant. Including a more diverse patient population in clinical trials allows for the collection of efficacy and safety information relevant to the patient population likely to be prescribed the approved therapy.

For example, in February 2021, ORPURM's Division of Urology, Obstetrics, and Gynecology (DUOG) and DPMH, in coordination with the Duke Margolis Center for Health Policy, led a two-day public workshop on including pregnant people in clinical trials, the first workshop led by FDA on this topic. The workshop included speakers from FDA, NIH, academia, bioethics, patient advocacy, and industry. Participant discussion addressed barriers to including pregnant people in clinical trials, the preclinical and clinical data needed, ethical and scientific considerations around including pregnant people in trials, and potential pathways forward. This discussion resulted in consensus on the need to include pregnant and lactating people in clinical trials.

Additionally, the conference touched upon the need to develop data (currently nonexistent) on approved medications used for common medical conditions that persist during pregnancy and developing medications specifically indicated for the treatment of pregnancy-related conditions. Other workshop outcomes included revising FDA draft guidance on the topic and developing a workshop proceedings manuscript for the *American Journal of Obstetrics and Gynecology*. The collaborative nature of this venture represents a significant advancement towards promoting healthy pregnancy.

Innovations in Using Data to Develop New Trial Designs and Treatments

The use of data collected through electronic health records, mobile health technology, and other electronic data-capture technology offers information regarding the usage and potential benefits and risks derived from various treatments. This type of data can be used with new trial designs and can streamline and improve the efficiency and outcomes of clinical studies.

For example, the innovative use of observational data led to the first FDA approval of an immunosuppressant drug to prevent rejection in adults and pediatric patients who receive lung transplants. Efforts to use real-world data and evidence have reflected a multi-year, cross-CDER collaborative effort, with key contributions from the Office of Medical Policy (OMP), the Office of Biostatistics (OB/OTS), the Office of Surveillance and Epidemiology (OSE), the Office of Regulatory Policy (ORP), and from a range of OND divisions that have evaluated RWD/RWE submissions.

As a result of an observational study providing real-world evidence of effectiveness, FDA approved a new use for Prograf (tacrolimus) in July 2021. This approval reflects how a non-interventional (observational) study, relying on fit-for-purpose (reliable and relevant) real-world data, compared to a suitable control, can be considered adequate and well-controlled under FDA regulations. FDA's approval came following years of proactive work by OII's DRTM with the transplant community and the applicant to ensure the adequacy of the data submission in the U.S. Scientific Registry of Transplant Recipients, supported by the Department of Health and Human Services.

Additionally, new data uses improved screening for risk factors for sudden cardiac death in the young (SCDY). The Office of Cardiology, Hematology, Endocrinology, and Nephrology's (OCHEN's) Division of Cardiology and Nephrology (DCN) launched an innovative SCDY pilot study with Duke University, the Cardiac Safety Research Consortium, several national and international companies, and 12 public screening groups (PSGs, primarily parent-led foundations). These partners launched the pilot study in response to the lack of accurate and reliable screening methods to identify underlying risks for SCDY and the fact that, in the U.S., PSGs perform most cardiac screening for the detection and possible prevention of SCDY. This unique pilot study collects high-quality, real-world data obtained by lay public groups, then applies an iterative approach to improve data quality, and enables researchers to establish best practices to prevent SCDY. The pilot study aims to organize and determine PSG screening practices, implement the use of a uniform screening dataset, and establish a national digital warehouse of screening data, including the electrocardiogram.

Clinical Trial Advancements for Transdermal Drug Delivery

With the support of staff from ORPURM's DUOG, among others, FDA published draft guidance for industry in July 2021 on clinical trials designed to assess the clinical adhesion performance of the Transdermal Delivery System (TDS). This is the first clinical guidance that provides recommendations on the development of TDS new drug applications (NDA) and supplemental NDA (sNDA) products. The TDS provides drug absorption via the skin and has many advantages over intravenous or oral administration. These benefits include simple administration and the ability to lessen side-effects and improve the dosage efficacy.

TDS development has evolved over the years, and many sponsors now use new technologies to develop TDS products because of the many benefits. The guidance provides recommendations for clinical trials to assess how well TDS adheres to the skin. The guidance discusses key considerations for the design of the TDS adhesion clinical study, including the selection of endpoints and FDA's current thinking on acceptable adhesion performance in the in vivo setting. It also standardizes both trial design and endpoints. Adequate clinical adhesion to the skin is critical to the safety and efficacy of a TDS product because adhesion failures can result in reduced effectiveness (suboptimal dosing) or potentially increased exposure when a new TDS needs to be applied sooner than the scheduled dose.

Innovative Consumer Behavior Studies for the Nonprescription Drug Market

The staff from ONPD advised industry on designing decentralized trials for novel prescription (Rx) to over-the-counter (OTC) switch programs, including Nonprescription Safe Use Regulatory Expansion (NSURE). These trials used web-based application tools to assist in pivotal self-selection and actual use trials, implementing virtual designs for the first time. In addition, ONPD staff provided advice to advance validation of virtual testing of consumer self-reported knowledge regarding medical conditions and prescriptions, target success thresholds, and the need to ensure equity in trial populations. FDA's advice and guidance provided industry with insight into decentralized consumer research in the OTC market and the regulatory implications of using this research for future Rx-to-OTC switch applications.

Progression in Product Development

This year, OND offices provided scientific leadership to facilitate product development in areas of unmet medical need, including the approval of novel therapies and drug products, the advancement of drug development tools and programs, guidance for sponsors on product development, contributions to regulatory policies and pathways for drug development, and the facilitation of workshops and outreach activities. These activities will hopefully help to reduce the time, cost, and risk associated with drug development and lead to more therapeutic options for patients, increase industry competition, and expand access.

Drug and Therapy Approvals

The CDER New Drug Therapy Approvals report provides a detailed listing and discussion of all the new drugs that OND, working with offices across CDER, have approved in 2021. This section presents a few highlights to emphasize the range of diseases with new therapeutics.

OID's DAV approved Cabenuva (cabotegravir/rilpivirine injectable), the first monthly injectable regimen for HIV-1, expanding patient options for a monthly rather than daily treatment regimen. OID's Division of Anti-Infectives (DAI) approved SOLOSEC (secnidazole), a single dose treatment for trichomoniasis — the first new drug since 2004 — as well as Brexafemme (ibrexafungerp), a first-in-class triterpenoid antifungal drug that acts by inhibiting a critical fungal enzyme. Additionally, OID approved Fexinidazole, the only entirely oral — and therefore more practical — treatment option for both stages of African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense, which is endemic in areas with limited health care resources.

ORPURM's Division of Rare Diseases and Medical Genetics (DRDMG) supported a cross-discipline review process to approve Nulibry (fosdenopterin) to reduce the risk of mortality in patients with Molybdenum Cofactor Deficiency (MoCD) Type A, a rare, genetic, metabolic disorder that typically presents in the first few days of life. This program leveraged innovative approaches to using a natural history, genotype-matched control and biomarker to bring an impactful first-in-class product to a disease with high unmet medical need.

The Office of Specialty Medicine (OSM) supported the development of Pylarify (piflufolastat F 18), the second positron emission tomography (PET) imaging drug directed at prostate-specific membrane antigen (PSMA) positive cancerous lesions. The first PSMA-targeted PET imaging drug, Ga 68 PSMA-11, approved in 2020, was only available at

two medical centers. By using a commonly available isotope of fluorine (F 18) with a longer half-life than Ga 68, the second approval makes PSMA-directed PET imaging more widely available nationwide and represents significant progress in product development for prostate cancer imaging.

With the support of ONPD, FDA approved a partial prescription to nonprescription (Rx to OTC) switch of Astepro, a nasal antihistamine for seasonal and perennial allergies. This partial switch provides a new safe and effective nasal antihistamine option for patients over six. Astepro is the first antihistamine nasal spray available for nonprescription use in the U.S. Its approval helps address unmet needs for consumers with allergic rhinitis.

Semglee is the first interchangeable biosimlar insulin product approved in the U.S. for the treatment of diabetes.

The approval of the first interchangeable biosimilar insulin product, Semglee (insulin glargine-yfgn), for the treatment of diabetes, represents the culmination of a collective effort by staff from the Office of Therapeutic Biologics and Biosimilars (OTBB), OCHEN's Division of Diabetes, Lipid Disorders, and Obesity (DDLO), and other internal partners across FDA. Semglee is the first interchangeable biosimilar insulin product approved in the U.S. for the treatment of diabetes, and the first interchangeable biosimilar of any kind. Semglee is both biosimilar to (has no clinically meaningful differences from) and interchangeable with (can be substituted for) its reference product Lantus (insulin glargine), a long-acting insulin analog. The approval resulted from a novel approach in the 351(k) Therapeutic Biologics Program. This approach was based on extensive multidisciplinary discussions and was consistent with recommendations in draft guidance, which clarified that immunogenicity studies may not be needed for proposed biosimilar or interchangeable products referencing currently approved insulins. This approval will influence the approval of many more biosimilar and interchangeable insulin products in the future, which could greatly reduce health care costs for the millions of Americans who rely on insulin daily to treat diabetes.

2021 was another high volume and exciting year for cancer drug development. The Office of Oncologic Diseases (OOD) approved four new drugs for non-small lung cancer (Tepmetko, Rybrevant, Lumakras, Exkivity), including one non-small cell lung cancer type previously thought to be resistant to treatment. OOD approved three therapies (Enhertu, Opdivo, and Keytruda) for patients with certain gastric cancers and gastroesophageal junction adenocarcinomas. Additionally, OOD approved the first immunotherapy (Keytruda) and the first CDK4/6 inhibitor (Verzenio) for early-stage breast cancer. Other innovative approvals for rare cancers included two treatments (Truseltiq and Tibsovo) for adults with certain kinds of cholangiocarcinoma, a treatment (Welireg) for use in adults to treat certain tumors that are

associated with von Hippel-Lindau disease, a treatment (Darzalex Faspro) to be used together with other treatments for light chain amyloidosis, and the first treatment (Fyarro) for locally advanced unresectable or metastatic perivascular epithelioid cell tumor (PEComa).

The Office of Neuroscience (ON), approved Vyvgart (efgartigimod), the first in a new class of therapies that block the neonatal Fc receptor (FcRN), for the treatment of adult patients with generalized myasthenia gravis (gMG) who are acetylcholine receptor antibody-positive (AchR ab). Vyvgart is an antibody fragment that binds to FcRn, preventing FcRn from recycling immunoglobulin G (IgG) back into the blood. The product causes a reduction in overall levels of IgG, including the abnormal antibodies that are present in myasthenia gravis. There is currently only one approved therapy for gMG (i.e., Soliris (eculizumab). The approval of Vyvgart represents substantial progress in the development of new therapies for gMG and provides support for the further study of Vyvgart and other novel FcRN-targeting therapies in autoimmune diseases with identified autoantibodies that may be responsive to reduction of IgG, such as immune thrombocytopenic purpura (ITP) and chronic demyelinating peripheral neuropathy (CIDP).

Medical Countermeasure Advancements

To support the development of medical countermeasures (MCMs) to manage radiation injuries due to a mass casualty public health emergency, in 2021, OND continued guiding the development of animal models that accurately reflect the emerging scientific understanding of biological pathways involved in the radiation damage response. To guide and support this work, OND staff participated in two public workshops and contributed to scientific publications on the current understanding of the clinical, histopathological, and functional manifestations of radiation injury in pulmonary and cutaneous sub-syndromes. These contributions helped to identify new pharmacologic targets for developing MCMs for pulmonary and cutaneous sub-syndromes of radiation injury.

In addition, OND staff from OSM provided advice on approaches to generate effectiveness data to support a marketing application using the Animal Rule. This regulatory pathway is intended to support development of drugs and biological products in scenarios where human efficacy studies are not ethical, and field trials to study the effectiveness of drugs or biological products are not feasible. The January 2021 approval of a new indication for Nplate (romiplostim) was a result of this advice and led to expanded MCM options with novel functionality for the U.S. public in the event of high levels of radiation exposure. Specifically, Nplate is now indicated to increase the survival of patients acutely exposed to myelosuppressive doses of radiation based on data in an animal model of hematopoietic acute radiation syndrome (ARS).

The approval of this new indication for Nplate represents important progress in the development of products for treating ARS by, for the first time, targeting thrombocytopenia and addressing the risk of hemorrhage associated with ARS.

When a new paradigm showed that clinically meaningful studies of ARS must model the dysfunction of various organs and their interactions with standard of care rather than individually evaluating sub-syndromes, OND staff, including those from OSM, began to participate in discussions with other Federal health agencies on the development of MCMs for gastrointestinal (GI) radiation injury. As a result of those discussions, FDA and NIH are planning a public workshop for summer 2022 to review developing data from studies of MCMs that target the GI tract to continue to provide scientific leadership and facilitate treatment options in this space.

Drug Development Tools and Programs

To create a home for new technologies aimed to support, streamline, and potentially speed up the development of drugs and biologics, FDA launched the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program in late 2020 and continued this program in 2021.

ISTAND, led by staff from the Office of Drug Evaluation Sciences (ODES), encourages the development and use of novel Drug Development Tools (DDTs) that incorporate the latest advances in science and technology but that may not have a clear path forward in FDA's existing DDT qualification programs. DDTs play an important role in bringing new therapies to the market, and FDA has established qualification programs for biomarkers (defined biological characteristics), clinical outcome assessments (COAs — which describe how patients feel, function, or survive), and some animal models. DDTs that FDA has qualified can be relied upon to have a specific interpretation and application in medical product development and regulatory review, thereby providing a valuable tool for product development.

ISTAND facilitates the development of these tools by providing for meetings with appropriate FDA staff to advise tool developers, developing guidance on using novel DDTs, and publishing white papers to raise considerations for implementing novel DDTs. Notably, OND Pharmacology/Toxicology staff provide assessment of DDTs for nonclinical safety contexts of use, which further facilitates drug development by filling gaps in current approaches and in some instances reducing reliance upon animal studies for select endpoints.

To date, more than 20 DDT developers have expressed interest in the pilot program, and OND has evaluated more than a dozen submissions. Additionally, OND staff engaged with external groups, including the Digital Medicine Society and the Clinical Trials Transformation Initiative, to shape the development and maturation of regulatory science related to DDTs. The development and maturation of the science that underpins the discovery, development, implementation, and assessment of novel DDTs, such as those that leverage Digital Health Technologies (DHTs), will enable more efficient, effective, and inclusive clinical trials.

Beyond ISTAND, ODES engaged with developers of novel COAs, biomarkers, and other tools to facilitate drug development for Parkinson's disease, non-alcoholic steatohepatitis (NASH), and infectious diseases, including COVID-19 and malaria. Novel COAs have the potential to evaluate what is most meaningful to patients, and DHTs can allow more remote clinical trials. For example, in 2021, ODES supported programs involving the development of automated tools for identifying patients that met inclusion criteria for trials in NASH, malaria biomarker monitoring, and prognostic biomarkers for heart failure with preserved ejection fraction (HFpEF). Novel DDTs in each of these therapeutic areas have the potential to help demonstrate clinical benefit, allow smaller and shorter trials, and help developers select the right patients for studies.

ODES staff are also in the process of developing biomarker-related guidance documents, working with a number of other CDER offices including the Office of Medical Policy (OMP), the Office of Biostatistics (OB/OTS), and the Office of Clinical Pharmacology (OCP/OTS) covering an evidentiary framework and analytic considerations around the measurable indicators that predict a treatment's effect. These guidance documents will help foster a greater understanding of how DDTs can be incorporated into clinical trials to facilitate drug development programs.

Initiative Highlight: OND Science Strategies

In 2020, OND launched the Science Strategies program to develop and execute strategic plans to address substantive issues in drug development, one of the goals of scientific leadership. The program enables divisions to systematically assess unmet medical needs (e.g., disease prevalence, disease burden, treatment burden); evaluate the state of clinical development (e.g., pipeline activity); and identify challenges and barriers to drug development. After assessing an unmet medical need and diagnosing drug development barriers, divisions can develop multi-year, disease-specific science strategies (strategic plans) to address the identified barriers.

Members of the Pharmacy Compounding Review Team in OSM, in collaboration with CDER's Office of Compliance, provided direct input on the design of a new system to manage the workflow for 503B Pharmacy Compounding nominations (drug products compounded by or under direct supervision of a licensed pharmacist in an outsourcing facility). This system will manage the workflow from the time a 503B Pharmacy Compounding nomination is received until a decision is made by FDA, including the clinical assessment workflow performed by OND. The workflow management tool provides a structured and consistent process to evaluate and make determinations regarding the existing backlog of 503B nominations and future nominations and improves the regulatory review process for 503B Pharmacy Compounding nominations. Once this system is fully implemented, it will allow for better estimates of workload and greatly improve efficiency of 503B nomination reviews.

As of 2021, OND's Division of Dermatology and Dentistry (DDD) and Division of Clinical Outcome Assessments (DCOA) are implementing science strategies to assess and overcome barriers to drug development in areas of unmet need. Beginning in 2020 and continuing in 2021, staff from DDD and DCOA collaborated with experts from the Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH) to create a non-healing chronic wound science strategy to identify barriers to product development in this disease area. Staff from these divisions and Centers undertook a landscape analysis to identify unmet medical needs in this disease area and recognized the notable lack of innovative products to treat non-healing chronic wounds.

They found that although there are more than 70 FDA-cleared products for managing wounds, there are only two FDA-approved therapies to treat non-healing chronic wounds, and these products do not fully satisfy the clinical need. They then identified barriers to product development for new treatments, including a shortage of biological models (organisms or systems that recreate aspects of human tissue function or disease), challenges to clinical trial execution, and limited commercial viability.

To address these barriers, the experts are collaborating with key wound healing stakeholders (e.g., patient groups and academia) to identify opportunities to standardize clinical trials, endpoints (primary outcomes measured by clinical trials), and drug development tools. They hosted a wound healing scientific workshop in April 2022 to determine the most pressing barriers to product development in this disease area and plan future activities to overcome them.

OND's Science Strategies program draws on innovations in trial design and collaboration with partners.

In spring 2022, the Science Strategies program will expand to address additional disease areas. The program's long-term vision is to enable each OND division to develop and execute a science strategy and refresh the strategy annually to address drug development challenges and increase patient access to treatments in areas of unmet medical need. The program draws on the exemplary scientific leadership activities that many OND divisions are already performing to achieve this goal. The Science Strategies program draws on innovations in trial designs and collaboration with partners, activities which are highlighted throughout this report.

Guidance Supporting Product Development

FDA guidances serve many purposes related to product development: they increase access to potentially life-saving interventions by communicating clear regulatory expectations; provide general considerations to sponsors, the academic community, and the public

as treatments for disease areas are developed; and assist sponsors in the clinical development of specific drugs. This section highlights select guidances published in 2021 that exemplified scientific leadership by driving progression in product development.

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guidances published in 2021 were authored by OND

This year, OND staff in collaboration with other Center and Agency colleagues, worked to publish a suite of four guidances providing recommendations on the development of individualized medicines for patients with severely debilitating or life-threatening genetic diseases, focused on the development of antisense oligonucleotide drugs. The ability to rapidly design and inexpensively manufacture ASO has ushered in the prospect of individualized medicine because a particular ASO may only be used to treat one patient by targeting the patient's unique ribonucleic acid (RNA). Over the course of the year, the four published guidances covered a range of issues, from administrative and procedural aspects of interacting with FDA on development programs for individualized ASO drug products, to pharmacology and toxicology considerations and nonclinical information that FDA recommends to support an investigational new drug application (IND), to clinical considerations for IND submissions to support initial and continued administration, dosing, and clinical monitoring of an individual in this context, and to chemistry, manufacturing, and controls considerations for such IND submissions. Focusing, for example, specifically on the guidance on non-clinical aspects of these submissions, the guidance leverages Pharmacology/Toxicology's knowledge and experience with other molecules in this same drug class to recommend an approach that would enable an abbreviated nonclinical assessment. By providing sponsors of drug development programs with clear guidance on what constitutes an acceptable abbreviated nonclinical safety assessment for ASO products, Pharmacology/Toxicology staff led scientific advancement in this novel area of drug development and opened the way for additional product development and potentially life-saving interventions.

In July 2021, FDA published draft guidance prepared by OID's DAV, to help sponsors develop monoclonal antibody (mAb) cocktails for the passive immunization component of PEP to prevent rabies. PEP prevents rabies in previously unvaccinated patients when administered immediately after contact with a rabid or possibly rabid animal. Anti-rabies virus immunoglobulin (RIG), one component of PEP treatment, is vital in preventing rabies after more serious exposures, including bites to the head and neck. However, RIG is not widely available globally, which has led to the development of mAb cocktails as an alternative. Given the challenges of product development and regulatory pathways discussed with multiple stakeholders at a public workshop in 2017 and an advisory committee in 2019, this guidance communicates a novel regulatory approach for combining nonclinical and clinical data to

demonstrate substantial evidence of effectiveness and safety for the intended use for rabies mAbs (where traditional trial designs would not be feasible).

Finally, in September 2021, FDA published draft guidance prepared by OID's Division of Anti-Infectives (DAI) to assist sponsors in the clinical development of drugs to treat nontuberculous mycobacterial pulmonary disease (NTM-PD), a chronic and progressive pulmonary disease. The draft guidance shares FDA's current thinking on clinical trial design issues, choice of study populations, and endpoints for the treatment of naïve and refractory NTM-PD caused by mycobacterium avium complex (MAC), discussed during an FDA public workshop in April 2019. This guidance aims to support the approval of drugs for the treatment of NTM-PD caused by MAC and ensure that drugs provide benefit on a clinically meaningful endpoint. The publication of this guidance (followed by the noted public workshop on the same topic) is an important step in the progression of product development, as the guidance outlines crucial information for identifying key trial design issues and potential trial design considerations (e.g., PRO development) for a disease characterized by heterogeneity with limited treatment options.

Regulatory Advancements

Over the past year, OND led regulatory advancements in a variety of areas. These advancements are intended to overcome existing inefficiencies, incorporate the most up-to-date scientific thinking, and facilitate drug development in areas of important need.

Safety Data Collection in Clinical Trials

An expert working group led by staff from OND's Immediate Office (IO), OCHEN, and other FDA Centers and offices is currently developing an International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline, ICH E19. This new guideline, A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials, provides advice to regulatory agencies and industry organizations on collecting human data in clinical trials and informs the implementation of this approach. Once finalized, ICH E19 will significantly impact global drug development by facilitating large-scale efficacy and safety clinical trials with many participants and long-term follow-up. Such clinical trials have proven very important in evaluating medicines, improving their appropriate use, and supporting public health outcomes.

Over-the-Counter (OTC) Monograph Reform

There are two regulatory pathways to bring a nonprescription drug to market in the U.S., one of which is the Over-the-Counter (OTC) Drug Review (OTC Monograph) process. On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) was signed into law, which includes statutory provisions that reform and modernize the way OTC monograph drugs are regulated in the United States (referred to as OTC Monograph Reform). OTC Monograph Reform is intended to improve efficiency, timeliness, and predictability in the OTC Drug Review process, which establishes conditions, such as active ingredients, uses (indications), doses, labeling, and testing, under which an OTC drug is generally recognized as safe and effective and may be marketed without an approved drug application.

This past year, ONPD continued to implement OTC Monograph Reform and delivered numerous presentations on the reform. For example, ONPD hosted a Small Business and Industry Assistance (SBIA) webinar to provide an overview of how FDA identifies and evaluates safety issues and explain the procedure and timeline for FDA-initiated administrative orders to address safety issues. Additionally, at an information-gathering meeting in June 2021 for the National Academies Committee on Environmental Impact of Currently Marketed Sunscreens and Potential Human Impacts of Changes in Sunscreen Usage, ONPD discussed the monograph specifically for OTC sunscreen drug products. Proposed updates to the sunscreen monograph were published in September 2021 in the first proposed order issued under the new OTC monograph procedures. These outreach activities provided industry and the public with timely and accurate information on OTC monograph drug development and regulation.

This past year, ONPD continued to implement OTC Monograph Reform and delivered numerous presentations on the reform.

Prescription Drug and Biosimilar User Fee Program Advances

OND also engages in scientific leadership through user fee negotiations, in which OND, along with other CDER offices and FDA centers, identify new programs or approaches that can lead to advances in drug development and regulation.

This past year, OND worked with other CDER offices and Centers in the pre-market negotiation group for the sixth reauthorization of the Prescription Drug User Fee Act (PDUFA VII). During the formal negotiations for PDUFA VII, which concluded in February 2021, FDA committed, subject to Congressional reauthorization, to a series of performance goals and procedures to facilitate timely access to safe, effective, and innovative new medicines. Among other commitments, FDA agreed to establish three programs to drive progress in product development in areas of unmet medical need: the Split Real-Time Application Review (STAR) pilot program and the Rare Disease Endpoint Advancement (RDEA) pilot program, and a program to

enhance use of Real-World Evidence (RWE). The goal of the STAR pilot program is to expedite patient access to novel uses for existing therapies. The program is intended to shorten the timeline from the date of complete submission to the action date to grant patients earlier access to therapies that address an unmet medical need. Through the RDEA pilot program, FDA will seek to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate more frequently with FDA throughout the efficacy endpoint development process. The RWE program will support increased interactions between FDA staff and industry in designing innovative and effective studies utilizing RWE, with the intention of increasing the potential for success of the subsequent study.

In 2021, OND also led negotiations for the second reauthorization of the Biosimilar User Fee Act (BsUFA III). Representatives from the OND IO, OPO, and OTBB, along with others from across CDER, helped negotiate significant changes to BsUFA III, including shortened timelines for the review of labeling supplements when review of data is not required. These negotiated commitments are subject to Congressional reauthorization of the program. One of the goals of these changes is to make biosimilar and interchangeable product labeling easier to be kept up to date with the latest safety information from the reference product labeling; thereby putting patient safety at the forefront.

OND engaged with stakeholders during workshops and public meetings to discuss challenges and potential improvements to drug development and labeling over the past year.

Workshops and Outreach Supporting Product Development

OND engaged with stakeholders during workshops and public meetings to discuss challenges and potential improvements to drug development and labeling over the past year. This section highlights a few of the workshops hosted or co-hosted by OND in 2021.

In October 2021, ORPURM's DPMH co-led a two-day virtual public workshop with the Office of Neuroscience's (ON's) Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) and the University of Maryland's CERSI to discuss the current state of therapies to treat acute pain in children and identify data gaps. The workshop discussions potentially will prompt policy changes related to product development for acute pain in patients under two and enable more clear paths to development of new products for this important patient population.

ONPD hosted a public workshop in June 2021 to evaluate the Drug Facts Label (DFL) for nonprescription drugs. The DFL enables consumers to appropriately self-select and use nonprescription drug products safely and effectively. During the workshop, stakeholders

from FDA, academia, and industry discussed potential improvements in the labeling format and content. The workshop was the FDA's first event to discuss ways to optimize the DFL for consumer use and sought ideas to make the DFL robust, user-friendly, compatible with traditional text and paper-based presentation, and adaptable for use with new technologies. The workshop has stimulated thoughtful dialogue on the strengths, weaknesses, and future possibilities of the OTC DFL. Following the workshop, FDA intends to review research, data, and information relevant to the public workshop topics submitted to the public docket. In addition, FDA will continue to invite stakeholders to provide their perspectives on optimizing the DFL to support novel product development.

To further the development of therapies for SLE, OII's DRTM regularly works with multiple stakeholder organizations (both non-profit and for-profit) to build knowledge and develop a common understanding of issues and potential solutions for SLE. For example, to address the challenges with studying SLE and expedite drug development, the division worked with stakeholders to support three patient listening sessions in March and April of 2021, led by FDA's Office of Minority Health and Health Equity. The goal of these patient listening sessions was to understand the lupus patient community's perceptions about participating in clinical trials and advance diversity in SLE clinical trials by developing multi-media health education tools and resources. FDA and DRTM's engagements with stakeholders resulted in several successful drug development programs likely not otherwise possible, including the approval of Lupkynis (voclosporin) to treat lupus nephritis (SLE affecting the kidneys) in January 2021. Most recently, in August 2021, FDA, with the support of DRTM, approved Saphnelo (anifrolumab-fnia) for adults with moderate to severe SLE.

In collaboration with the Office of Clinical Pharmacology and Duke Margolis Center for Health Policy, OTBB hosted a public workshop in September 2021 to discuss the current and future role of pharmacodynamic biomarkers in improving the efficiency of biosimilar product development and approval. The development and validation of pharmacodynamic biomarkers tailored to biosimilar development has the potential to reduce or eliminate expensive, lengthy comparative clinical studies using efficacy endpoints. OTBB is also planning a scientific workshop with OB in CDER's OTS to discuss methodologies to improve the efficiency of comparative clinical studies in biosimilar development programs. These efforts support the Biosimilars Action Plan (BAP) goals to improve the efficiency of the biosimilar and interchangeable product development and approval process.

11
patient listening sessions with OND staff participation organized by PASE in 2021

18
patient listening sessions with OND staff participation organized by OC/Office of Patient Affairs in 2021

Collaboration and Information Sharing

Despite the constraints of the ongoing pandemic, OND staff identified new avenues to engage in scientific leadership by deepening their scientific expertise to enhance regulatory decision-making and sharing knowledge with partners to foster drug development strategically. These collaborative activities enable the FDA to continually improve the regulatory process to create more therapeutic options for patients, increase completion, and expand access, while reducing the time, cost, and risk associated with drug development. Working with external and internal partners can take different forms, and the following sections highlight OND's scientific leadership with partners in 2021.

OND collaborated with partners throughout FDA and beyond through virtual consortia, national and international meetings, conferences, and other engagements. OND staff supported drug development through collaborations, including partnerships to advance drug development tools, a public-private partnership to address heart failure, and conferences and training to advance the use of biosimilars. The following sections highlight these activities.

Partnerships to Advance New DDTs (COAs and Biomarkers)

OND staff continued to collaborate with external partners in 2021 to support drug development. Staff from ODES participated in national and international consortia and provided grant funding to support the development of new DDTs, including COAs and biomarkers. The following collaborations enabled ODES staff to deepen their subject matter expertise and share information:

- ODES staff engaged with the Foundation for the National Institutes of Health (FNIH) Biomarker Consortium on developing biomarkers for oncology and Alzheimer's. This engagement deepened ODES staff's expertise regarding state-of-the art science and biomarkers concerning immuno-oncology and Alzheimer's and will facilitate future biomarker qualification programs.
- Through the FNIH Accelerating Medicines Partnership group, ODES staff discussed developing biomarkers to predict patients most at risk of developing schizophrenia. Engagement with FNIH on this project will facilitate the development of prognostic biomarkers to enrich future trials of drugs for schizophrenia for those patients most likely to experience an outcome, allowing faster progression of drugs through proof-of-concept and efficacy trials.
- ODES provided grant funding in the amount of US$1.5 million to support the progression of biomarker and COA programs toward the goal of qualification and the development of biomarkers for traumatic brain injury (TBI). The lack of biomarkers for TBI impedes development of new therapies for this area of unmet need. Qualification of prognostic and biodynamic biomarkers will help progress new products by facilitating proof-of-concept studies and dose finding and potentially allowing smaller clinical trials.

Additionally, in 2021, staff from ODES participated in numerous engagements with external partners to discuss the use of DHTs in new trial designs. For example, ODES staff participated in the following engagements:

- ODES attended six meetings with counterparts in the European Medicines Agency (EMA) to share approaches to incorporating DHT data in outcome assessments to evaluate the impact of disease on patient function and identify obstacles and solutions to sharing data to qualify safety biomarkers. This engagement with EMA deepens the subject matter expertise of ODES staff by exposing them to DHT initiatives outside of the U.S. In addition, these meetings align American and European regulators' approaches to reducing delays in agreement on clinical trial designs for new products that incorporate DHTs.
- Several staff members of ODES were panelists at a meeting organized by the Clinical Trials Transformation Initiative on Novel Endpoint Acceptance in July 2021, focusing on challenges in utilizing DHTs in novel endpoints and FDA's approach to evaluating DHT-based endpoints, the measurable outcome of a clinical trial. Since industry was a key participant at this meeting, FDA participation can facilitate innovation in trial design for drug development programs by incorporating DHT-based endpoints.

594

speaking engagements with OND staff participation in 2021

Heart Failure Collaboratory (HFC)

The Heart Failure Collaboratory identifies areas of common interest to key researchers in the community and sets up working groups to address those needs.

To foster the development of therapies for heart failure and increase the efficiency of clinical trials, staff from OCHEN's DCN assisted in developing the Heart Failure Collaboratory (HFC). HFC is a PPP established between FDA, the Inova Heart and Vascular Institute (IHVI), and major stakeholders in the heart failure community to advance new therapies and develop solutions to address obstacles within the heart failure community. Over the past year, DCN staff contributed to HFC projects to develop standardized case report forms and patient-reported outcomes. In October 2021, DCN staff also attended an HFC meeting on the impact of COVID-19 on heart failure drug and device development. HFC is unique in the heart failure space in that it identifies areas of common interest to key researchers in the community and sets up working groups to address those needs with shared assets like new data or common case report forms.

Improving Public Understanding of Biosimilars

The Biosimilar Action Plan (BAP) is intended to expand knowledge about and use of biosimilar and interchangeable biologic drugs. A key element of the BAP is developing effective communication to improve understanding of biosimilars among patients, clinicians, and payors. In support of this goal, OTBB staff provided direct education and outreach on biosimilars and biologics through over three dozen events in 2021, including conferences and training activities. These efforts, reinforced by legislation such as the Advancing Education on Biosimilars Act of 2021, allow FDA to expand its reach and build knowledge of the complexity of biologics and biosimilars.

For example, OTBB staff participate annually in the Drug Information Association (DIA) Biosimilars Conference and the Association for Accessible Medicines' Generics + Biosimilars (GrX + Biosims) Conference. Notably, the OND Director provided the keynote address on the impact of regulations on furthering biosimilars and progress biosimilar development at the DIA Biosimilars Conference in October 2021.

In addition, at the 2021 GrX + Biosims Conference in November, key officials from FDA, including the Acting Commissioner of FDA and the Acting Director of OTBB, gave keynote addresses. During the three-day conference, OTBB staff attended sessions on topics including in vitro immunogenicity methods for biosimilars and ensuring the sustainability of biosimilars.

OND Future Outlook

As evidenced by the exciting, diverse, and innovative activities that are outlined in this 2021 OND Annual Report, OND takes a broad view of how to support achieving the CDER mission to bring safe and effective drugs to the American public. Key areas of focus for our work include guiding and regulating IND drug development, conducting thorough and intensive reviews of marketing applications, working to monitor and manage the safety of drugs after approval, providing scientific and regulatory expertise in the management of OTC drugs, evaluating candidates for compounded drugs, and regulating biosimilar and interchangeable drug development. These activities are, of course, essential in assuring the effectiveness and safety of drugs for use by the public.

However, our focus goes beyond the intensive efforts on specific drugs and drug development programs. OND is also fully engaged in efforts to enhance drug development by improving efficiencies that may stimulate development, particularly in areas of unmet medical need. OND achieves this in a multitude of ways, including assisting in the development of tools that developers can use to establish a drug's efficacy or identify risks, clarifying the requirements for drug development through the publication of guidances, expanding the types of evidence that can be utilized to demonstrate the safety and effectiveness of drugs, including assessing endpoints that measure what is important to patients, and rigorously exploring novel trial designs and data sources that may better reflect real-world use of a drug. This "twin"

focus — on specific drugs and drug development programs and on expanding the knowledge and tools to enhance drug development — are not separate efforts, but rather intertwined endeavors. Our staff's deep and extensive experience with evaluating and regulating specific drugs, throughout their lifecycle, provides the expertise and insight necessary to understand how to enhance the pathways that can most efficiently and effectively lead to the development of new drugs that can serve the unmet needs of the American public. As this report also makes clear, the efforts — both in guiding and regulating specific drug programs and in expanding the tools and knowledge to facilitate future drug development programs — is not the work of a single CDER office, but a highly collaborative effort in which our OND staff work hand-in-hand with staff from other CDER offices, as well as with other FDA centers, USG agencies, and many external stakeholders.

I hope you will find that the OND Annual Report reflects the many successful efforts of our organization to expand available knowledge, tools, and capabilities, meeting the challenges of the evolving landscape.

The CDER annual report of novel drug approvals in 2021 reflects the evolving landscape of drugs, with novel drugs targeting more rare diseases, disease subsets and subpopulations, employing novel platforms, and reaching more challenging targets. This evolving landscape means that OND must expand its knowledge and expertise, providing direction, guidance, and regulatory review in new areas, for development programs where there may be little or no precedent. OND works to meet these challenges every day. I hope you will find that the OND Annual Report reflects the many successful efforts of our organization to expand available knowledge, tools, and capabilities, meeting the challenges of the evolving landscape.

Peter Stein, M.D.
Director, Office of New Drugs

Appendix: Acronyms

Acronym	Definition
AchR ab	Acetylcholine receptor antibody positive
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ARS	Acute radiation syndrome
ASO	Antisense oligonucleotide
BAP	Biosimilars Action Plan
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Applications
BsUFA	Biosimilar User Fee Act
CARES	Coronavirus Aid, Relief, and Economic Security
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CERSI	Center of Excellence in Regulatory Science and Innovation
CIDP	Chronic demyelinating peripheral neuropathy
COA	Clinical outcome assessment
COVID	Coronavirus disease

Acronym	Definition
CPIM	Critical Path Innovation Meeting
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
DDD	Division of Dermatology and Dentistry
DDLO	Division of Diabetes, Lipid Disorders, and Obesity
DDT	Drug Development Tool
DFL	Drug Facts Label
DG	Division of Gastroenterology
DHT	Digital Health Technology
DIA	Drug Information Association
DPACC	Division of Pulmonology, Allergy and Critical Care
DPMH	Division of Pediatrics and Maternal Health
DRDMG	Division of Rare Diseases and Medical Genetics
DRTM	Division of Rheumatology and Transplant Medicine

Appendix: Acronyms (continued)

Acronym	Definition
DUOG	Division of Urology, Obstetrics, and Gynecology
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FcRN	Fc receptor
FDA	U.S. Food and Drug Administration
FNIH	Foundation for the National Institutes of Health
GI	Gastrointestinal
gMG	Generalized myasthenia gravis
HAT	African trypanosomiasis
HFC	Heart Failure Collaboratory
HFpEF	Heart failure with preserved ejection fraction
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IHVI	Inova Heart and Vascular Institute
IND	Investigational New Drug Application
IO	Immediate Office
ISTAND	Innovative Science and Technology Approaches for New Drugs
ITP	Immune thrombocytopenic purpura
mAb	Monoclonal antibody
MAC	Mycobacterium avium complex
MCM	Medical countermeasures
MoCD	Molybdenum Cofactor Deficiency
NASH	Non-alcoholic steatohepatitis
NDA	New Drug Application
NDRP	New Drugs Regulatory Program
NIH	National Institutes of Health
NME	New Molecular Entity
NSURE	Nonprescription Safe Use Regulatory Expansion
NTM-PD	Nontuberculous mycobacterial pulmonary disease
OB	Office of Biostatistics
OCHEN	Office of Cardiology, Hematology, Endocrinology, and Nephrology
ODES	Office of Drug Evaluation Sciences
OID	Office of Infectious Diseases
OII	Office of Immunology and Immunization
OMP	Office of Medical Policy
ON	Office of Neuroscience
OND	Office of New Drugs

Appendix: Acronyms (continued)

Acronym	Definition
OND-RP	OND Research Program
ONPD	Office of Nonprescription Drugs
OOD	Office of Oncologic Diseases
OPO	Office of Program Operations
ORC	OND Research Committee
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
OTS	Office of Translational Sciences
PDIMS	Program Development, Implementation, and Management Staff
PDUFA	Prescription Drug User Fee Act
PEComa	metastatic perivascular epithelioid cell tumor
PEP	Post-exposure prophylaxis
PET	Positron emission tomography
PFDD	Patient-Focused Drug Development
PPP	Public-private partnership
PSG	Public screening group
PSMA	Prostate-specific membrane antigen
PTCC	Pharmacology/Toxicology Coordinating Committee
rcPMP	Recombinant cyclic pyranopterin monophosphate
RDDDC	Rare Disease Drug Development Council
RDEA	Rare Disease Endpoint Advancement
REMS	Risk Evaluation and Mitigation Strategy
RIG	Rabies immunoglobulin
RNA	Ribonucleic acid
RSR	Regulatory science research
Rx	Prescription
SCDY	Sudden cardiac death in the young
SLE	Systemic lupus erythematosus
sNDA	Supplemental new drug application
SPRT	Safety Policy Research Team
STAR	Split Real-Time Application Review
TBI	Traumatic brain injury

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