December 31, 2024

The Honorable Brett Guthrie
Chairman, Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chair Guthrie:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the May 22, 2024, hearing before the Subcommittee on Health, Committee on Energy and Commerce entitled "Check Up: Examining FDA Regulation of Drugs, Biologics, and Devices." This letter is a response for the record to questions posed by the committee.

Sincerely,

Aubrie L. Paulos -S

Digitally signed by Aubrie L. Paulos -S
Date: 2024.12.31 14:26:12 -05'00'

Lauren Paulos
Acting Associate Commissioner for Legislative Affairs

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Questions for the Record
Subcommittee on Health, Committee on Energy and Commerce
"Check Up: Examining FDA Regulation of Drugs, Biologics, and Devices"
May 22, 2024
Questions for Dr. Patrizia Cavazzoni, Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

The Honorable Cathy McMorris Rodgers

Dose Optimization

1. **The January 2023 draft guidance on dose optimization in oncology drug development does not address recommendations on dose optimization for rare diseases. Many of the dose optimization principles outlined in the draft guidance, such as randomization and having a trial sized for sufficient assessment of dosage, won't work in oncology, particularly for rare cancers. Does FDA agree that there is a lack of guidance for rare diseases?**

FDA does not agree that there is a lack of guidance on dose optimization for rare diseases. FDA's recent 2023 guidance for industry, *Rare Diseases: Considerations for the Development of Drugs and Biological Products* provides guidance on dose selection for rare diseases. The guidance states that, in general, sponsors should evaluate the effects of more than one dosage on response and that biospecimens for analysis of pharmacokinetics and/or pharmacodynamics should be obtained from all clinical investigation participants to aid in evaluation of exposure-response relationships and selection of the most appropriate dosage. In addition, the guidance discusses the identification and use of biomarkers for dose selection and other purposes in rare disease drug development. Lastly, the guidance urges industry to consider using data from animal models of disease for different doses, a range of exposure response, intrapatient dose escalation studies, or quantitative modeling approaches (e.g., physiologically based pharmacokinetic modeling, quantitative system pharmacology, or pharmacokinetic/pharmacodynamic modeling) to facilitate dose selection. FDA is

working on finalizing guidance on optimizing the dosage of human prescription drugs and biological products for the treatment of oncologic diseases and should have additional updates regarding that document on FDA's website.[1]

a. How does FDA plan to address challenges in dose optimization for rare diseases, including rare oncologic diseases?

Various offices in the Center for Drug Evaluation and Research (CDER) are routinely engaged in facilitating, accelerating, and supporting the development of new drugs and biological products for the benefit of patients with rare diseases. Many of these activities are related to dose selection in clinical development and dose optimization for clinical use. Examples of our activities include:

- encouraging early interaction and regularly meeting with sponsors to provide advice about drug development, study design and dosage selection.
- providing opportunities for sponsors to discuss innovative approaches for dosage optimization in specific drug development programs through the Model-Informed Drug Development (MIDD) Paired Meeting Program.[2]
- encouraging modeling tool developers to discuss potential modeling tools that can be applied to inform dose selection/optimization through the Fit-for-Purpose program.[3]
- establishing the CDER Quantitative Medicine Center of Excellence, CDER Center for Clinical Trial Innovation, and CDER's Accelerating Rare disease Cures (ARC) Program to promote broader adoption and integration of innovative approaches to streamline and advance drug development through engagement and education for FDA review staff and the rare disease community.[4] Many of these innovative approaches are aimed at tackling problems around dosage optimization in rare diseases.

Similarly, FDA's Oncology Center of Excellence (OCE) launched Project Optimus[5] in 2021 to reform the dosage optimization and dosage selection paradigm in oncology drug development. OCE is working to publish a final guidance, entitled *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases*.[6] Project Optimus works in conjunction with other OCE efforts such as OCE's Pediatric Oncology[7] and Rare Cancer Programs[8] to facilitate integration

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases
[2] https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program
[3] https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative
[4] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program
[5] https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases
[7] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[8] https://www.fda.gov/about-fda/oncology-center-excellence/oce-rare-cancers-program

of tailored, seamless approaches to obtaining the information needed for dosage selection in rare oncology populations without prolonging development timelines. Additionally, OCE's Project *Beyond Breakthrough* is conducting a pilot project to facilitate early engagement and dose selection planning with sponsors of promising new oncology treatments.

Additional information regarding OCE's recommended approaches to dosage optimization for rare cancers is provided in the responses below.

2. **Does FDA support other more flexible approaches to dose optimization for rare oncologic diseases, including non-randomized approaches?**

Yes. While the FDA draft guidance *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases* recommends a randomized trial to compare multiple dosages when feasible because randomization ensures similarity of patients and ensures interpretability of the dose- and exposure-response relationships, it is not the only way to optimize dosages. Alternative or additional approaches may include evaluating additional dose cohorts and investigating multiple dosages in an expansion phase following the initial dose-escalation phase for dosages that are being considered for further development, with the understanding of their limitations. These approaches are often included in FDA recommendations following review of the protocol for the initial first-in-human trial.

FDA recognizes that the best approach for dosage optimization may vary based on the specific development program, including if the program is for a rare oncologic disease, and strongly encourages sponsors to discuss their plans with FDA during formal meetings, including early in clinical development, to get product-specific advice.

3. **The January 2023 draft guidance on dose optimization in oncology drug development outlines the risks of the maximum tolerated dose (MTD) strategy but doesn't discuss the risks of potentially under-dosing patients with life-threatening diseases. Does FDA believe there are risks associated with under-dosing patients?**

It is important to note that an investigational agent in a clinical trial is not known to be effective, and which dosage level(s) would provide the optimal effect without posing serious risks to patients is also not known. However, we recognize that an overly cautious approach to dosage selection could potentially put patients with a life-threatening disease at risk of receiving a dosage that is too low to have a therapeutic effect.

   a. **If so, will this concern be incorporated into the final guidance, or a separate guidance? If not, why not?**

   As reflected in the draft guidance *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases*, the focus of dosage

optimization is finding the dosage that can maximize the benefit/risk profile of a drug or provide the desired therapeutic effect while minimizing toxicity. The risk of under dosing leading to ineffective therapy is well-understood and therefore, our recommendations emphasize selecting doses that can provide a therapeutic benefit while minimizing toxicities. The dosage selected that could be effective may be lower than the current paradigm of selecting the maximum tolerated dose (MTD), which carries greater risk of toxicities. Most modern oncology drugs, such as kinase inhibitors and monoclonal antibodies, often demonstrate different dose-response relationships compared to cytotoxic chemotherapy, such that doses lower than the MTD may have similar efficacy to the MTD but with fewer toxicities.

4. **The January 2023 draft guidance on dose optimization in oncology drug development infers that there will be multiple dosages for an individual product with the same clinical benefit, which is not always the case with newer therapies. Does the FDA believe that there will be multiple dosages for all cancer therapies, including newer therapies? If so, please explain why. If not, why not?**

Depending on the indicated patient population, drug development program, and the data supporting the dosages, some oncology drugs could have multiple effective dosages recommended for the same indication. Other drugs may continue to have a single recommended dosage for the indicated population. FDA considers the clinical benefit as well as the toxicities when determining the recommended dosage(s). Even if multiple dosages have similar clinical activity, they may have differing toxicities such that not all dosages would be recommended.

Where a drug is approved for multiple indications, the drug may demonstrate different dose- or exposure-response relationships across different diseases (i.e., breast vs. gastric cancer), settings (i.e., adjuvant vs. metastatic) or other patient or disease factors, and different recommended dosages may be appropriate. Further, the duration of treatment may be different in different disease settings or the dosage may be different when a drug is administered in combination therapy.

FDA supports taking a holistic approach that evaluates and integrates the nonclinical and clinical data appropriate for the stage of development to select dosages to be evaluated in clinical trials for each indication or usage in order to optimize the benefit/risk for patients with cancer who will be receiving these drugs.

5. **Does FDA plan to expand Project Optimus' dose optimization principles to other Therapeutic Areas?**

It is important across all therapeutic areas to identify a recommended dosage(s) that maximizes clinical benefit. FDA strongly emphasizes that dosage optimization should occur prior to drug approval so that the recommended dosage in labeling has been optimized for patients. FDA has long articulated these principles across many

of its guidance documents such as *E4 Dose-Response Information to Support Drug Registration (1996)* and *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (2003)*. FDA provides opportunities and encourages drug developers across therapeutic areas to meet with review divisions early in their development programs, well before conducting pivotal trials, to discuss dose-finding and dosage optimization. The Model-Informed Drug Development (MIDD) Paired Meeting Program is one such avenue that focuses on dosage selection and optimization.

Project Optimus employs the same dosage optimization principles as FDA does in other therapeutic areas.

Staffing and Telework

6. What will it take to fill the open roles for review staff and related administrative staff at FDA?

a. What efforts are under way to attract talent and hire these critical roles?

Offering incentives like workplace flexibilities, in addition to modern hiring tools and competitive compensation, help the Agency to keep pace with industry and the tech sector for the most qualified staff.

FDA has prioritized recruitment and accompanying marketing strategies. We will be aligning vacant positions to a specific recruitment strategy to include monthly/quarterly distributions of opportunities to professional associations and organizations, including colleges and universities with diverse populations. We will also leverage all recruitment and outreach efforts to both educate about career opportunities at FDA and recruit and hire candidates. The immediate goal is to leverage each touch point with potential candidates in order to hire immediately or to create an interest for future hiring.

We currently announce open positions via a variety of avenues including USAJOBS, LinkedIn, Twitter, and Title 21 Website page. We are expanding our outreach to other media outlets such as scientific journals that will point the candidate back to the hiring product center to become informed and educated on the center and its mission. We are also working on the capability to accept resumes for Title 21 positions via our Jobs at FDA Website page to quickly link candidates with vacant positions and hiring managers.

FDA is committed to meeting the user fee hiring goals. This includes effectively utilizing Title 5, Title 42(g), Schedule A, Veterans Recruitment Authority (VRA), Title 21 hiring authorities, and coordinating with the Office of Talent Solutions. The Agency is also committed to communicating about our progress and reporting regular updates made towards hiring goals

for fiscal years (FY) 2023-2027. See Performance Reports[9] and Quarterly Hiring Updates.[10]

7. **The FDA along with many other federal agencies instituted virtual work policies during the COVID-19 pandemic. There have been concerns that the ongoing virtual schedule has impacted the frequency and quality of interactions between the FDA and important stakeholders. Does the FDA plan to bring staff back to in-person work and meetings with sponsors and patients?**

8. **The Committee understands that the term "telework" refers to a work flexibility arrangement that allows an employee to work from an approved alternative worksite other than the employee's official duty location for an approved number of days each pay period. Within each center, what percentage of employees telework?**

    a. **What is the range of approved numbers of days each work period?**
    b. **What is the most typical number of approved numbers of days each work period?**
    c. **How is the specified number of days enforced?**
    d. **Within each center, what percentage of employees are fully remote?**
    e. **Can FDA provide a summary of actions it is taking to increase the frequency and quality of interactions with sponsors?**

Answer for 7 and 8:

As of January 29, 2023, FDA has transitioned into our Business-Driven Hybrid Workplace model which bases eligibility for workplace flexibilities on the nature of an employee's work and the business needs of the organization. As part of this model, FDA staff maintain official telework agreements. One of the considerations for our Business-Driven Hybrid Workplace model is the ability for FDA to recruit and retain talent. However, in-office presence and in-person interactions with supervisors, peers, other offices and centers, and external stakeholders is often beneficial for advancing and facilitating the multidisciplinary and often public facing nature of our critical work. In these circumstances, the Agency continues to ensure Agency personnel are on site.

One specific example are formal meetings with industry, as agreed to in the Prescription Drug User Fee Act (PDUFA) VII[11] and Biosimilar User Fee Amendments (BsUFA) III.[12] As of January 22, 2024, FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research

[9] https://www.fda.gov/about-fda/user-fee-reports/user-fee-performance-reports
[10] https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-and-bsufa-quarterly-hiring-updates
[11] https://www.fda.gov/media/151712/download?attachment
[12] https://www.fda.gov/media/152279/download?attachment

(CBER) expanded in-person face-to-face industry meetings with a hybrid component to allow maximum participation to include all PDUFA, BsUFA, and Over-The-Counter Monograph Drug User Fee Program (OMUFA) meeting types. All meetings have a hybrid component to enable attendees who may not be able to attend in-person to participate. However, anyone who is invited from FDA or industry may attend in-person if they prefer. Completed upgrades to FDA conference rooms have enabled FDA to fully return to these in-person meetings.[13]

Thus far, FDA has received positive feedback from industry regarding the flexibility that virtual, hybrid, and in-person meetings provide. FDA will continue to work with industry to fully meet our user fee commitments and to ensure the FDA workforce operates at the highest level as we work to further our public health mission.

In addition, FDA Advisory Committees and other patient engagement sessions invite participation via an online teleconferencing and/or video conferencing platform to support face-to-face engagements.

The productivity of FDA staff is higher than it has ever been, and the pandemic has taught us that much of our work can be accomplished efficiently and effectively while continuing to leverage workplace flexibilities.

Biomarkers

9. For the development of treatments for ultra-rare conditions, affecting far less than 200,000 patients per year in US, what tools, such as leveraging biomarker endpoints, can the FDA use to help sponsors to conduct efficient clinical trials to bring treatments to patients faster?

FDA recognizes the challenges associated with rare disease drug development and applies flexibility to address particular challenges posed by each disease, while upholding our regulatory standards. Flexibilities include, for example, Accelerated Approval based on a surrogate endpoints that are reasonably likely to predict clinical benefit or intermediate clinical endpoint for serious conditions with an unmet medical need, reliance on one adequate and well controlled trial plus the use of confirmatory evidence instead of two adequate and well-controlled trials, use of natural history study data as a source of external control data, novel trial designs, and novel statistical methodologies. FDA considers all relevant statutory authorities and any available flexibilities when making decisions appropriate to the particular rare disease and therapeutic product under consideration.

[13] Beginning February 13, 2023, prior to expiration of the COVID-19 Public Health Emergency, CDER and CBER started a phased return to in-person meetings. From Feb. 13, 2023 until Jan. 21, 2024, industry requested 83 in-person meetings. 90% of those meetings were granted as in-person. No meetings were delayed or denied due to conference room availability.

FDA's 2023 draft guidance, *Considerations for Design and Conduct of Externally Controlled Trials for Drug and Biological Products*, provides recommendations to sponsors and investigators considering the use of externally controlled clinical trials to provide evidence of the safety and effectiveness of a drug product. In addition, FDA's 2019 draft guidance, *Rare Diseases: Natural History Studies for Drug Development*, provides recommendations to help inform the design and implementation of natural history studies[14] in planning controlled trials of investigational drugs to treat rare diseases.[15]

FDA understands that biomarkers, especially those that can be leveraged for accelerated approval, can help facilitate more efficient clinical trial designs and drug development programs. FDA engages in a number of public private partnerships through the Critical Path Institute that are focused on identifying new biomarkers, including support of the Critical Path Critical Path Institute's Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP®) that provides a centralized and standardized infrastructure to support and accelerate rare disease characterization, with the goal of accelerating the development of treatments and cures for rare diseases, including identification of biomarkers. The RDCA-DAP platform continues to expand since going live September 2021, and now contains data for 34 different rare disease areas. CDER and CBER also have a biomarker qualification program to work with drug developers on new biomarkers.

Under CDER's Accelerating Rare disease Cures (ARC) Program, CDER has formed a Translational Science Team (TST) that can assist review teams in evaluating challenging aspects of novel surrogate biomarker endpoint evaluation and confirmatory evidence. The TST is a multidisciplinary group comprised of experts and senior leadership from various offices within CDER. The TST collaborates with review teams to evaluate proposals for surrogates or confirmatory evidence and in providing input to sponsors on these complex and challenging programs.

In May, CDER and CBER announced a Rare Disease Innovation Agenda (the Agenda). The Agenda will focus on products intended for smaller populations or for diseases where the natural history is variable and not fully understood, as we recognize that development of therapies for these conditions can be particularly challenging. One of the Agenda's goals will be to advance regulatory science with dedicated workstreams for consideration of novel endpoints, biomarker development and assays, innovative trial design, real world evidence, and statistical methods.

Wound Dressings and AMR

10. The Food and Drug Administration (FDA) has proposed a new rule, Medical Devices; General and Plastic Surgery Devices; Classification of

[14] Natural history studies are preplanned observational studies intended to track the course of a disease to identify demographic, genetic, environmental, and other variables that correlate with the disease's development and outcomes.

[15] These three guidances are draft guidances. When finalized, they will reflect the Agency's current thinking.

Certain Solid Wound Dressings; Wound Dressings Formulated as a Gel, Creams, or Ointment; and Liquid Wound Washes, which would require reclassification of certain wound products containing antimicrobials or other chemicals. This proposed re-classification would fundamentally change the regulatory status of both future and existing wound care products by making them subject to 510(k) requirements with special controls or premarket approval (PMA), regardless of how long they have been on the market. The FDA has cited concerns that these products are potentially increasing human antimicrobial resistance (AMR) as the reason for this reclassification. Please explain the scientific evidence that supports FDA's belief that certain relevant products are contributing to AMR.

For a point of clarification, please note that this proposed rule is not a "reclassification," as stated, but rather the Agency's proposal to initially classify this large group of products that are currently unclassified preamendments devices. An unclassified preamendments device is a device that was on the U.S. market prior to the Medical Device Amendments of 1976 and for which a classification regulation has not been promulgated. This effort is critical to providing the medical device industry with much needed clarity and transparency regarding the regulatory requirements to demonstrate safety and effectiveness for wound dressings and liquid wound washes containing antimicrobials and/or other chemicals. FDA proposed to classify over 99% of these previously cleared devices as Class II, requiring premarket notification via a 510(k) submission, which is the same submission type used to currently authorize these products. Additionally, the controls outlined in the proposed rule largely mirror the Agency's review practices over the past decade and beyond.

As part of this classification action, and with the input of multiple advisory panel meetings, the Agency has identified the potential risks to health, of which antimicrobial resistance (AMR) is one, and corresponding mitigations associated with these products. Regarding your question on the impact of the antimicrobials used in wound dressings and liquid wound washes to potentially contribute to the development and dissemination of AMR, the following information and scientific evidence from the literature referenced in the proposed rule supports the identification of AMR as a risk to health that needs to be mitigated as part of this classification effort:

- There is a wide range of antimicrobials previously cleared in this group of products, including both "medically important" and "non-medically important" antimicrobials.
- While an antimicrobial is effective when applied at an appropriate concentration, effectiveness is only exhibited on a limited segment of the microbial world. Some species of bacteria are naturally resistant to a given antimicrobial, while others may

eventually acquire resistance (Ref. 23 of the proposed rule[16]).

- AMR is not limited to "medically important" antimicrobials, as the scientific literature details resistance mechanisms associated with the myriad of biocidal agents not considered to be medically important.
- Many resistance genes are found on plasmids, which play an integral role in the horizontal transfer of resistance between organisms and stack multiple resistance genes together on a single mobile element (Ref. 24 of the proposed rule[17]). As a result, many hospital-acquired infections involve bacteria that are resistant to multiple classes of antimicrobials, including both "medically important" and "non-medically important" antimicrobials (Refs. 25 and 26 of the proposed rule[18,19]).
- The application of a "non-medically important" antimicrobial has the potential to contribute to the selection and dissemination of "medically important" antimicrobial resistance mechanisms via co-selection phenomena such as co-resistance and cross-resistance.

As such, it is important to evaluate the risk of AMR in all antimicrobial-containing wound dressings and liquid wound washes to understand the potential for selecting resistant organisms at the patient-level and further limiting a clinician's therapeutic options.

11. Assuming there is evidence that certain wound care products are contributing to AMR, how will reclassifying these products prevent patients from developing antimicrobial resistance?

As stated in response four, the cited action is an initial classification rather than a reclassification. In terms of how the proposed classification of antimicrobial-containing wound dressings and liquid wound washes mitigates the risk of these products contributing to the spread of AMR, in the proposed rule, concerns with AMR are primarily focused on the impact of resistance to "medically important" antimicrobials that pose a high level of AMR concern, such as antibiotics. For those products that contain "medically important" antimicrobials, we are proposing to classify them as Class III, the highest risk category of devices, requiring a premarket approval application (PMA) to demonstrate there is a benefit to using the product that outweighs the risk of contributing to the spread of AMR. As noted in response to Question 4, we anticipate that only a small minority of

[16] https://www.federalregister.gov/d/2023-26209/p-140
[17] https://www.federalregister.gov/d/2023-26209/p-141
[18] https://www.federalregister.gov/d/2023-26209/p-143
[19] https://www.federalregister.gov/d/2023-26209/p-145

these products (less than one percent) would be subject to PMA.

The proposed rule takes a different approach for wound dressings and liquid wound washes that do not contain "medically important" antimicrobials, as they pose a medium or low level of AMR concern that is proposed to be mitigated with special controls as part of the evaluation of a 510(k). The Agency has proposed the following as part of a least burdensome approach to mitigate the AMR risks in these products that do not contain "medically important" antimicrobials:

Antimicrobial Characterization and Preservative Effectiveness Testing- This testing is routinely requested as part of the Agency's current review practices and ensures that the concentration of antimicrobial is not too high as to create safety concerns, and also not too low as to condition microorganisms in sublethal concentrations that contribute to AMR development.

AMR risk assessment- Conducting an AMR risk assessment based on a literature review to understand emerging resistance mechanisms and the presence of resistant organisms that may compromise the effectiveness of the antimicrobial and may indirectly contribute to the spread of antibiotic resistance via co-selection mechanisms. As AMR is an evolving topic with expected novel resistance mechanisms and resistant organisms emerging in the future, it is important for the device manufacturer to be informed with AMR trends as this information will be critical to their selection of antimicrobial applications and concentrations needed to remain effective.

Labeling controls- Improved labeling to better inform the end-user of the potential presence of resistant organisms and the risks of AMR associated with the product. This information is critical to aid the end user in better understanding the potential risks of selecting for resistant organisms and determining when the use of an antimicrobial-containing wound dressing is prudent.

Taken together, we believe the combination of this proposed split classification approach, which classifies a limited number of products containing medically important antimicrobials into class III (less than one percent), along with the majority of these products being proposed for classification as class II (more than 99 percent), with the identified special controls, will provide a balanced approach to mitigate the risks to health of these products contributing to the spread of AMR, while maintaining patient access to these important products.

The Honorable Brett Guthrie

Antisense oligonucleotides

1. **The FDA is tasked with applying rigorous safety and efficacy standards to many new and emerging treatment types including cell and gene therapies and antisense oligonucleotides (ASOs). These therapies have the potential to deliver unprecedented positive outcomes for patients. How, if at all, is the FDA educating its review staff and the agency more broadly on the unique nature of ASOs and other therapies?**

   Oligonucleotide therapeutics are an emerging therapeutic modality with increasing numbers of drugs in development. Seventeen antisense and small interfering RNA oligonucleotide therapeutics have been approved by FDA in recent years, almost all to treat rare diseases; in addition, many oligonucleotide therapeutics are currently in development to treat common chronic diseases. FDA is working to finalize the draft guidance for industry entitled "Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics," which describes FDA's recommendations regarding clinical pharmacology considerations during the development of oligonucleotide therapeutics, including characterizing the potential for QT interval prolongation, performing immunogenicity risk assessment, characterizing the impact of hepatic and renal impairment, and assessing the potential for drug-drug interactions. The intent of the draft guidance is to assist industry in the conduct of these studies.[20]

   FDA has conducted staff training about the development of oligonucleotide therapeutics, and FDA staff have published manuscripts to share experience gained from reviewing oligonucleotide therapeutics more broadly with the public.

   Finally, FDA representatives regularly participate in conferences with topics that include regulatory considerations for developing oligonucleotide drugs, and scientific and technical considerations for this class of drugs.

   a. **How can sponsor companies and patient groups work with the FDA to ensure the agency understands the challenges of developing these complex therapies?**

      FDA encourages sponsors to communicate with appropriate review Divisions during the pre-investigational new drug application (pre-IND) or investigational new drug application (IND) stage to discuss the development of these therapeutics. FDA also seeks public input through workshops and through comments on our guidance documents relating to these products. For example, FDA has worked with the Drug Information Association (DIA) to conduct workshops that bring together leading

[20] https://www.fda.gov/media/159414/download

experts to inform, educate, and share advancements in oligonucleotide-based therapeutic product development; the next workshop will be held in October 2024.

b. For some innovative ASO programs, countries outside the US have progressed development while FDA has implemented strict dose escalation. What are the lessons from this experience, and will the FDA adapt their practices?

FDA recommendations and decision-making are risk based and consider all available information. FDA is not aware of differences in the practices of other regulatory authorities that are unique to oligonucleotide therapeutics or the outcome of such practices. Of note, toxicity can be unique for each oligonucleotide therapeutic. To ensure patient safety, FDA recommends a measured approach to first-in-human studies, given the long duration of effect that is typical of this therapeutic class and considering FDA's experience with prior programs. It is crucial to allow for an adequate safety assessment within each cohort before proceeding with dose escalation. FDA continues to adapt its practices based on emerging information about the efficacy, safety, and dosing of oligonucleotide therapeutics.

The Honorable Michael Burgess, M.D.

PRVs

1. **In December, FDA made news by approving two essentially curative treatments for Sickle Cell Disease. This was welcome news for the 100,000+ Americans suffering with this disease. However, as part of that news, FDA made a surprising decision in denying a PRV for one of those treatments. We've heard other manufacturers express concern about the impact the FDA's decision to not award a PRV in at least one recent case, and the implications that decision could have on critical incentives for rare disease programs. How is the FDA ensuring there is a consistent, predictable application of the PRV program?**

FDA remains committed to ensuring that there is a consistent and predictable application of the Rare Pediatric Disease Priority Review Voucher program. For sponsors to receive such a voucher, the drug must qualify as a drug for a "rare pediatric disease" as defined in Section 529(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the application for the drug must meet the remaining eligibility criteria as outlined in Section 529(a)(4) of the FD&C Act:

- A human drug application as defined in section 735(1) of the FD&C Act
    - For a drug or biological product that is for the prevention or treatment of a rare pediatric disease;
    - For such a drug
        - That contains no active moiety (as defined in 21 CFR 314.3 (or any successor regulations)) that has been previously approved in any other application under subsection (b)(1), (b)(2), or (j) of section 505 of the FD&C Act; and
        - That is the subject of an application submitted under section 505(b)(1) of the FD&C Act; or
    - For such a biological product
        - That contains no active ingredient that has been previously approved in any other application under section 351(a) or 351(k) of the Public Health Service Act; and
        - That is the subject of an application submitted under section 351(a) of the Public Health Service Act (PHS Act);
    - That FDA deems eligible for priority review;
    - That relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population;
    - That does not seek approval for an adult indication in the original rare pediatric disease product application; and
    - That is approved after the date of enactment of the Advancing Hope Act of 2016 (September 189 30, 2016).

FDA determined that BLA 125788 was not a human drug application for a biological product that contained no active ingredient that had been previously approved in any other application under section 351(a) or 351(k) of the PHS Act. Specifically, BLA 125788 was for a biological product that contained an active ingredient that was previously approved in another application under section 351(a) of the PHS Act. The active ingredient was previously approved, on August 17, 2022, in BLA 125717 for Zynteglo (betibeglogene autotemcel).[21]

2. **The Pediatric Priority Review Voucher represents one of the great partnerships and collaborations between FDA and industry. It has come to our attention that FDA may be interpreting the "active ingredient" requirements in a broader way than Congress intended. This is particularly concerning regarding some of the**

[21] See Approval Letter for BLA 125788, available at: https://www.fda.gov/media/174617/download?attachment.

transformative gene therapies coming through the agency. Many of these therapies may use the same delivery system – viral vectors – despite there being significant differences between the drugs themselves. Is there a statutory requirement that mandates FDA treat these viral vector delivery systems as the same "active ingredients" for purposes of awarding PRVs?

FDA derives its authority to issue Rare Pediatric Disease Priority Review Vouchers under Section 529 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). For an application for a biological product to qualify for a rare pediatric disease priority review voucher, the application must, among other requirements, be for a biological product that contains no active ingredient that has been previously approved in any other application under section 351(a) or 351(k) of the Public Health Service Act. Section 529 of the FD&C Act does not explicitly address examples such as viral vector delivery systems.

a. **Has FDA considered how many fewer treatments may be developed if it interprets this "active ingredient" language in this broad manner?**

   FDA cannot speak to decisions made by manufacturers, including choices regarding which technologies and products to develop.

b. **Has FDA considered how this interpretation might inadvertently incentivize manufacturers to pursue separate delivery systems (even if they are less efficient or effective) to treat rare diseases?**

   FDA cannot speak to decisions made by manufacturers, including choices regarding which technologies and products to develop.

The Honorable Robert Latta

PRVs

1. **Congress created the Priority Review Voucher (PRV) Program to provide an important incentive for the development of drugs and biologics to prevent or treat tropical and pediatric diseases. While FDA is required to establish and update a list of rare diseases that qualify for this program, this list has not been updated since July 2020. My understanding is that there are at least 11 new rare diseases that are awaiting a decision by FDA. The Further Consolidated Appropriations Act, which was recently signed into law, included report language that directs FDA "to maintain the**

necessary resources to evaluate PRV candidates in a timely manner." Does FDA anticipate making a decision on if these diseases qualify for the PRV this year?

Section 524(a)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) establishes a list of tropical diseases that may qualify for a priority review voucher (PRV) and includes a provision that the Secretary may designate by order "[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations[.]" As described on FDA's webpage, we evaluate additional tropical disease candidate submissions on an ongoing basis and publish in the Federal Register either a final order listing any disease that FDA has determined meets the statutory standard for a "tropical disease," or a notice explaining which disease(s) FDA believes do(es) not meet the statutory standard for a "tropical disease." Section 524 of the FD&C Act does not provide a time period for designation of tropical diseases, and we review submissions in the order they are received. However, FDA understands the importance of these tropical disease candidate submissions to stakeholders, and we are working expeditiously to finalize our reviews while balancing this work with other public health priorities.

For the rare pediatric disease PRV program, there is no statutory requirement that FDA establish and update a list of rare pediatric diseases that are PRV eligible. Instead, for purposes of PRV eligibility, FDA will make a determination of whether the drug is for the prevention or treatment of a rare pediatric disease prior to approval of a new drug application or biologics license application. Such determinations are made in the context of the particular drug at issue and, among other things, considers the size of the population affected by the disease at the time of the determination. A sponsor may also choose to request rare pediatric disease designation for its drug prior to submitting a marketing application for that drug. In response to such requests, FDA will determine whether to designate the drug as a drug for a "rare pediatric disease."

OTC Naloxone

2. **Last year, FDA authorized the first naloxone products for over-the-counter (OTC) use. This important step was intended to increase naloxone access by allowing patients to purchase it at retail locations like drug stores, convenience stores, grocery stores, and online. The switch to OTC for this life-saving medication was intended to remove barriers created by prescription requirements. To encourage OTC use, FDA also developed a consumer-friendly Drug Facts label (DFL) with easy-to-understand instructions on how to use naloxone. Since last year's switch to OTC, has FDA seen an increase in naloxone use via retail locations?**

Nonprescription (OTC) naloxone products became available in September 2023

via retail locations, and there has been an increase in OTC naloxone sales as a result. However, overall naloxone product use, including OTC or prescription from retail pharmacy settings, does not appear to have substantially increased in the 12-month period from April 2023 through May 2024. FDA continues to monitor trends in naloxone sales as additional nonprescription naloxone products are approved, including generic versions.

a. Approximately what percentage of naloxone products are sold OTC today compared to 2022?

As noted above, OTC naloxone did not become available in retail locations until September 2023, and there has been an increase in OTC naloxone sales as a result. However, it is challenging to estimate the percentage of naloxone products sold OTC because sales data for retail OTC purchases do not capture purchases of OTC naloxone for distribution through non-traditional health care settings, e.g., harm reduction programs, convenience stores, and vending machines. These data challenges are discussed in a 2023 summary report titled *Naloxone Economic View*,[22] published by the Reagan-Udall Foundation in collaboration with the FDA.

b. Does FDA see any additional barriers to ensuring patients can access naloxone OTC? If so, what steps does FDA support to remove these barriers?

In 2023, the Reagan-Udall Foundation collaborated with the FDA to publish a summary report titled *Naloxone Economic View*[1]. The report cited numerous barriers to accessing naloxone beyond (at the time) its prescription-only status, including issues with insurance coverage, prescription fill limits, out-of-pocket costs, bias and stigma, and limited physical accessibility of naloxone. FDA has taken steps within its authorities to help address these barriers, including efforts to encourage the development of more generic naloxone to help facilitate access to these products and increase competition. FDA also has taken steps to facilitate the development and review of additional opioid overdose reversal agents, including additional non-prescription naloxone options. As of May 22, 2024, FDA has approved two branded and two generic over-the-counter naloxone nasal sprays, as well as the first prescription nalmefene hydrochloride nasal spray to reverse opioid overdose.

Additionally, FDA continues to collaborate with federal partners, harm reduction programs, and other stakeholders through research, public workshops, and other activities to understand and address the complexity of identified barriers. For example, in September 2022, FDA published a

[22] https://reaganudall.org/sites/default/files/2023-03/Naloxone%20Report%20FINAL%203.8.23.pdf

final guidance for immediate implementation, *Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act (DSCSA) for the Distribution of FDA-Approved Naloxone Products During the Opioid Public Health Emergency*. This guidance was intended to clarify the scope of the public health emergency exclusion and exemption under the DSCSA as they apply to the distribution of FDA-approved prescription naloxone products to harm reduction programs during the opioid public health emergency. This guidance, including a related compliance policy, was designed to help address some of the barriers harm reduction programs face in terms of accessing naloxone, including directly from manufacturers and distributors, and to facilitate increased public availability of this critical medicine.

PDUFA

3. **User fee resources were provided in the last Prescription Drug User Fee (PDUFA) agreement to help the Agency upgrade and modernize its Information Technology. This includes resources to pilot cloud submissions demonstration projects. According to the PDUFA VII Goals letter, FDA will launch at least three cloud-technology pilots. Aside from the Digital Health Technology (DHT) pilot, what is the status of selecting the next two? What does FDA hope to learn with these demos?**

   The intent of the cloud-based demonstration projects is to explore opportunities to further leverage and expand cloud-based capabilities to enhance data and information exchange. In addition to the DHT pilot, FDA has initiated two demonstration projects: *Cloud-based transnational regulatory platform for multi-region regulatory collaboration* and *Information Exchange Foundations.* Each demonstration project will test cloud-based capabilities and functionalities.

   The primary objective for the *Cloud-based transnational regulatory platform for multi-region regulatory collaboration* is to provide technology support for international collaboration in conducting quality assessment of regulatory submissions. This collaborative assessment effort focuses on regulatory submissions that facilitate global implementation of innovative scientific and/or regulatory approaches. Learnings from this project could be scaled for other global collaborative use cases.

   Information requests (IR) are issued by FDA to sponsors when additional information or clarification is needed on submitted human drug applications. The review team can issue an IR at any point in the review cycle for any section of the drug or biologic application. The primary objective for the *Information Request Foundations* is to build a proof of concept and test a collaboration capability between sponsors and the FDA to improve operational efficiency in

generating, exchanging, tracking, triaging and archiving IR for human drug applications.

a. The PDUFA VII Cloud Assessment summary states multiple times that maintaining legacy systems are a barrier for cloud adoption and cause high costs due to updates. Given the intent of the PDUFA VII commitment is to leverage cloud technology, is FDA using PDUFA funds to maintain legacy systems?

Leverage Cloud Technology to Progress Regulatory Digital Transformation ("Digital Transformation") PDUFA VII funding is not used to fund legacy systems. As mentioned in Question 3, digital transformation funding is used to support exploration of cloud-based capabilities to enhance information exchange.

b. What strategies does FDA plan to implement to mitigate the ongoing maintenance costs of legacy systems while facilitating a transition towards cloud adoption?

FDA IT Strategy 2024-2027 outlines the next steps in our technological advancement, including reduction of our legacy systems and modernization of our technology, data, and cybersecurity/compliance processes.

Testosterone Therapy

4. Given a recent longitudinal study concluded Testosterone Therapy does not increase cardiovascular risk, in addition to data demonstrating Testosterone Deficiency Syndrome leads to all-cause mortality risks, what steps are the FDA taking on labels given this new data?

FDA maintains a system of postmarketing surveillance and risk assessment programs to monitor the benefit-risk profile throughout the drug product life cycle and takes regulatory action as appropriate.

On January 31, 2014, FDA announced that it was investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products. This review was prompted, in part, by the publication of two observational studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone products. On September 17, 2014, FDA convened a joint meeting of two Advisory Committees (the Bone, Reproductive, and Urologic Drugs Advisory Committee [BRUDAC] and the Drug, Safety and Risk Management Advisory Committee [DSaRMAC]) to discuss this safety issue. The

members voted that to revise the current indication in the labeling for FDA-approved testosterone products. They commented that the labeling should limit the indication to men with classical hypogonadism and stated that efficacy and safety in age-related hypogonadism have not been established. The majority of the Advisory Committees' members also voted that FDA require sponsors of testosterone products to conduct a study to further assess a potential cardiovascular risk with the use of approved testosterone products for certain indications, such as age-related hypogonadism.

On March 3, 2015, in a Drug Safety Communication,[23] FDA stated that there is a possible increased cardiovascular risk associated with the use of testosterone products. FDA also announced that FDA was requiring labeling changes for all prescription testosterone products to reflect the possible increased risk of heart attacks and strokes associated with testosterone use. FDA further announced that sponsors of testosterone products were required to conduct an outcomes trial to evaluate whether testosterone products were associated with an increased risk of major adverse cardiovascular events. Results of this cardiovascular outcomes trial (the TRAVERSE study) were published in June 2023.[24]

Additionally, FDA has required individual sponsors to conduct ambulatory blood pressure monitoring (ABPM) studies for their own testosterone products. This requirement was based on new information regarding increased blood pressure related to the use of oral formulations of testosterone products, and it was unknown whether formulations of testosterone approved for administration by other routes, such as intramuscular or topical use, may also potentially cause increases in blood pressure. The timing of when these completed studies for the approved testosterone products are submitted to the FDA varies, depending on factors such as when FDA accepted the final protocol.

In addition to assessing published studies and data from FDA's postmarketing surveillance system, FDA is reviewing data from the cardiovascular outcomes trial and ABPM studies submitted to the applications of the testosterone products and will consider the need for any appropriate regulatory actions, including requesting or requiring updates to the labeling of testosterone products, if warranted.

Coordination with DEA on Tianeptine

5. **As the fight against opioids, synthetics, and analogues continues to evolve, the FDA must remain vigilant to emerging threats like Tianeptine commonly referred to as "gas station heroin." According to the FDA, Tianeptine is not a dietary supplement. Executive and Medical Director of New Jersey's Poison Center, Dr. Diane Calello stated earlier this year, "If it [Tianeptine] got scheduled as a drug it would need to be clearly labeled. And right**

[23] https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-cautions-about-using-testosterone-products-low-testosterone-due
[24] https://www.nejm.org/doi/full/10.1056/NEJMoa2215025

now, it's not scheduled at all. That's when we get into trouble because that's when the compounds can literally contain anything." Ohio's Board of Pharmacy has already classified Tianeptine as a Schedule I controlled substance banning its sale in my state.

The FDA's Center for Drug Evaluation and Research has a memorandum of understanding with the Drug Enforcement Agency that allows for information sharing in areas of mutual concern. In the wake of the current public health emergency declaration tied to opioids, can you discuss how CDER has utilized its existing MOU with DEA to address this growing public health threat nationally and, if not, will you commit to utilizing your existing MOU with DEA to address this area of serious concern?

Under the Controlled Substances Act, the final responsibility of designating any drug into a schedule lies with the Drug Enforcement Administration (DEA), but FDA recognizes the important role the Agency has in informing any scheduling decision and continues to be in close contact with DEA on a number of issues related to the overdose crisis. The Memorandum of Understanding that FDA's Center for Drug Evaluation and Research has with the DEA continues to be a valuable tool to facilitate timely and confidential communications between the agencies. DEA may have more information regarding potential scheduling of tianeptine.

OTC

6. **On September 6th of last year, I wrote to you, along with Congresswoman Dingell and Congressman Crenshaw, outlining the reason for this concern the proposed concept of simultaneous marketing of both prescription and nonprescription versions of the same drug. This flies in the face of a decades-old law to prevent this from occurring: When two products are used for the same condition, with the same indication, same dose, same strength, same form, and same route of administration, they ought to have the same legal classification. That provision in law has served its intended function for decades: Reduce the possibilities for confusion, and not allow two companies making the same thing to arbitrarily decide whether they are going to sell it with or without a prescription. As proposed, the rule departs from the law. Will you commit today that the final rule will not contradict existing law?**

   Thank you for your follow-up concerning the proposed rule entitled, "Nonprescription Drug Product with an Additional Condition for Nonprescription Use."[25]

[25] https://www.federalregister.gov/documents/2022/06/28/2022-13309/nonprescription-drug-product-with-an-additional-condition-for-nonprescription-use

As you are aware, FDA issued this proposed rule in the Federal Register on June 28, 2022 (87 FR 38313). If finalized, the proposed rule would establish requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU). Public comments were due to the docket (Docket No. FDA-2021-N-0862) by November 25, 2022.[26]

Under the proposed rule, an applicant would be required to explain why the ACNU is necessary to ensure appropriate self-selection or appropriate actual use, or both, by consumers of the nonprescription drug product. The applicant would have to explain why labeling alone cannot be sufficient for meeting the approval requirements as a nonprescription drug product (proposed 314.56(c)(1)(ii), proposed 314.56(c)(1)(v), and 87 FR 38320). In addition, FDA proposed that an applicant would be required to submit a separate application for a nonprescription drug product with an ACNU (proposed § 314.56(b) and 87 FR 31318). For cases where there is an approved prescription drug product, we proposed that a nonprescription drug product with an ACNU could not be approved through a supplement to the approved application for prescription use of the drug product. Section 503(b)(4) of the FD&C Act allows simultaneous marketing of drug products with the same active ingredient as prescription and nonprescription if some meaningful difference exists between the drug products that makes the prescription product safe and effective only under the supervision of a healthcare practitioner licensed by law to administer the drug (87 FR 31321; see also 83 FR 13994, April 2, 2018; see also 70 FR 52050, September 1, 2005). Therefore, we proposed to establish that because the ACNU would allow the nonprescription drug product to be used safely and effectively without the supervision of a healthcare practitioner, the ACNU itself would be a meaningful difference between the prescription drug product and the nonprescription drug product with the ACNU. Thus, as proposed, a prescription drug product and a nonprescription drug product with an ACNU that contain the same active ingredient could be simultaneously marketed even if they do not have other meaningful differences, such as different indications or strengths (proposed § 314.56(d) and 87 FR 31322).

We proposed the requirements described above to increase consumer access to appropriate drug products. In cases where there is an approved prescription drug product, the requirements would create a pathway for the simultaneous marketing of the prescription drug product, along with the nonprescription drug product with an ACNU. Continued access to the prescription drug product, along with availability of the nonprescription drug product approved with an ACNU, would ensure greater access to needed drugs by providing flexibility in how to obtain them (see 87 FR 38319).

We note that similar comments about the possibility for confusion were submitted in the docket for the proposed rule. We carefully consider public

[26] https://www.regulations.gov/docket/FDA-2021-N-0862/comments and 87 FR 64178

comments received as we work to finalize the proposed rule.

The Agency appreciates your continued interest and comments concerning this proposed rule.

Developer Engagement

7. **We had a hearing in February where this topic came up, and I asked about feedback on how the FDA is engaging with companies seeking to advance these innovations in rare diseases like ALS. I support the mission of the Agency to ensure that treatments are safe and effective before coming to market. However, I have also heard from some drug manufacturers that they desire more collaboration with the Agency in the approval process that more assistance is needed from CDER especially around clinical testing and approval. How do you intend to improve collaboration with companies making drugs for the rare disease community including ALS?**

   In 2023 CBER and CDER announced the Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program, where participants will be able to obtain frequent advice and regular informal communication with FDA staff to address product-specific development issues, including, but not limited to, clinical study design, choice of control group and fine-tuning the choice of patient population. The program is open to sponsors of products currently in clinical trials under an active Investigational New Drug application (IND). CDER-regulated products must be intended to treat rare neurodegenerative conditions, including those of the rare genetic metabolic type. The Agency has selected three pilot participants for each center. The pilot launched recently, and we look forward to seeing whether this type of frequent and informal communication between sponsors and FDA staff can help to move development programs for rare diseases forward more efficiently. In addition, CDER's Advancing Rare Disease Cures (ARC) Program recently published *Leader 3D:Learning and Education to Advance and Empower Rare Disease Drug Developers*.[27] The findings of this report will guide ARC's activities to develop and expand educational resources identified as priorities by our stakeholders to advance rare disease drug development. Finally, under the authorities granted in the ACT for ALS, FDA launched the Critical Path for Rare Neurodegenerative Diseases (CP-RND) – a public-private partnership aimed at advancing the understanding of neurodegenerative diseases and fostering the development of treatments for amyotrophic lateral sclerosis (ALS) and other rare neurodegenerative diseases. The aim of the Critical Path Institute is to foster collaboration between the FDA and rare disease stakeholders. FDA continues to look for ways to improve this ongoing communication to improve and promote rare disease drug development.

[27] https://www.fda.gov/media/176557/download?attachment=

The Honorable Gus Bilirakis

Neurology Program

1. **In Fiscal Year 2023, the Omnibus funding bill provided $2 million to support and enhance the Neurology Drug Program. The agreement urged the FDA to use this funding to develop policies and guidance that keep pace with scientific discovery in these areas, particularly as they apply to the prevention and early detection of neurological disease. I am pleased that the recently passed Omnibus funding bill of FY'24 continues the funding for the Neurology Drug Program at $2 million. We know an estimated 100 million Americans live with brain disorders such as Alzheimer's, Parkinson's, Depression, Schizophrenia or Huntington's Disease and this number is likely to increase with our aging population. Can you please provide us with an update on how the Center and the Agency is utilizing these funds to improve coordination and collaboration internally and externally, ultimately with the goal of accelerating treatments and cures for complex brain diseases?**

   Thank you for the opportunity to update the Committee regarding the Neurology Drug Program (NDP) and the funding provided to the Agency in FY 2023 and FY 2024.

   In FY 2023, CDER utilized the appropriated funding for the NDP to hire 2 FTEs to support the program. In FY 2024 a third FTE, with training in neurodevelopmental disorders, has been hired to support drug development for rare pediatric neurogenetic disorders. These staff members have provided critical support to develop new policy and guidance in this area. For example, the three new staff members contributed to the new draft guidance for industry on *Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development* issued by FDA in February 2023, a new draft guidance on *Migraine: Developing Drugs for Treatment* in June 2023, and the updated guidance on *Early Alzheimer's Disease: Developing Drugs for Treatment* issued in March 2024. These staff members were also instrumental to the review and approval of four new therapies for neurological disease in 2023: Skyclarys (omaveloxolone) for the treatment of Friedreich's ataxia approved on February 28, 2023; Qalsody (tofersen) for the treatment of amyotrophic lateral sclerosis (ALS) in patients who have a mutation in the superoxide dismutase 1 (SOD1) gene approved on April 25, 2023; Leqembi (lecanemab) on January 6, 2023 and July 6, 2023 for the treatment of Alzheimer's disease; and Agamree (vamorolone) for the treatment of Duchenne muscular dystrophy. In 2024, these staff also contributed to the review and approval of Duuvyzat (givinostat) for the treatment of Duchenne muscular dystrophy.

   Within the FDA, these staff members provide their expertise across the medical

product centers and ensure alignment of advice for medical product development in neurologic diseases, use of digital health technologies, and incorporation of patient experience data into regulatory review. Additionally, NDP staff directed a multi-year grant to address challenges in neurological disease drug development through the development of innovative model-informed drug development to inform clinical trial design.

These staff members are extensively involved in external engagement as members of public-private partnerships, consortia, and speaking opportunities. Examples including being liaisons to the five disease specific (Alzheimer's Disease, Parkinson's Disease, Duchenne Muscular Dystrophy, Huntington's Disease, and Ataxias) consortia through the Critical Path Institute public-private partnership with FDA, members of the steering committee for Accelerating Medicine Partnerships Program for Alzheimer's Disease, ALS, Parkinson's disease, and Schizophrenia, and the steering committee for the Biomarkers Consortium for Neuroscience at FNIH, planning committee for Frontotemporal Dementia Research Roundtable and the Epilepsy Research Roundtable. NDP staff are also part of working groups to advance biomarkers for Alzheimer's disease including the use of imagining biomarkers of brain tau, development of clinical outcome assessments for early Parkinson's disease, and the development of an integrated staging system for neuronal alpha-synuclein disease.

During FY 2023 and FY 2024, NDP staff members have spoken at meetings regarding various disease areas and covering an array of topics including, biomarkers and surrogate endpoints, use of digital health technologies in clinical trials, use of patient experience data in regulatory decisions, rare neurologic disease drug development, clinical outcomes assessment development, and measurement in rare disease. Examples of those meetings include the Duke-Margolis Rare Disease Endpoint Advancement Pilot Program Workshop and the Duke-Margolis Advancing the Development of Therapeutic Through Rare Disease Patient Community. Disease areas covered include Alzheimer's Disease, Parkinson's Disease, epilepsy, multiple sclerosis, traumatic brain injury, ALS, Duchenne muscular dystrophy, Limb Girdle muscular dystrophy, Myotonic Dystrophy, Rett Syndrome, Angelman Syndrome, Frontotemporal Dementia, and Schizophrenia. These staff members are active participants in FDA patient listening sessions and externally-led Patient-Focused Drug Development meetings.

Funding also supported efforts under Section 3 of the Act for ALS to support the advancement of regulatory science and rare neurodegenerative drug development. The Critical Path for Rare Neurodegenerative Diseases public-private partnership at the Critical Path Institute fosters collaboration with patients and drug development stakeholders to identify gaps in regulatory science and implement strategies and research to address those gaps and advance science to inform drug development. Specifically, we funded efforts to examine clinical outcome assessments in ALS and identify measurement gaps of needed data that would improve the assessment and utility in clinical trials, as well as the

comparability evaluation of an ALS scale to be used via remote data collection instead of a traditional in-person study visit.

Additionally, CDER utilized the funding to support a meeting and workshop regarding Parkinson's Disease (PD) and schizophrenia. NDP funding provided a grant to support a meeting focused on trial design in early PD with a goal to help advance drug development in PD and will support an upcoming public workshop on the evaluation of negative symptoms in clinical trials for schizophrenia.

Additional funding would help support efforts in the NDP in three ways. First, the Agency currently receives a large number of requests for external engagement activities in the neuroscience space, and many of these requests must be declined due to inadequate resources. Additional funding would allow for the recruitment of additional FTEs to be hired and trained to assist with these activities. Second, additional funding would allow for the NDP to fund more research efforts in the neuroscience space to address and advance drug development. And finally, additional funding would allow for continued expansion of patient engagement and educational activities specific to neurologic and psychiatric diseases. The NDP staff recognize the need for patient engagement and the critical information that both FDA and patients learn from one another. With the growing innovation in clinical trial design and the uptake of innovation in neurology and psychiatry trials, the NDP will need to actively engage with key stakeholders to better understand, develop and implement these innovations into clinical trials.

Patient-focused Drug Development and Rare Disease Efforts

2. **I strongly believe that patients' perspectives and real-world experience must be front and center when it comes to FDA weighing what benefits truly matter to patients and what risks they are willing to accept in taking a new drug product. I know that you have several patient-focused drug development meetings coming up, including some for rare diseases with limited treatment options, and I hope you and your staff will listen carefully to what those patients have to say and apply those critical insights to your work. Can you speak to how FDA utilizes information gathered from such meetings, particularly around disease burden and current treatment options, in the agency's approval and labeling decisions?**

   FDA routinely incorporates how a disease impacts patients and their unmet medical needs in regulatory decisions—in particular for life-threatening and severely debilitating diseases, especially where no satisfactory alternative therapy exists, many of which are rare diseases. Of the 18 novel drug and biological products approved using accelerated approval for non-oncology rare diseases from 2015 to 2023 in CDER and CBER, the review team considered data on the impact of the disease on patients with the disease in all but five cases. Of these five cases in which patient experience data were not considered, two

were agents to reverse anticoagulation, and since accelerated approval for each was supported by trials done in healthy volunteers, patient experience data was not available. The patient experience data across the applications was varied, including patient reported outcomes on aspects of everyday functioning, clinical outcome measures of symptoms, and disease specific listening sessions, as well as patient experience data considered during previous applications for the same or related diseases.

3. **CDER's Accelerating Rare disease Cures (ARC) Program aims to provide "strategic overview and coordination" of CDER's rare disease activities. ARC's stated mission is to "drive scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases." What metrics does ARC use to measure how it has accelerated the development of treatments for rare diseases?**

   ARC is a CDER-wide effort governed by senior leadership from the Office of the Center Director, Office of New Drugs (OND), and Office of Translational Science (OTS). The ARC Program supports the development and approval of safe and effective treatment options for people living with rare diseases through scientific and regulatory engagement. ARC has focused on engagement with the rare disease drug development community as well as on strengthening our scientific and regulatory initiatives to provide direction and enhance CDER's engagement in innovative scientific design.

   The CDER ARC Program's engagement efforts are designed to share regulatory and scientific information, as legally permissible and otherwise appropriate, to help the rare disease community partner in effective drug development. The ARC Program currently tracks metrics to measure our progress in this area, among others. For example, to ensure we are sharing information the community finds useful, we track metrics related to the effectiveness of our listserv (such as subscriber numbers and open rates), usage of our website based on community feedback such as organizing selected FDA guidance relevant to rare disease drug development by topic, and attendance at public workshops such as the recent workshop, entitled Natural History Studies and Registries in the Development of Rare Disease Treatments. We work to ensure our engagement encompasses the information we have gathered from the rare disease drug development community through the Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) program. Through LEADER 3D, we analyzed and published a report summarizing the priorities identified by the rare disease community to identify knowledge gaps about the regulatory process of rare disease drug development with the goal of creating or expanding educational resources for both internal and external interested parties.

The CDER ARC program also tracks metrics related to regulatory and scientific innovations, such as the Translational Science team. The Translational Science Team, a multidisciplinary team comprised of experts and senior leadership that collaborates with review teams to provide advice on translational science issues, such as surrogate endpoints and confirmatory evidence. The Translational Science Team provides input on key regulatory drug development decisions that involve translational science issues across the continuum of drug development. For initiatives such as the TST, CDER ARC tracks metrics related to number of consults, types of consults, and implementation of advice, and follows the long-term outcomes of these drug development programs.

a. Can you share any specific examples of products for rare diseases advanced through ARC's regulatory innovations, and how ARC specifically helped to advance such innovation?

FDA has engaged with several developers but is unable to share non-public information on specific, non-approved products. Examples of how specific programs will benefit from innovations under the CDER ARC rare disease umbrella can be seen with the CDER-CBER Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program.[28] Selected programs will benefit from enhanced support and communication in their clinical study designs and other aspects of their drug development programs through access to innovations managed by the CDER ARC Program such as CDER's Translational Science Team or the Rare Disease Endpoint Advancement Pilot.

PRVs

4. The Priority Review Voucher Program has been a critical incentive for sponsors to pursue treatments in rare populations that would otherwise be too risky to conduct trials in. In what ways has the agency seen the positive impact of the PRV program?

The industry is in the best position to provide an answer as to whether the PRV programs provide incentives for sponsors to pursue treatments for certain at-risk populations. In the case of the rare pediatric disease PRV, we have heard that such vouchers may be key to making certain development programs for small pediatric populations be financially viable. While acknowledging the existence of academic studies questioning whether PRVs promote innovation, a GAO study published in 2020 stated that all seven drug sponsors GAO surveyed mentioned that PRVs were a factor in drug development decisions—six sponsors said they were one of a number

[28] https://www.fda.gov/news-events/press-announcements/fda-launches-pilot-program-help-further-accelerate-development-rare-disease-therapies

of factors, while one sponsor said they were pivotal in its development of a drug.[29]

Advisory Committees

5. **While there may only be a handful of true experts in specific rare diseases and conditions, these experts contribute invaluable insight and experience to supplement the Agency's understanding of a rare disease during the drug review process. Yet, there are instances where FDA Advisory Committees have not included academic, medical and other scientific experts with specialized expertise concerning the pathophysiology of the rare disease at issue. As the Agency considers Advisory Committee reform, how are you approaching this issue?**

   The Agency is prioritizing efforts to optimize our use of advisory committees, including exploring ways to modernize and improve our systems, and to enhance the expertise of Special Government Employees who serve the public as members. To further the discussion on these efforts, FDA will host a public meeting titled, "Optimizing FDA's Use of and Processes for Advisory Committees."

   We know that the best therapies and care for patients are grounded in solid scientific data, research, and expertise. The topics FDA takes to advisory committees are often intricate, and given the complex nature of their work, it is important that advisory committees are composed of the right experts for the topic. For this reason, FDA's advisory committees involve technically qualified experts with the experience to reflect the breadth of expertise necessary to provide meaningful advice. FDA's advisory committees include committee members from a wide variety of scientific backgrounds and generally also include patient and/or consumer representatives, whose role is to provide a voice for those most impacted by our decisions. As advances in science and technology continue to expand, and the opportunities for new treatments and approaches grows, it is increasingly important for all parties to be aware of and understand the work of advisory committees and how that work is factored into FDA's decision-making.

   While ensuring that our advisory committees are comprised of those with relevant expertise to provide meaningful advice to FDA and represent the breadth of interested parties, FDA must also adhere to the rules relating to conflicts of interest that may limit the pool of available members for a given advisory committee.

[29] https://www.gao.gov/products/gao-20-251

Rare Disease Therapies

6. What actions is FDA taking to prioritize the development of rare disease therapies, given that 95% of rare diseases lack an approved treatment?

CDER's Accelerating Rare disease Cures (ARC) Program is a CDER-wide collaborative effort that brings together expertise from many CDER Offices and Programs. The Center's Rare Diseases Team works closely with FDA's rare disease stakeholders to fulfill its user fee commitments to facilitate, support, and accelerate the development of drug and biological products, in addition to leading the development of crosscutting rare disease guidance documents and ensuring that policies and practices are shared across the Center.

CDER's ARC has also launched the Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) project. The project aims to better understand the unique challenges in bringing rare disease products to market and produce educational materials on fundamental topics. To compliment the LEADER 3D effort, CDER's Patient-Focused Drug Development staff is working with the National Organization for Rare Disorders to develop an advanced drug development education series for patients and patient groups.

Another key development for CDER is setting up the Genetic Metabolic Diseases Advisory Committee (GeMDAC), which will allow the Office of New Drug's Division of Rare Diseases and Medical Genetics to seek expert advice from a committee of clinicians, industry experts, academics, patients, caregivers and other external stakeholders when evaluating the potential benefits and risks of a new therapy for genetic metabolic diseases.

Together, CBER and CDER established the Rare Disease Endpoint Advancement (RDEA) Pilot Program to support novel endpoint efficacy development for drugs that treat rare diseases. The RDEA Pilot Program is designed to:

- Advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process;
- Promote innovation and evolving science by sharing learnings on novel endpoint;
  development through FDA presentations, guidance documents, public workshops, and a public-facing website; and
- Develop FDA staff capacity to enable and facilitate the development and use of novel endpoints to evaluate the efficacy of rare disease therapies.

In 2023, CBER and CDER announced the Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program, where participants will be

able to obtain frequent advice and regular informal communication with FDA staff to address product-specific development issues, including, but not limited to, clinical study design, choice of control group and fine-tuning the choice of patient population. The program is open to sponsors of products currently in clinical trials under an active Investigational New Drug application (IND), regulated by CBER or CDER. CBER regulated products must be a gene or cellular therapy intended to address an unmet medical need as a treatment for a serious rare disease or condition, which is likely to lead to significant disability or death within the first decade of life. CDER-regulated products must be intended to treat rare neurodegenerative conditions, including those of the rare genetic metabolic type. The Agency has selected pilot participants for each center. The pilot launched recently, and we look forward to seeing whether this type of frequent and informal communication between sponsors and FDA staff can help to move development programs for rare diseases forward more efficiently.

In addition, as we discussed in the hearing, FDA aims to initiate a Rare Disease Innovation Agenda, which will be based on a shared vision for advancing therapies for rare diseases. The Agenda will leverage expertise across the Agency to advance regulatory science on key issues critical to rare disease development programs, including novel endpoints, biomarker development, and innovative trial designs, while also enhancing collaboration and consistency across offices and centers related to product review.

The Rare Disease Innovation Agenda will set forth a plan for collaboration by scientists, clinicians, and other staff on the use of novel biomarkers across development programs for the same rare disease, as well as consider cross disciplinary approaches related to product review. Under the leadership of the CDER and CBER Center Directors, the proposed Agenda will help shape a shared vision and comprehensive cross-center strategy for advancing rare disease therapies. In addition, the Agenda will prioritize coordinated engagement with the rare disease community, to support enhanced opportunities for stakeholders to gain insight into FDA's thinking, to the extent legally permissible and otherwise appropriate, and for the Agency to learn more about important perspectives from patients, researchers, and other stakeholders and find common ground.

More information can be found *here*.

7. **How can regulatory flexibility support adaptive and single-study trials that accelerate the development of rare disease therapies and help patients access safe and effective therapies in as timely a manner as possible?**

FDA recognizes the challenges associated with rare disease drug development and applies regulatory flexibility to address the particular challenges posed by

each disease, while upholding our regulatory standards. Regulatory flexibilities include, for example, Accelerated Approval based on a surrogate endpoint that is reasonably likely to predict clinical benefit or intermediate clinical endpoint for serious conditions with an unmet medical need, reliance on one adequate and well controlled trial, use of natural history study data as a source of external control data, novel trial designs, and novel statistical methodologies. FDA considers all relevant statutory authorities and any available flexibilities when making decisions appropriate to the particular rare disease and therapeutic product under consideration.

Further, FDA has developed several guidance documents that help inform both Agency staff and the public about the Agency's proposed or current thinking on medical product development in the rare disease space.[30] For example, FDA's 2019 draft guidance, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, discusses CDER and CBER's longstanding flexibility when considering the types of data and evidence that can meet the substantial evidence standard for effectiveness in rare disease drug development and similar contexts. In 2023, FDA followed up with another draft guidance – *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*. This guidance specifically addresses meeting the substantial evidence standard for effectiveness with a single adequate and well-controlled clinical trial and confirmatory evidence. In addition, FDA's 2023 draft guidance, *Considerations for Design and Conduct of Externally Controlled Trials for Drug and Biological Products*, provides recommendations to sponsors and investigators considering the use of externally controlled clinical trials to provide evidence of the safety and effectiveness of a drug product. Finally, FDA's 2019 draft guidance, *Rare Diseases: Natural History Studies for Drug Development*, provides recommendations to help inform the design and implementation of natural history studies[31] in planning controlled trials of investigational drugs to treat rare diseases.

8. **Last year, you both made public comments about launching a version of Operation Warp Speed for rare diseases. It was noted that this framework could be used specifically to modernize the regulatory policy related to cell and gene therapies. As we've heard, the FDA is about to commence the Support for Clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program. Mirroring the spirit of Operation Warp Speed, the program would enhance communications between qualifying sponsors and the Agency, earlier in the process. Could you**

[30] The four guidances discussed below are draft guidances. When finalized, they will reflect the Agency's current thinking.

[31] Natural history studies are preplanned observational studies intended to track the course of a disease to identify demographic, genetic, environmental, and other variables that correlate with the disease's development and outcomes.

elaborate on what would be necessary to expand and broaden the START program idea for the benefit of rare disease patients?

9. **How does the FDA plan to incorporate the improved communication timelines that START participants will receive into its regular review process?**

Answer for 8 and 9:

FDA is committed to supporting innovation and continued progress in the development of gene therapies. The Agency is working to provide as much clarity as possible regarding our review standards and, as you note, has initiated an enhanced communication pilot to assist developers of these products, particularly those focused on rare diseases. More detailed information can be found on FDA's website: *FDA Opens Doors for More Treatments for Rare Diseases through the New START Pilot Program.*[32]

CBER and CDER initiated the START Pilot Program, which offers increased interactions with rare disease sponsors to address product-specific development issues, with hopes that the insight gained through this pilot would provide information on how best to facilitate more efficient development of potentially life-saving therapies for rare diseases and help sponsors generate high-quality, actionable data to support future new drug or biologics license applications. We plan to evaluate the START Pilot Program after the pilot has been fully operationalized to determine how much more efficiently key issues related to development programs for rare diseases were resolved, what additional resources may be necessary to expand the pilot, and other lessons learned from FDA's perspective and that of the sponsors. With more experience and that information in hand, we can then determine the best approach to potentially expanding the communication timelines in the pilot to other sponsors.

The Honorable Richard Hudson

NRTs

1. **Dr. Cavazzoni, dozens of my colleagues and I have encouraged this Administration to expedite consideration of long-pending FDA applications for smoke-free tobacco products that could improve public health by providing adult smokers access to less harmful options. In May of last year, the Center for Drug Evaluation and Research issued guidance to assist sponsors in the clinical development of nicotine replacement therapy (NRT) drug products, including those intended for smoking cessation.**

[32] https://www.fda.gov/drugs/our-perspective/fda-opens-doors-more-treatments-rare-diseases-through-new-start-pilot-program

- **Link: https://www.fda.gov/regulatory-information/search-fda-guidance- documents/smoking-cessation-and-related-indications-developing-nicotine-replacement-therapy-drug-products**

a. Would you please provide an update on the industry response to that guidance?

In May 2023, CDER finalized the draft guidance *Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy [NRT] Drug Products*. CDER issued the draft version of this guidance in February 2019 and opened a docket for public comments (Docket # FDA-2019-D-0297). CDER took comments from the docket, which included industry comments, into account while finalizing the guidance in May 2023.

b. Has your office seen a material increase in interest from the pharmacological community in developing NRT products?

Historically, FDA has seen limited interest from sponsors in developing nicotine replacement therapy products, and we have not seen a recent change.

c. Isn't it the case that a new NRT product must first be approved as a smoking cessation drug product before even being able to seek an indication for reducing the urge to smoke or relief of cue-induced cravings?

FDA's 2023 NRT Guidance provides recommendations to sponsors in the clinical development of NRT drug products intended to help cigarette smokers stop smoking cigarettes or maintain abstinence from smoking. While the guidance reflects FDA's current thinking on the topics it covers, it does not bind sponsors or FDA. FDA encourages sponsors that wish to discuss their drug development program to request a meeting with the appropriate review division. Each year, FDA review staff participate in many meetings with requesters who seek advice relating to the development and review of investigational new drugs and biologics, and drug or biological product marketing applications. FDA reviews New Drug Applications (NDAs) based on the best available science as applied to the data submitted in the NDA.

d. How is that approach consistent with making drug development easier, efficient, and streamlined?

The NRT Guidance provides recommendations for applicants to make NRT development easier, efficient, and streamlined:

- Clarifying recommendations for companies that seek approval for a product that alters the route of administration compared to approved

NRT drug products, e.g., products with pulmonary route of administration rather than an oral route of administration.

- Explaining when simplified efficacy study requirements may be used (e.g., recommending a 4-week study as the minimum period of efficacy ascertainment for smoking cessation).
- Clearly outlining the abbreviated review pathways available for NRT products, including how to use FDA's previous findings of safety and how already approved NRT products and published literature can be leveraged.
- Encouraging sponsors to consider expedited development and review pathways and providing details on how to qualify.

2. How is limiting the indications for reducing the urge to smoke or relief of cue-induced cravings to already approved products (versus new investigational drug products) consistent with the most streamlined approach to development and doing all that CDER can to help smokers seeking to quit have access to new safe and effective products that will help them be more successful in their quit attempts?

Please see the response to 1c.

3. The agency's guidance sets forth that a trial is considered to demonstrate effectiveness if significantly more subjects achieve abstinence when treated with the investigational NRT drug product as compared to subjects treated with the placebo. The agency is defining abstinence as no cigarette use over the entire course of the efficacy ascertainment period, which depending on the product, may be many months long. The agency has repeatedly acknowledged how hard it can be to quit because of the addictive qualities of nicotine and that often smokers seeking to quit relapse. Yet, under the agency's guidance, if a clinical trial participant relapses, even if just one time, and smokes just one cigarette they would be considered a non-responder in the trial even if over the course of the entire trial they were able to reach the cessation endpoint despite a relapse. How much longer will it take sponsors to develop new safe and effective smoking cessation NRT drug products with such a zero-tolerance relapse dynamic?

A relapse is considered a return to smoking, whereas a "slip-up" is considered a pre-defined number of cigarettes that a subject might consume during the efficacy ascertainment (i.e., measurement) period of a clinical trial. CDER's NRT Guidance does not put forth a "zero tolerance" stance on slip-ups during the ascertainment period for a trial that is many months long. The Guidance states:

> In general, abstinence is defined as no cigarette use over the entire course of the efficacy ascertainment period by subject self-report and biological verification at intervals of approximately 1 to 2 weeks. A longer interval between self-reporting and verification visits may be acceptable in some instances (e.g., trials that are more than 3 months long). *For trials with longer efficacy ascertainment periods of 6 or 12 months, sponsors can consider defining abstinence to incorporate a maximum allowable number of cigarettes*. (Emphasis added).

With regard to reduction of risk in relapse, the NRT Guidance states:

> The clinical trials intended to support this maintenance indication should have the definition of relapse prespecified in the protocol, an ascertainment window, at a minimum, of 6 months to 1 year, and use the proportion of trial subjects not relapsing as the primary endpoint.[31]
>
> Footnote 31: For example, sponsors may consider a study design *where treatment success is defined as smoking no more than five cigarettes during the efficacy ascertainment period.* (Emphasis added).

Regarding the endpoint of abstinence, CDER previously recommended complete abstinence of 8-12 weeks for approval. Based on additional data on the shortest time period necessary to predict long-term abstinence, the new NRT guidance has reduced this timeframe to a minimum of 4 weeks as the shortest time frame that could still show health benefits. In addition, 4 weeks is the typical period necessary for the majority of nicotine physiological withdrawal symptoms to subside.

a. Please explain how the agency sees the public health impact of the additional time it will take to develop new safe and effective smoking cessation drug products with the continued staggering mortality and morbidity resulting from the inability of smokers seeking to quit to be more successful in their quit attempts with the current products available to them and how the agency's current posture on this issue will result in net public health benefit (if any)?

FDA's 2023 NRT Guidance outlines nonprescription drug development considerations specific to NRT drug products and makes recommendations for nonprescription label development, efficacy studies, and consumer behavior studies. It also outlines the abbreviated review pathways available for NRT products, including how to use FDA's previous findings of safety and how already approved NRT products and published literature can be leveraged. Finally, the NRT Guidance encourages sponsors to consider expedited development and review pathways and provides details on how to qualify for this review.

b. How is such a "zero tolerance" relapse stance consistent with an

easier and more efficient development pathway or helping patients to be able to benefit from safe and effective innovations in as timely a manner as possible?

See the response to Question 3.

c. Why isn't the agency employing a more realistic real-world approach to its considerations of NRT products similar to the agency's approach to the development of other addiction therapies in which the agency has acknowledged the public health benefit of the reduction of use of such harmful and addictive substances?

Nicotine use disorder and other substance use disorders (e.g., opioid use disorder) are very different, even though they fall into the same general category of addictive disorders.

In general, different substance use disorders have different mechanisms of action and clinical effects that may lead to differences in clinical presentation and responses to treatment. As a result, study designs, patient populations, and endpoints may differ across therapeutic areas targeting different forms of addiction.

In the case of smoking cigarettes, we are concerned primarily with long-term health effects. There are limited and mixed data on whether reduction in smoking short of cessation leads to net positive clinical outcomes, while smoking cessation is associated with demonstrated positive clinical outcomes. However, we are eager to work with sponsors and other stakeholders to advance scientific understanding of novel endpoints demonstrating meaningful reductions in harms associated with smoking.

d. Why is CDER holding new smoking cessation products to a less realistic and more burdensome development framework than products being developed in other areas of addiction?

Please see the response to 3c.

4. It seems CDER has set up a bifurcated approach to products for smoking cessation in your 2023 guidance. The products that are eligible to benefit from the modest provisions in that guidance are almost exclusively currently approved products that, as you know, are remarkably ineffective in the real world. Why has CDER taken such an approach knowing the very limited real-world effectiveness of the handful of currently approved products?

See response to Question 1c.

a. What more can and should CDER do to stimulate the interest of sponsors to come to you with truly innovative products to reduce the death toll?

See response to Questions 1b, 1c, and 1d. In addition, as smoking results in many serious or life-threatening conditions (e.g., heart and lung disease and cancer), FDA recognizes there is an unmet need for novel therapies particularly for individuals who have not been able to quit despite available therapies.

Because we consider nicotine dependence to be a serious or life-threatening condition with an unmet medical need, in the 2023 final NRT guidance, we are encouraging development of novel smoking cessation drug therapies that show benefit over existing products by ensuring manufacturers are aware of the expedited development pathways such as fast track, breakthrough, and priority review and encouraging them to discuss eligibility with the agency.

In addition, because the data are so strong in demonstrating that quitting smoking can lower a person's chance of having lung disease, heart disease, and certain types of cancer, drug products that have been demonstrated to be effective for cessation are approved with labeling claims regarding these benefits without additional data supporting benefit of the particular product on these outcomes.

To support the majority of smokers who wish to quit and to increase utilization of cessation products and interventions, FDA and the National Institutes of Health (NIH) are collaborating to identify treatment gaps and opportunities for the development of novel therapies, support innovative trial designs, and facilitate product development for smoking cessation therapies. Opportunities for innovation exist in many areas including collaboration with researchers to help identify novel targets, use of innovative clinical trial design and conduct, inclusion of individuals underrepresented in research, developing a better understanding of quit failures and relapse, and utilizing FDA's expedited programs for medical product development.

To this end, FDA will hold a joint public meeting with NIH this fall to discuss innovations in development of smoking cessation products, and we anticipate the Federal Register notice for that meeting to be announced in the near future.

The Honorable Earl "Buddy" Carter

DDT Qualification Program

1. In 2016, Congress established the Drug Development Tools (DDT) Qualification Program through the passage of the 21st Century Cures Act. The DDT Qualification Program aimed to expedite drug development by qualifying novel tools, such as biomarkers, clinical

outcome assessments, and other scientific methods. Congress intended for the program to provide clarity and predictability to stakeholders, including drug developers, academic researchers, and non-profits regarding the acceptance and utilization of such tools in the regulatory review process. Director Cavazzoni - It has been almost 8 years since the passage of 21st Century Cures, could you give us an update on the performance of the FDA DDT Qualification Program since its enactment?

See answers below.

a. How has the program impacted drug development, particularly in light of the limited number of DDTs qualified post-enactment and their very sparse use to approve drugs to date?

FDA has developed drug development tool (DDT) programs and published a guidance for industry and FDA staff describing the DDT qualification process.[33] Under this process, the terms "qualification" and "qualified" mean a determination by FDA that a DDT and its proposed context of use can be relied upon by multiple development programs to have a specific interpretation and application in drug development and regulatory review under the FD&C Act. An important distinction between the qualification route to acceptance of clinical outcome assessments (COAs), biomarkers, and other novel approaches as compared to the IND/NDA/BLA route is that acceptance of DDTs in the IND/NDA/BLA route applies only to that particular drug development program, and FDA's views are not necessarily shared publicly, so other stakeholders cannot routinely learn FDA's judgment on the DDT. In contrast, qualified DDTs may be used in any drug development program for that same context of use (COU) without further validation work, which mandates a highly rigorous qualification process. At each stage of the qualification process, FDA shares publicly on our searchable database our judgement on the utility of the DDT and what methods are appropriate to validate the tool.

The potential for qualified DDTs to impact drug development programs is illustrated by KIM-1, which was qualified as a safety biomarker for detection of kidney injury. Following qualification, there was a documented increase in the number of regulatory applications referencing KIM-1 as a DDT and an increase in the number of pharmaceutical company sponsors' planned or actual use of KIM-1 in their drug development programs.[34] With additional programs entering the final stages of qualification there will be additional

[33] Qualification Process for Drug Development Tools (November 2020), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-process-drug-development-tools-guidance-industry-and-fda-staff.
[34] R Chen et al. Clin Pharm & Therapeutics. 104:1175-1181, 2018.

opportunities to document use of qualified tools in drug development programs.

b. Do you think this program is a success?

The program is showing signs of success. Under the COA Qualification Program, five DDTs have been qualified since passage of the 21st Century Cures Act for asthma, depression, constipation in irritable bowel syndrome, non-small cell lung cancer, and heart failure. At present, the COA Qualification Program has 68 projects in various stages of review, including 40 accepted letters of intent (LOIs), 25 qualification plans (QPs) and three full qualification plans (FQPs). Submissions with accepted QPs that are entering the last stage of qualification include COAs for pediatric asthma, fatigue in rheumatoid arthritis and multiple sclerosis (MS), and cognitive disability in MS. Of note, the program has several projects related to substance use disorders including a project evaluating the World Health Organization (WHO) Risk Drinking Levels of alcohol consumption as an endpoint. Another substance abuse-related project involves a patient-reported outcome measure to assess opioid craving funded in part by a grant under the 21st Century Cures Act undergoing qualitative research with patients; and an accepted LOI for opioid use disorder severity. In addition to providing a pathway to qualification through meaningful interactions with Agency experts, the program also serves as a platform where current guidance is communicated to academic researchers, consortia, and industry through meetings with external stakeholders and participation in conferences.

At the present time, the biomarker qualification program has 46 programs in development, including 41 accepted LOIs. A total of five programs have accepted qualification plans, including some with full qualification packages (FQPs) under review, indicating that they are either in or ready to enter the last phase of qualification. Two accepted qualification plans are for non-alcoholic steatohepatitis, one is a safety biomarker to assess drug-induced chromosomal damage, and one is a safety biomarker to detect drug-induced liver injury. One program has progressed to the FQP stage, a surrogate endpoint biomarker for osteoporosis, a condition of great public health importance. As more programs progress to the FQP stage it should become possible to learn from the successful programs to provide more general advice to requesters to speed the process for future submissions.

c. The goal of the pathway was to help leverage novel tools and technologies to expedite drug development. Can the existing DDT qualification program, with its current success rate, enable regulatory acceptance of emerging newer technologies, such as alternatives to animal testing and artificial intelligence tools?

The biomarker qualification program is complemented by other FDA initiatives designed to address advancements in DDTs that utilize emerging technologies. To address innovative DDTs that utilize novel technologies, FDA initiated the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program, which is designed to expand drug development tool types by encouraging the development of tools that are out of scope for existing DDT qualification programs but may still be beneficial for drug development. Projects accepted under ISTAND may enter the DDT qualification program. FDA may also pursue other outcomes, such as a public meeting or the issuance of a white paper or guidance. Detailed information on how drug sponsors can engage with the Agency about this program and the steps needed to submit a qualification package are available on the ISTAND Pilot Program webpage.[35] Since its inception in 2020, ISTAND has received a total of 22 LOI submissions, of which four have been accepted:

1) a method to screen biotherapeutics for improved safety profiling;
2) an AI-based, digital health technology method of assessing depression and anxiety severity in patients with major depressive disorder that is intended to replicate expert clinician judgment;
3) an in vitro method to assess local tolerance of epidurally and intrathecally-administered leachables; and
4) an AI-based method of evaluating events in cardiovascular (CV) outcome trials to determine whether they represent CV outcome events that are intended to replicate expert-adjudicated CV events.

Non-animal method tools are eligible for submission under ISTAND, and in fact, FDA has accepted three proposed tools into the DDT qualification program, including through ISTAND, that may achieve the objectives of the 3Rs (replacing, reducing, and refining animal testing). One is the ISTAND-accepted LOI for an in vitro method to assess local tolerance of epidurally/intrathecally-administered leachables. If ultimately qualified, this method has the potential to replace animal testing for this purpose. Another is an ISTAND-accepted LOI for an imaging safety biomarker that measures in life an imaging safety biomarker (MRI T2 relaxation) in non-clinical animal models to assess neurotoxicity. This DDT has the potential to refine use of animals in safety testing. The last is the accepted QP in the biomarker qualification program for a tool designed to identify in vitro structural chromosomal damage.

With respect to artificial intelligence (AI)-based tools, the ISTAND pilot and the biomarker qualification program have demonstrated that they can help enable regulatory acceptance of novel AI-based tools. As mentioned above, the ISTAND program has two accepted LOIs for AI-based tools: the AI-based method of assessing depression and anxiety severity in patients with major

[35] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program.

depressive disorder and the AI-based method of assessing whether reported events represent CV outcomes. In addition, an AI-based method to replicate expert pathologist readings of liver histopathology has an accepted qualification plan in the biomarker qualification program.

Advisory Committees

2. **The FDA has announced plans to carry out advisory committee reform, a point that has been reiterated by Commissioner Califf in public comments that it is his belief that it is not necessary to take a vote at most meetings. In some diseases with small patient populations and few clinical/scientific experts, FDA Advisory Committees have failed to include academic medical and other scientific experts with specialized expertise. For rare and ultra-rare diseases, there are often very few true experts. It is critically important that FDA ensures that Ad Com members have expertise in the specific disease states the product is intended to treat. Why is that not always the case and what can we do to change that?**

    a. **If the objective is to gather and assess the best scientific advice, what is the Agency doing to address this inherent challenge in small patient populations?**

    b. **Are Advisory Committee members trained on the regulatory requirements and standards for making decision on product applications?**

    c. **How does the FDA ensure that the appropriate experts have a seat at the advisory committee table, including patients?**

    The Agency is prioritizing efforts to optimize our use of advisory committees, including exploring ways to modernize and improve our systems, and to enhance the expertise of Special Government Employees who serve the public as members. To further the discussion on this initiative, FDA is planning a public meeting for June 2024 titled, "Optimizing FDA's Use of and Processes for Advisory Committees." The meeting will invite comment on issues including the categories of expertise, viewpoints, or voices that are particularly important for representation on advisory committees; whether there are ways that FDA can better ensure that a variety of diverse perspectives and experiences are incorporated into advisory committee meetings, and if so, how; and if there are ways that FDA can adjust the processes for discussion and/or voting that would improve public understanding of how FDA receives external advice through the exchange of information at advisory committee meetings, and the ultimate import of the advisory committee's discussion.

We know that the best therapies and care for patients are grounded in solid scientific data, research, and expertise. FDA relies on advisory committees as needed to provide advice on scientific, technical, and policy questions and share their perspectives on patient and consumer experience issues, to help the FDA make decisions based on the best science available. The topics FDA takes to advisory committees are often intricate, and given the complex nature of their work, it is important that advisory committees are composed of the right experts for the topic. For this reason, FDA's advisory committees involve a diversity of membership and experiences to reflect the breadth of expertise necessary to provide meaningful advice and includes representation from interested parties such as a patient advocate representative. FDA's advisory committees include committee members from a wide variety of backgrounds, generally including patient and/or consumer representatives, whose role is to provide a voice for those most impacted by our decisions. As advances in science and technology continue to expand, and the opportunities for new treatments and approaches grow, it is increasingly important for all parties to be aware of and understand the work of advisory committees and how that work is factored into the FDA's decision-making.

While ensuring that our advisory committees are comprised of those with relevant expertise to provide meaningful advice to FDA and represent the breadth of interested parties, FDA must also adhere to the rules relating to conflicts of interest that may limit the pool of available members for a given advisory committee.

With regard to advisory committee member training, we have developed free, online, on-demand regulatory science learning modules that provide an overview of advisory committee meetings and cover topics related to common issues discussed at human drug advisory committee meetings. We are continuing to add additional training modules over time. We inform advisory committee members of this training when they first become advisory committee members and again prior to upcoming service on a subsequent advisory committee meeting. We also note that while advisory committee members are generally provided training that may include an overview of relevant FDA regulatory standards, the role of advisory committee members is to provide expert advice to FDA and not to opine on the approvability of a product, which is an FDA determination. As such, while FDA carefully considers the advice advisory committee members provide, the approvability of an application is a regulatory decision made by FDA alone.

Decentralized Trials

3. **In May 2023, FDA released its draft guidance titled, "Decentralized Clinical Trials for Drugs, Biological Products, and Devices" which displays the current thinking of the Agency on the implementation of decentralized trials (DCTs). This would mean that clinical trials could occur in places beyond a traditional clinical trial site, like**

homes or local health care facilities. For many patients, especially those with rare diseases or other comorbidities, leveraging telehealth with decentralized trials would help reach those who previously could not gain access to clinical trials. How has adoption of decentralized trials gone to date and what if any additional efforts from FDA are needed to ensure robust implementation of decentralized trials?

FDA has been working to help enhance convenience for trial participants, reduce the burden on caregivers, expand opportunities for different patient populations to participate, improve trial efficiencies, and facilitate research on rare diseases and diseases affecting populations with limited mobility. FDA published a draft guidance on DCTs in May 2023[36] to facilitate implementation of these trials. FDA has reviewed the public comments on the draft guidance and is in the process of finalizing the guidance. FDA has also established the Digital Health Technologies Steering Committee where external stakeholders may engage with FDA on topics related to the conduct of DCTs to further support sponsors conducting DCTs.

In addition, our new Center for Clinical Trial Innovation (C3TI) aims to address the need for streamlined adoption of innovative methodologies and technologies in clinical research. C3TI will help facilitate the adoption of novel trial designs and approaches that have the potential to reduce barriers to participation, such as decentralized trial models, patient-centric clinical trial designs, and integration of point-of-care elements in trials. C3TI aspires to track the adoption of these innovative approaches in clinical trials.

There is growing external support for decentralization of trial-related activities. Several new companies have emerged that provide software and infrastructure to support DCTs. Some of the components of a DCT, such as electronic informed consent, have been supported by the patient community with representatives indicating that this improves their sense of autonomy. Patients with rare diseases and their caregivers have emphasized the importance of DCTs to avoid the stress, disruption, time, and expense of repeated travel to distant trial sites. Patients with degenerative neurological disease have reported the value of DCTs which, while helping gather trial data, also assist them in managing their conditions.

However, several practical challenges remain that fall beyond the jurisdiction of the Agency. For example, medical licensing requirements for telemedicine differ from state to state. Companies planning DCTs struggle to meet these requirements by trying to find clinical investigators whose medical licenses allow them to practice in many states. FDA will continue to work with sponsors

[36] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices

to help facilitate DCTs.

Shortages

4. **Domestic 503B outsourcing facilities have the ability to fill gaps in the commercial drug market when shortages arise – how is FDA working with 503Bs to mitigate the shortage problem, and what challenges do 503Bs face?**

FDA understands drug shortages can delay needed care for patients, creating a potential lapse in medical care, and can also lead prescribers to use second-line alternatives, which may be less effective or pose additional risks compared to the drug in shortage. Preventing and mitigating drug shortages is a priority for FDA. The Agency has worked with outsourcing facilities to mitigate certain drug supply disruptions and drug shortages.

As background, section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b) describes the conditions that must be satisfied for human drug products compounded by an outsourcing facility to be exempt from the following three sections of the FD&C Act: section 505 (concerning the approval of drugs under new drug applications or abbreviated new drug applications); section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and section 582 (concerning drug supply chain security requirements).

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for these exemptions is that the outsourcing facility does not compound drug products using a bulk drug substance unless (a) it appears on a list established by the Secretary of Health and Human Services identifying bulk drug substances for which there is a clinical need (the 503B Bulks List), or (b) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act at the time of compounding, distribution, and dispensing (see section 503B(a)(2)(A) of the FD&C Act). Another condition that must be met for a compounded drug product to qualify for the exemptions under section 503B of the FD&C Act is that "the drug is not essentially a copy of one or more approved drugs," as defined in the statute (see section 503B(a)(5) and (d)(2)).

FDA has issued guidance that describes policies related to compounding drugs on FDA's drug shortages list. FDA's guidance for industry *Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, states:

> "FDA does not intend to take action against an outsourcing facility for filling orders that it received for a compounded drug that is identical, or nearly identical, to an approved drug that was on FDA's drug shortage list at the time that the outsourcing facility received the order, provided the

drug also appeared on the FDA drug shortage list within 60 days of the outsourcing facility distributing or dispensing the drug."

Similarly, FDA's guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, states:

> "FDA does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that is not on the 503B Bulks List if the drug compounded from the bulk drug substance: (i) appeared on FDA's drug shortage list within 60 days of distribution and dispensing, and (ii) was to fill an order that the outsourcing facility received for the drug while it was on FDA's drug shortage list."

FDA also issued temporary policies on compounding certain drugs for hospitalized patients during the COVID-19 public health emergency.

FDA continues to evaluate these and other policies to help mitigate drug shortages through compounding by outsourcing facilities, when appropriate. FDA is engaged in ongoing outreach to drug compounders to understand potential barriers to production of drugs during shortages to inform future policy considerations. FDA is actively considering feedback on these matters.

Clinical Reviewers

5. **The FDA constantly claims that it has a shortage of adequately trained physician reviewers so that it cannot offer customized guidance. Can you tell me how many physicians are in direct front-line reviewer roles versus administrative and managerial roles in CDER?**

   In the Center for Drug Evaluation and Research (CDER), we have sufficient review staff, including physicians and other relevant experts, that provide individualized advice to product sponsors. Indeed, CDER has physicians across a wide range of specialties who work closely with sponsors of drug development programs to provide program-specific advice, in response to questions that these sponsors submit. The Office of New Drugs, which houses the majority of CDER's physicians who act as primary reviewers, currently has approximately 340 primary reviewers and 176 team leads or supervisors who are physicians. In 2023 alone, CDER granted more the 3,400 meetings with sponsors where our reviewers provided specific advice and guidance.

6. **You are a physician, and I am a pharmacist. We are clinically-oriented people and yet today I know that the farther we get from clinical practice the more we lose some of that pragmatic know-how of the challenges that patients face. What percentage of your front- line clinical reviewers in the Office of New Drugs are**

actively practicing clinically?

We do not track the exact number of staff in the Office of New Drugs who actively practice clinical medicine. But there are many who participate in a combination of professional development activities at local healthcare facilities (up to 8 hours per week) as part of their official duties, and others who continue to practice outside of their official duties as an approved outside activity. This includes physicians, pharmacists, and nurses. In addition, new, recently practicing physicians join our ranks routinely, and physicians already on staff who do not actively practice, attend conferences and keep up to date on their specialty in a variety of ways.

7. **Ongoing clinical experience is critical to being at the edge of cutting science. A new hospital opened up next door. What are you going to do to transform the role of the reviewer and ensure that they are still close to patients? This is critical to ensuring that reviewers understand the barriers to conducting trials in community setting, implementing patient-reported outcomes, and innovating in how we generate clinical evidence.**

We agree that clinical experience informs clinical research and the evaluations of drug candidates that our reviewers must conduct. Our reviewers keep up with the latest clinical advances and new scientific knowledge in their areas. Reviewers consider the patient's perspective, as well as the current knowledge of the practice and science in their specialty areas when making decisions regarding new drug products. To ensure our reviewers have patients and clinical practice in mind, we look for physicians who have relevant clinical practice experience, typically in their specialty area, to provide guidance on drug development programs. We fully agree that increasing efforts to conduct trials in community settings is valuable and important. We have issued guidances to industry on using decentralized trials, which have the potential to expand trials to greater numbers of participants, and we also encourage efforts to simplify trial designs to reduce barriers to incorporating trials in point of care sites. Further, CDER has launched a new C3TI that is focused on expanding the use of innovative approaches to trial conduct, including streamlined trials, trials that incorporate pragmatic elements, and trials with point of care sites. C3TI will also increase internal training to support these goals and facilitate external interactions such as during public meetings or other discussions.

NRTs

8. **At the recent hearing, you testified that CDER tries to do everything it can as regulators to make drug development easier, efficient and streamlined as a contribution to innovation but actions speak louder than words. More than 8.6 million Americans have**

died from smoking since the last new product was authorized by CDER for smoking cessation. The bottom line is that CDER has set up a bifurcated approach to products for smoking cessation in your 2023 guidance. The products that are eligible to benefit from the modest provisions in that guidance are almost exclusively currently approved products that, as you know, are remarkably ineffective in the real world. Why has CDER taken such a bifurcated approach knowing the very limited real-world effectiveness of the handful of currently approved products and what more can and should CDER do to stimulate the interest of sponsors to come to you with truly innovative products so that new, safe and effective smoking cessation therapies reach patients in as timely a manner as possible?

As smoking results in many serious or life-threatening conditions (e.g., heart and lung disease and cancer), FDA recognizes there is an unmet need for novel therapies, particularly for individuals who have not been able to quit despite available therapies.

Because we consider nicotine dependence to be a serious or life-threatening condition with an unmet medical need, in the 2023 final NRT guidance, we are encouraging development of novel smoking cessation drug therapies that show benefit over existing products by ensuring manufacturers are aware of the expedited development pathways such as fast track, breakthrough, and priority review and encouraging them to discuss eligibility with the agency.

In addition, because the data are so strong in demonstrating that quitting smoking can lower a person's chance of having lung disease, heart disease, and certain types of cancer, drug products that have been demonstrated to be effective for cessation are approved with labeling claims regarding these benefits without additional data supporting benefit of the particular product on these outcomes.

To support the majority of smokers who wish to quit and to increase utilization of cessation products and interventions, FDA and the National Institutes of Health (NIH) are collaborating to identify opportunities for the development of novel therapies, support innovative trial designs, and facilitate product development for smoking cessation therapies. Opportunities for innovation exist in many areas including collaboration with researchers to help identify novel targets, use of innovative clinical trial design and conduct, inclusion of individuals underrepresented in research, developing a better understanding of quit failures and relapse, and utilizing FDA's expedited programs for medical product development.

To this end, FDA will hold a joint public meeting with NIH this fall to discuss innovations in development of smoking cessation products, and we anticipate the Federal Register notice for that meeting to be announced in the near future.

The Honorable Neal Dunn, M.D.

Compounding

1. **As you are aware, several payers and their associated PBMs have imposed coverage requirements which mandate physician-administered drugs to be provided through a PBM-affiliated specialty pharmacy to another site for administration, a practice also known as payer-mandated white bagging. This practice can cause myriad issues for patients as needed care can be unnecessarily delayed. Further, payer-mandated white bagging adds unnecessary steps to the normal flow of medications through the supply chain, can threaten patient access to critical treatment, and can lead to patient harm, such as if drugs are not properly stored/transported. Additionally, the specialty pharmacy tends to view these medications as dispensed, resulting in situations where the administering providers lack tracing information that would otherwise be available under more traditional models, creating a gap in drug supply chain security for these products. It appears this practice was not contemplated when the Drug Supply Chain Security Act (DSCSA) was enacted—and DSCSA Pilot Project Program results indicated that additional guidance is needed for dispensers regarding payer-mandated white bagging. Can you provide clarity regarding payer-mandated white bagging in the context of DSCSA?**

   For purposes of the DSCSA, the term "transaction" does not include dispensing a product pursuant to a prescription.

   a. **Could a legislative change help address this gap in the supply chain?**

      DSCSA addresses the pharmaceutical supply regarding changes of ownership of product as drugs move from the manufacturer to the pharmacy, prior to dispensing to patients. The FDA has prioritized its efforts towards successful implementation of existing DSCSA requirements and are happy continue to provide technical assistance as needed regarding the specifics of any proposed legislative changes being considered by Congress.

2. **In the wake of the COVID-19 emergency flexibilities, what specifically is the FDA doing to facilitate the compounding and availability of critical drug shortage items experienced by 503B Outsourcing Facilities?**

   FDA understands drug shortages can delay needed care for patients, creating a potential lapse in medical care, and can also lead prescribers to use second-line

alternatives, which may be less effective or pose additional risks compared to the drug in shortage. Preventing and mitigating drug shortages is a priority for FDA.

FDA has issued guidance that describes policies related to compounding drugs on FDA's drug shortages list. FDA's guidance for industry "Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act," states:

> "FDA does not intend to take action against an outsourcing facility for filling orders that it received for a compounded drug that is identical, or nearly identical, to an approved drug that was on FDA's drug shortage list at the time that the outsourcing facility received the order, provided the drug also appeared on the FDA drug shortage list within 60 days of the outsourcing facility distributing or dispensing the drug."

Similarly, FDA's guidance for industry "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act," states:

> "FDA does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that is not on the 503B Bulks List if the drug compounded from the bulk drug substance: (i) appeared on FDA's drug shortage list within 60 days of distribution and dispensing, and (ii) was to fill an order that the outsourcing facility received for the drug while it was on FDA's drug shortage list."

FDA also issued temporary policies on compounding certain drugs for hospitalized patients during the COVID-19 public health emergency. Those policies expired on May 11, 2023, concurrent with the expiration of the COVID-19 public health emergency declaration issued pursuant to section 319 of the Public Health Service Act. In January 2023, FDA issued an immediately-in-effect guidance on compounding certain ibuprofen oral suspension products under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in an effort to improve supply amid record high demand.

a. In follow up, is the FDA developing guidance to streamline the start-up process for the compounding of drug shortage items by 503B Outsourcing Facilities?

b. Also, will the FDA extend the allowable sale period for a compounded drug after it is removed from the shortage list?

FDA is actively considering feedback it has received on its copies guidance documents, including feedback on the periods described in the guidance documents that were noted above.

3. In the Fall 2023 Unified Agenda, FDA indicated it would issue a

proposed rule by the end of 2023 outlining a memorandum of understanding (MOU) between the Agency and states regarding the distribution of human drug products, compounded by 503A pharmacies, across state lines. When can we expect to see this proposed rule?

FDA continues our work on the proposed rule and standard MOU and will provide updates, as appropriate. Additional information is available on FDA's website regarding the MOU Addressing Certain Distributions of Compounded Drugs,[37] and in the current Unified Agenda entry.[38]

As background, section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions that must be satisfied for drug products compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or a licensed physician, to be exempt from the following sections of the FD&C Act: (1) section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements), (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use), and (3) section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications).

One of the conditions to qualify for the exemptions listed in section 503A of the FD&C Act is that: (1) the drug product is compounded in a State that has entered into an MOU with the FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State or (2) if the drug product is compounded in a State that has not entered into such an MOU, the licensed pharmacist, pharmacy, or physician does not distribute, or cause to be distributed, compounded drug products out of the State in which they are compounded in quantities that exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician (statutory 5 percent limit) (see section 503A(b)(3)(B)(i) and (ii) of the FD&C Act).

In the *Federal Register* of October 27, 2020 (85 FR 68074), FDA announced the availability of a standard MOU describing the responsibilities of a State Board of Pharmacy or other appropriate State agency that chooses to sign the standard MOU in investigating and responding to complaints related to drug products compounded in such State and distributed outside such State and in addressing the interstate distribution of inordinate amounts of compounded human drug products. The standard MOU was developed in consultation with the National

[37] https://www.fda.gov/drugs/human-drug-compounding/memorandum-understanding-addressing-certain-distributions-compounded-drugs
[38] https://www.reginfo.gov/public/do/eAgendaViewRule?pubId=202404&RIN=0910-AI71

Association of Boards of Pharmacy (NABP) as described in section 503A of the FD&C Act and was the product of more than 20 years of collaborative dialogue and stakeholder input.

Soon after announcing the availability of the standard MOU, FDA was sued by several compounding pharmacies regarding the standard MOU in the U.S. District Court for the District of Columbia. In September 2021, the court remanded the standard MOU to FDA to either certify that it will not have a significant economic effect on small businesses or prepare a regulatory flexibility analysis. To undertake this analysis more fully and ensure a robust framework for these important public health protections, FDA intends to engage in notice-and-comment rulemaking regarding the provisions on certain distributions of compounded human drug products, including the MOU, under section 503A of the FD&C Act.

FDA considers the standard MOU published in October 2020 to be suspended. This means that during the rulemaking process, FDA will not enter into new agreements with States based on the October 2020 standard MOU. FDA does not expect States that have signed the October 2020 standard MOU to carry out the activities described in the MOU. In the *Federal Register* of October 21, 2022 (87 FR 63947), FDA extended the period before FDA intends to begin enforcing the statutory 5 percent limit on distribution of compounded human drug product out of the state in which they are compounded in States that have not entered into a standard MOU with FDA until the effective date of a final rule regarding certain distributions of compounded human drug products under section 503A of the FD&C Act and publication of an updated standard MOU. The October 2020 standard MOU will be updated based on the content of a final rule, and FDA intends to announce a new opportunity for all States to consider and sign the updated standard MOU.

Cloud Services

I appreciate FDA's response to a recent bipartisan letter from me and several other members on the use of cloud services by regulated industry, including drug and medical device companies. As FDA has indicated, cloud services offer benefits—including enabling product sponsors to use the most advanced analytic and AI tools to support innovation. Are entities regulated by your center able to use cloud services?

Yes, regulated industries are able to use cloud-services.

a. And what steps do you plan to take to train FDA reviewers and investigators on the ability for cloud services to support product quality, facilitate innovation, and meet compliance requirements?

FDA shares the goal of maximizing the potential of technological advances to protect the public health, including clearer communications and digital

experiences via modern platforms, streamlining data storage, ensuring data security, and promoting innovation.

The current submission processes for a variety of applications allow regulated entities to submit information electronically, in a secure and efficient manner. FDA recognizes that submissions are increasingly complex and may involve multiple data sources. The Agency is continuing to explore approaches that ensure electronic data can be robustly managed for regulatory purposes. This includes, but is not limited to, exploring the use of cloud-based platforms.

Importantly, the Agency does not prescribe how regulated entities store the data used to support their applications. The decision to store data using cloud-based applications, such as Software-as-a-Service (SaaS), or on-premises data storage is left to each regulated entity to determine which method best suits their needs. The Agency does not endorse, nor prohibit, the use of any of these data storage methods or the use of any particular service or system, as long as the chosen method meets applicable regulatory requirements. FDA agrees that there are many potential benefits for both the Agency and regulated entities to embrace IT modernization, and that there are a variety of data storage solutions that regulated entities can use to meet regulatory requirements for recordkeeping, such as those for clinical trials or manufacturing processes.

FDA investigators undergo rigorous training and are kept up to date on current industry best practices and the Agency's expectations regarding data and information that support marketing applications and other submissions from regulated entities. FDA is committed to advancing our data and IT modernization to provide cloud-based, agile, integrated platforms that streamline and improve the ability to access, utilize, and protect electronic data.

The Honorable Dan Crenshaw

Substantial Evidence of Effectiveness

1. **In September 2023, the Food and Drug Administration issued a draft guidance for industry entitled "Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence." How is the agency ensuring that the agency's current and best thinking on this topic is being applied consistently across the agency in its regulatory decision-making, including in the review of products intended to treat children and/or rare diseases?**

In recent years, the majority of the drugs in CDER's rare disease drug development programs are approved based on one adequate and well-controlled clinical investigation and confirmatory evidence.

FDA's medical product Centers collaborate through a variety of avenues to advance the development of rare disease therapies and disseminate our policy and experience with drug development through these avenues, including formal workgroups and training, guidance, internal meetings, and informal communications. FDA announced the creation of a Rare Disease Innovation Agenda, which will be based on a shared vision for advancing therapies for rare diseases. The Agenda will provide a single point of connection and engagement and enhance inter-center collaboration to address common scientific, clinical, and policy issues. In addition, Center policy offices work to foster internal consistency in regulatory review by working closely with the review divisions to help ensure that laws, regulations, and policies are applied consistently, with due regard for the particular facts and circumstances underlying each decision.

FDA review staff have robust mechanisms available for policy, training, and consultation regarding guidance and flexibility for the development of rare disease therapies. In rare diseases, for example, these approaches are the topic of our FDA Annual Reviewer Training Day and CDER Rare Disease Seminar Series and are a topic for discussion during Rare Disease Drug Development Council meetings.

a. **When does FDA intend to finalize this draft guidance?**

   FDA is reviewing comments submitted to the docket and is working on issuing the final guidance.

2. **Traditional clinical trial design may pose challenges for the study of rare diseases as patient pools are small and often geographically dispersed. Clinical trial challenges are further compounded in pediatric populations where participation may be especially burdensome for these populations. How is CDER thinking about new ways to define surrogate endpoints in trial design, particularly for meeting an unmet need via priority review, breakthrough therapy, accelerated approval, or fast track?**

   CDER works with CBER to continue to promote innovative clinical trial designs and endpoint discovery through our Rare Disease Endpoint Advancement (RDEA) Pilot Program. The RDEA Pilot Program is designed to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA

throughout the efficacy endpoint development process. RDEA also promotes innovation and evolving science by sharing learnings on novel endpoint development through FDA presentations, guidance documents, public workshops, and a public-facing website. Further, RDEA aims to develop FDA staff capacity to enable and facilitate the development and use of novel endpoints to evaluate the efficacy of rare disease therapies. Under the CDER Accelerating Rare disease Cures (ARC) Program, CDER formed a Translational Science Team (TST), a multidisciplinary group composed of experts and senior leadership from various offices within CDER. The TST collaborates with review teams to evaluate proposals for translational aspects of rare disease clinical trial design, such as surrogates, and helps to provide input to sponsors on these complex and challenging programs.

FDA has four generally applicable expedited programs that are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. These expedited programs are important tools in rare disease drug development. Between 2015 and 2023, 88% of CDER's novel rare disease drug approvals utilized at least one expedited program and 28% of these utilized accelerated approval, which allows an effect to be demonstrated on a surrogate endpoint that is reasonably likely to predict clinical benefit.

Platforms

3. **In May of 2024 the agency issued the Platform Technology Designation Program for Drug Development. How does FDA expect to staff the platform technology designation process to ensure capacity for review and approval of platform designation applications – in addition to current workflow of review requirements?**

    a. **How does the agency plan to proactively address any discrepancies between what the guidance recommends and what FDA reviewers accept?**

    Although additional funding for FTEs has not been provided, FDA is working to implement the Platform Technology Designation program. To ensure the capacity for review and designation of platform technology designation requests in addition to the current workflow, the FDA plans to implement several measures. Relevant offices across CDER and CBER have convened working groups to develop process guidelines, templates, and tools, including resources such as knowledge management databases. These

resources are designed to help reviewers make consistent and well-informed determinations.

b. Are there mechanisms to track successful implementation of the program?

We will periodically evaluate submissions received under the program and FDA's review of such submissions to assess implementation of the program and fulfill the statutory reporting requirements associated with the program. Section 2503(c) of the Consolidated Appropriations Act, 2023 included a requirement that the agency report on the following: (1) the number of requests for designation under the program; (2) the number of designations issued, active, and revoked; (3) the resources required to carry out the program (including the review time used for full-time equivalent employees); (4) any efficiencies gained in the development, manufacturing, and review processes associated with such designations; and (5) recommendations, if any, to strengthen the program to better leverage platform technologies that can be used in more than one drug and meet patient needs in a manner as timely as possible, taking into consideration the resources available to the Agency for carrying out such program.

c. Does the FDA plan to streamline the regulatory pathway to support a serial therapeutic strategy, particularly for monoclonal antibodies and antivirals, to protect the public against evolving pathogens of concern – similar to influenza vaccines?

FDA plans to continue to encourage efficiencies with respect to both the development of products and the potential regulatory pathways to protect the public against pathogens of concern. These efficiencies may vary depending on scientific considerations related to pathogen- and product-specific factors. In general, where feasible and scientifically appropriate, FDA will leverage available relevant data to speed development of safe and effective drugs to benefit the public health.

NRTs

4. At the recent Energy and Commerce Committee hearing you stated that CDER is interested and willing to work with developers on the issue of new tobacco cessation therapeutics. The agency's guidance sets forth that a trial is considered to demonstrate effectiveness if significantly more subjects achieve abstinence when treated with the investigational nicotine replacement therapy (NRT) drug product as compared to subjects treated with the placebo. The agency is defining abstinence as no cigarette use over the entire course of the efficacy ascertainment period, which depending on the

product, may be many months long. The agency has repeatedly acknowledged how hard it can be to quit because of the addictive qualities of nicotine and that often smokers seeking to quit relapse. Yet, under the agency's guidance, if a clinical trial participant relapses, even if just one time, and smokes just one cigarette they would be considered a non-responder in the trial even if over the course of the entire trial they were able to reach the cessation endpoint despite a relapse.

a. Is the "zero tolerance" relapse stance consistent with an easier and more efficient development pathway or helping patients to be able to benefit from safe and effective innovations in as timely a manner as possible?

A relapse is considered a return to smoking, whereas a "slip-up" is considered a pre-defined number of cigarettes that a subject might consume during the efficacy ascertainment (i.e. measurement) period of a clinical trial. CDER's NRT Guidance does not put forth a "zero tolerance" stance on slip-ups during the ascertainment period for a trial that is many months long. The Guidance states:

> In general, abstinence is defined as no cigarette use over the entire course of the efficacy ascertainment period by subject self-report and biological verification at intervals of approximately 1 to 2 weeks. A longer interval between self-reporting and verification visits may be acceptable in some instances (e.g., trials that are more than 3 months long). *For trials with longer efficacy ascertainment periods of 6 or 12 months, sponsors can consider defining abstinence to incorporate a maximum allowable number of cigarettes*. (Emphasis added).

With regard to reduction of risk in relapse, the NRT Guidance states:

> The clinical trials intended to support this maintenance indication should have the definition of relapse prespecified in the protocol, an ascertainment window, at a minimum, of 6 months to 1 year, and use the proportion of trial subjects not relapsing as the primary endpoint.[39]

Regarding the endpoint of abstinence, CDER previously recommended complete abstinence of 8-12 weeks for approval. Based on additional data on the shortest time period necessary to predict long-term abstinence, the new NRT guidance has reduced this timeframe to a minimum of 4 weeks as the

[39] For example, sponsors may consider a study design where treatment success is defined as smoking no more than five cigarettes during the efficacy ascertainment period. (Emphasis added).

shortest time frame that could still show health benefits. In addition, 4 weeks is the typical period necessary for the majority of nicotine withdrawal symptoms to subside.

b. Will the agency consider employing a real-world approach to its considerations of NRT products similar to the agency's approach to the development of other addiction therapies in which the agency has acknowledged the public health benefit of the reduction of use of such harmful and addictive substances?

Nicotine use disorder and other substance use disorders (e.g., opioid use disorder) are very different, even though they fall into the same general category of addictive disorders.

In the case of smoking cigarettes, we are concerned primarily with long-term health effects. Other addictive substances, e.g., opioids, have more consequential short-term effects (in addition to long-term effects), including the potential for single dose lethality. In addition, data do not support that reduction in smoking short of cessation leads to net positive clinical outcomes; however, we are eager to work with sponsors and other stakeholders to advance scientific understanding of novel endpoints demonstrating meaningful reductions in harms associated with smoking. These differences make shorter-term endpoints regarding reduction in use more clinically meaningful in the case of, for example, opioid use disorder than in the case of nicotine use disorder.

In general, different substance use disorders have different mechanisms of action and clinical effects that may lead to differences in clinical presentation and responses to treatment. As a result, study designs, patient populations, and endpoints may differ across therapeutic areas targeting different forms of addiction.

c. Is CDER holding new smoking cessation products to the same development framework as products being developed in other areas of addiction?

Please see the answer to Question 4b.

ACNU

5. On September 6th of last year, I wrote to you, along with Congressman Latta and Congresswoman Dingell, about your proposed rule on ACNU, Nonprescription Drug Product with an Additional Condition for Nonprescription Use. Particularly, the proposed concept of simultaneous marketing of both prescription and nonprescription versions of the same drug. There are concerns

that this interpretation contravenes previous law. Can you commit to addressing these concerns in the final rule?

Thank you for your follow-up comments concerning the proposed rule entitled, "Nonprescription Drug Product with an Additional Condition for Nonprescription Use."[40]

As you are aware, FDA issued this proposed rule in the *Federal Register* on June 28, 2022 (87 FR 38313). If finalized, the proposed rule would establish requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU). Public comments were due to the docket (Docket No. FDA-2021-N-0862) by November 25, 2022.[41]

Under the proposed rule, an applicant would be required to explain why the ACNU is necessary to ensure appropriate self-selection or appropriate actual use, or both, by consumers of the nonprescription drug product. The applicant would have to explain why labeling alone cannot be sufficient for meeting the approval requirements as a nonprescription drug product (proposed 314.56(c)(1)(ii), proposed 314.56(c)(1)(v), and 87 FR 38320). In addition, FDA proposed that an applicant would be required to submit a separate application for a nonprescription drug product with an ACNU (proposed § 314.56(b) and 87 FR 31318). For cases where there is an approved prescription drug product, we proposed that a nonprescription drug product with an ACNU could not be approved through a supplement to the approved application for prescription use of the drug product. Section 503(b)(4) of the FD&C Act allows simultaneous marketing of drug products with the same active ingredient as prescription and nonprescription if some meaningful difference exists between the drug products that makes the prescription product safe and effective only under the supervision of a healthcare practitioner licensed by law to administer the drug (87 FR 31321; see also 83 FR 13994, April 2, 2018; see also 70 FR 52050, September 1, 2005). Therefore, we proposed to establish that because the ACNU would allow the nonprescription drug product to be used safely and effectively without the supervision of a healthcare practitioner, the ACNU itself would be a meaningful difference between the prescription drug product and the nonprescription drug product with the ACNU. Thus, as proposed, a prescription drug product and a nonprescription drug product with an ACNU that contain the same active ingredient could be simultaneously marketed even if they do not have other meaningful differences, such as different indications or strengths (proposed § 314.56(d) and 87 FR 31322).

[40] https://www.federalregister.gov/documents/2022/06/28/2022-13309/nonprescription-drug-product-with-an-additional-condition-for-nonprescription-use

[41] https://www.regulations.gov/docket/FDA-2021-N-0862/comments and 87 FR 64178

In cases where there is an approved prescription drug product, the requirements would create a pathway for the simultaneous marketing of the prescription drug product, along with the nonprescription drug product with an ACNU. Continued access to the prescription drug product, along with availability of the nonprescription drug product approved with an ACNU, would ensure greater access to needed drugs by providing flexibility in how to obtain them (see 87 FR 38319).

In your recent comments, you continue to express concern that simultaneous marketing of both the prescription drug product and the nonprescription drug product with an ACNU would create possibilities for confusion. We note that similar comments were submitted in the docket for the proposed rule. We carefully consider public comments received as we work to finalize the proposed rule.

The Agency appreciates your continued interest and comments concerning this proposed rule.

The Honorable Troy Balderson

Patient-focused Drug Development

1. **The FDA must consider the patient voice when reviewing new therapies. Congress passed the Patient Focused Impact Assessment Act as a part of the 21st Century Cures Act, which has accelerated the patient-focused drug development (PFDD) process. PFDD ensures patients' perspectives, needs, and priorities are captured and meaningfully incorporated in drug evaluation. FDA has provided patient groups and industry with guidance on how to appropriately collect and use patient experience data. People with lived disease experience, advocacy groups, and industry are investing significant time, energy, and resources into developing this data. What steps is CDER taking to ensure that the PFDD guidance is being utilized consistently across the divisions to incorporate patient experience data into product development and regulatory decision-making?**

   FDA review staff across review divisions have robust mechanisms available for policy, training, and consultation regarding patient-focused data and applicable guidance.

   As this relates specifically to patient focused drug development (PFDD) and patient experience data, the patient voice is most impactful when it is incorporated throughout medical product development. For example,

through PFDD meetings and rigorous qualitative work, patients can inform potential targets for therapies and clinical trial endpoints. Patient input can provide important information about what patients consider a meaningful change in their condition, can help inform clinical trial design and conduct, can provide important information about what it is like for them to live with and manage their condition, and can help regulators and others to understand where areas of unmet need exist. Clinical Outcome Assessments (COAs) such as Patient Reported Outcome (PRO) measures may be used as endpoints in clinical trials, and patient preference studies can provide important information on how patients view benefit-risk tradeoffs.

During the IND phase of drug development, the Patient Focused Statistical Scientists and the Division of Clinical Outcome Assessments work with the clinical review divisions to ensure that recommendations provided to sponsors are consistent with the PFDD guidance documents and that sponsors are aware of PFDD resources. When a marketing application is submitted, the same groups continue to work with the clinical review divisions as the review of clinical outcome assessments, patient preference studies, and other data are conducted.

As noted in the question above, to advance the incorporation of the patient voice, FDA has developed a series of four methodological patient-focused drug development guidance documents to address, in a stepwise manner, how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers for medical product development and regulatory decision making.

As part of the issuance of the guidance documents, CDER has led the conduct of training webinars for the public and for FDA staff.[42] CDER has developed intranet staff resources and provides updates and trainings as necessary.

To increase staff awareness of existing patient experience data, PFDD staff review the proposed indications of incoming marketing applications and reach out to review staff to ensure that they are aware that patient-experience data from PFDD meetings or Patient Listening sessions exist for the application they are reviewing. PFDD staff also maintain a publicly available website of these reports, as well as other condition-specific patient experience data.[43]

[42] See: https://www.fda.gov/drugs/news-events-human-drugs/public-webinar-patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose *and* https://www.fda.gov/drugs/news-events-human-drugs/public-webinar-patient-focused-drug-development-incorporating-clinical-outcome-assessments-endpoints

[43] https://www.fda.gov/industry/prescription-drug-user-fee-amendments/condition-specific-meeting-reports-and-other-information-related-patients-experience

Shortages

2. **I understand that there have been recent shortages of insulin. I've heard from my constituents who have Type 1 Diabetes (T1D) or have children with T1D. They are very troubled by this. Are insulin manufacturers required to report insulin shortages to the FDA?**

   Insulin is not currently listed as in shortage on FDA's drug shortages list, but we were made aware of manufacturer Eli Lilly's discontinuation in March 2024 of their 3 ml vials of both Humulin R and Humalog insulin. Eli Lilly reports their 10 ml vials continue to be available as an alternative for the Humulin R insulin and their 10 ml vials and KwikPens remain available as an alternative for the Humalog insulin. We have continued to be in communication with Eli Lilly as well as the other insulin manufacturers for how we can assist with helping to ensure ongoing supply.

   Since the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, manufacturers, including insulin manufacturers, have been required to notify FDA of changes in the production of certain finished drugs and biological products that may, in turn, help the Agency in its efforts to prevent and mitigate shortages. Currently, applicants and manufacturers of certain finished prescription drug or biological products must notify FDA of:

   - A permanent discontinuance in the manufacture of such drug and biological products
   - An interruption in the manufacture of such drug and biological products that is likely to lead to a meaningful disruption in supply of the product in the United States
   - A permanent discontinuance in the manufacture of active pharmaceutical ingredient (API) for such drug and products
   - An interruption in the manufacture of API for such drug and biological products that is likely to lead to a meaningful disruption in the supply of the API for those products

   a. **And what does the FDA do with this information?**

      FDA responds to potential drug shortages by taking actions to address their underlying causes and to enhance product availability. FDA determines how best to address each shortage situation based on its cause and the public health risk associated with the shortage.

      For manufacturing/quality problems where the manufacturer reports a potential or actual shortage to FDA, FDA works with the firm to address the shortage. Problems can vary in significance, such as relatively low risk problems (e.g., minor error on the label) to high risk (e.g., particulate in product, sterility issues). Regulatory discretion may be employed for a drug

to be distributed to address shortages after additional controls are implemented to mitigate significant risk to patients as needed.

FDA also works with other firms making the drugs that are in shortage to help them ramp up production if they are willing to do so. Often, they need new production lines approved or need new raw material sources approved to help increase supplies. FDA can and does expedite review of these to help resolve shortages of medically necessary drugs. FDA can't require the other firms to increase production.

When a shortage occurs and a firm has inventory that is close to expiry or already expired, if the company has data to support extension of the expiration dating for that inventory, FDA is able to review this and approve the extended dating to help increase supplies until new production is available.

FDA also collaborates with members of the HHS Supply Chain Resilience Working Group such as the HHS Supply Chain Resilience Coordinator, ASPR, and other operating divisions of HHS on other steps to resolve shortages as quickly as possible.

PDUFA

FDA Clarification: CDRH is not part of PDUFA, as such, Dr. Cavazzoni has responded to the questions below.

1. **Strict security requirements result in a restricted pool of vendors who can provide FISMA approved solutions. This smaller pool of vendors means higher costs for products and services as the FDA has less negotiation power during the selection phase. This limits the overall technical innovation due to lower variety in solution selection. How does FDA plan to effectively balance the need for stringent security requirements and meeting the PDUFA VII commitments?**

   To ensure we meet our PDUFA VII commitments, FDA will effectively balance and sustain our technology and innovation excellence by partnering with industry-leading vendors while ensuring high standards of compliance with Office of Management and Budget (OMB), Federal Information Technology Acquisition Reform Act (FITARA), Federal Information Security Management Act (FISMA), Federal Risk and Authorization Management Program (FedRAMP), and other federal government security requirements to prevent and protect against foreign nation state threats and other nefarious cyber threat actors.

   a. **Can you elaborate on FDA's plans to put out an RFP for third-party**

vendors?

FDA follows government procurement procedures for a request for proposal (RFP), as managed for the Agency's Office of Acquisition and Grants (OAGS). To meet PDUFA VII commitments, FDA has incorporated those requirements with existing procurements such as for the Information Request (IR) demonstration project as well as targeted procurements such as the Pharmaceutical Quality Knowledge Management (PQKM) demonstration project to support the requirements. Additionally, FDA has used public comment received pursuant to Federal Register notices to incorporate input from third parties, consistent with its PDUFA commitment of establishing FDA's Data and Technology Modernization Strategy.

b. What is the projected timing?

For projects in progress such as the Electronic Submissions Gateway (ESG) modernization, Information Requests (IR) demonstration project and Pharmaceutical Quality Knowledge Management (PQKM) demonstration project, those contracts have already been awarded to vendors, and the projects are in progress. For awareness and transparency, FDA shares the timelines and milestones with PDUFA stakeholders on an ongoing basis.

2. PDUFA VII states that, within 6 months of completion of a demonstration project, the FDA must compile a summary of outcomes and next steps and share with industry at the regularly scheduled FDA-industry meetings. What measures will FDA put in place to encourage engagement and feedback from industry?

FDA uses the quarterly scheduled FDA-industry meetings to provide interactive updates on the demonstration projects. These meetings include detailed solution demonstrations and interactive discussions with FDA leadership and industry representatives, such as the meeting on Oct 8, 2024, for the IR demonstration project. For the PQKM demonstration project, industry representative input has been incorporated in the project, and industry representatives actively participate in supporting deliverables for that demonstration project.

a. What can industry expect after the demonstration projects have concluded?

FDA will ensure its commitment to provide written recommendations on outcomes and next steps for all of its demonstration projects. Specifically, within six months of completion of a demonstration project, a summary of outcomes and next steps will be compiled and shared with industry at the regularly scheduled FDA-industry meeting. FDA will also post the information on its website.

3. **Are there barriers that are delaying or impacting FDA's ability to formally select additional demonstration projects for the regulatory information exchange reforms?**

   FDA plans to propose two additional demonstration projects that address regulatory information exchange reforms at its quarterly meeting on October 8, 2024. We currently do not anticipate any barriers to proceeding with these projects.

   a. **Does FDA plan to engage going forward with Industry on demonstration project selection?**

      FDA will continue to consult industry to ensure input from industry on demonstration project selection. Through progress updates and discussions at the FDA-Industry quarterly meetings, FDA will gather feedback and provide plans that include industry's participation in those projects.

The Honorable Diana Harshbarger

Rare Disease

1. **FDA has initiated several initiatives to facilitate and improve rare disease development, such as the CDER Rare Diseases Team, the CDER Accelerating Rare disease Cures (ARC) program, the CDER-CBER Rare Disease Endpoint Advancement (RDEA) pilot program, the CBER Rare Disease Coordinating Committee, the CBER Support for Clinical Trials Advancing Rare disease Therapeutics (START) pilot program, and the Bespoke Gene Therapy Consortium. How do you plan to leverage the lessons learned from these initiatives to broadly improve the development and review of treatments for rare diseases?**

   FDA regularly leverages lessons learned from our rare disease initiatives and translates them into our education and engagement for both FDA staff and the rare disease community. FDA review staff attend programs such as Rare Disease Annual Reviewer Training on topics such as the use of translational science to construct confirmatory evidence and programs such as CDER ARC's Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) is developing educational content based on lessons learned for the rare disease drug development community.

   . Many of those lessons led FDA to announce the creation of a Rare Disease Innovation Agenda, which will be based on a shared vision for advancing therapies for rare diseases. The Agenda will provide a single point of connection and engagement with the rare disease community and enhance inter-center

collaboration to address common scientific, clinical, and policy issues. It will leverage expertise across the Agency to advance regulatory science on key issues critical to rare disease development programs, including novel endpoints, biomarker development, and innovative trial designs, while also enhancing collaboration ..

Rare Disease Trials

2. **We can all agree that bringing new therapies to people living with rare diseases, especially children, is very challenging, but incredibly important, work. Could you explain to the committee how CDER and other FDA stakeholders are coordinating on rare disease clinical trial designs, understanding and appreciating that developing appropriate study endpoints is challenging given extremely small patient populations?**

   Novel endpoint development is a critical component for a rare disease drug development program. CDER works with CBER to continue to promote innovative clinical trial designs and endpoint discovery through our joint PDUFA VII Rare Disease Endpoint Advancement (RDEA) Pilot Program. The RDEA Pilot Program is designed to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process. RDEA also promotes innovation and evolving science by sharing learnings on novel endpoint development through FDA presentations, guidance documents, public workshops, and a public-facing website. Further, RDEA aims to develop FDA staff capacity to enable and facilitate the development and use of novel endpoints to evaluate the efficacy of rare disease therapies.

3. **There are long timelines associated with the identification of relevant biomarkers for a rare disease. There is also an increased need for public-private partnerships that allow developers and regulators to learn more about biomarkers and their mechanisms. Does the FDA have a plan to address the importance of data sharing, a uniform approach to data collection, and collaboration with rare disease drug developers?**

   CDER acknowledges the challenges associated with the identification of biomarkers that can be used to support the development of rare disease therapies, particularly where the pathophysiology may not be well defined and the relationship between a biomarker and clinical outcome is not well-established. CDER currently participates in multiple public-private partnerships as collaboration can be very helpful in rare disease drug development, including the appropriate selection of biomarkers.

   FDA additionally supports standardization for data collection and a cooperative approach to build clinical trial readiness. To this end, CDER was instrumental in

supporting the development and expansion of the Rare Disease Cures Accelerator - Data Analytics Platform (RDCA-DAP). The RDCA-DAP provides an integrated database and analytics hub designed to promote the secure sharing of existing patient-level data and encourage the standardization of new data collection. Multiple stakeholders, including drug developers, can contribute to and access this database. This database allows authorized users to access patient-level clinical data for a particular rare disease, which may be analyzed to better understand disease progression and the disease heterogeneity across the affected patient population. This in turn can inform trial design, including the characterization and selection of biomarkers and other important considerations for drug development.

RDCA-DAP now contains data for 34 different rare disease areas, including Polycystic Kidney Disease, Duchenne Muscular Dystrophy, mitochondrial diseases, neurodevelopmental disorders, rare epilepsies and rare neurodegenerative disorders, including Friedreich ataxia. We anticipate more data will be added and made accessible as outreach efforts continue. C-Path has partnered with the National Organization for Rare Disorders (NORD) to leverage its IAMRARE® registry platform and extensive expertise to help identify data contributors and establish contacts with the contributing organizations.

FDA will continue to engage with CPATH and other stakeholders to advance development of new biomarkers, including with NIH through the new Accelerated Medicines Partnership for ALS, which is also collaborating with CPATH on data sharing activities and has a particular focus on biomarker identification.

4. **Approving a new drug requires both "substantial evidence of effectiveness" and a conclusion that a drug's benefits outweigh its risk. Do you believe that the FDA should have the authority to approve drugs which have a positive benefit or risk profile even if there is not substantial evidence of effectiveness, especially for life-threatening diseases where there is no other option for the patient?**

No. Even if a drug is relatively safe, it can still cause great harm to patients if it is ineffective. Ineffective drugs can divert or delay patients from taking therapies that are effective for their disease or condition. An assessment of benefit and risk requires that there be adequate evidence to assess effectiveness. FDA has and does exercise flexibility in determining the data and information necessary to demonstrate effectiveness, including through the Accelerated Approval program which allows for earlier approval of drugs that treat serious conditions and fill an unmet medical need, based on a surrogate endpoint..

We understand that there are significant unmet needs but the difficulty in drug development for patients with serious illnesses often lies in the lack of scientific understanding of their diseases, which can make it challenging to identify appropriate clinical or surrogate endpoints and design appropriate trials. Better science is integral to better drug development (e.g., learning which pathways to target with therapy), better study design (e.g., identifying appropriate endpoints), and better use of existing innovative tools (e.g., digital health technologies). Investment in these areas will better serve patients rather than lowering evidentiary standards and providing unproven drugs.

Acetaminophen Dosing

5. **Acetaminophen is one of the most commonly used over-the-counter (OTC) medicines for the safe and effective treatment of fever and pain in children, with 80 percent of children experiencing an antipyretic effect within 30 to 60 minutes if properly dosed. In fact, one study indicates that "as many as 95 percent of children are exposed to acetaminophen by age 9 months. Although widely used in the pediatric population, dosing varies widely based on age, body weight, and other factors. This issue is compounded for very small children below two years of age.**

   For years, weight-based dosing information for acetaminophen for children ages six months to two years has been available from several sources, including the American Academy of Pediatrics. Instead, the label instructs parents and caregivers to consult a physician on proper dosing. For many parents and others caring for young children, consulting a physician is burdensome, especially in rural areas where access to providers is limited or when pain or fever occur outside of normal business hours. The lack of readily available information places parents and caregivers in a difficult situation – either being forced to seek additional medical care with an associated cost and time burden, or risk giving a child an inappropriate dose of medicine. Parents and caregivers need accurate and accessible dosing information to help prevent dosing errors, adverse events, and inadequate treatment of fever and pain.

   Over a decade ago, the FDA Nonprescription Drugs Advisory Committee and Pediatric Advisory Committee recommended weight-based dosing instructions be added to the labeling based on scientific data. Despite these conclusions, weight-based dosing information for young children has still not been added to the acetaminophen label. Even with new authorities granted under the Coronavirus Aid, Relief, and Economic Security (CARES) Act that reformed the outdated system for updating monographs for OTC products to a more expeditious administrative order process, FDA

has not taken action.

Given that evidence-based information has been available for decades to inform weight- based dosing instructions for young children, why has FDA not used its authorities under the CARES Act to add this information to the acetaminophen label per the recommendations of the Agency's own Advisory Committees?

FDA took an important foundational step on October 14, 2022, in posting the deemed final order, under section 505G of the FD&C Act, setting forth Over-the-Counter Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (OTC Monograph M013), which addresses labeling of OTC monograph acetaminophen products.[44] Additionally, FDA is actively working on updates regarding pediatric acetaminophen dosing, to propose as changes to OTC Monograph M013. Specifically, FDA is working on a proposed safety-related order on pediatric acetaminophen dosing that addresses dosage strengths of oral, single-ingredient pediatric acetaminophen products, and will propose adding weight- and age-based dosing for children under the age of 12. The Agency has included the proposed safety order on its publicly available Annual Forecast for Planned Monograph Activities, which covers a three-year horizon.[45]

NRTs

6. **More than 8.6 million Americans have died from smoking since the last new product was authorized by CDER for smoking cessation. That is a public health tragedy. What more can and should CDER do to stimulate the interest of sponsors to come to you with truly innovative products to reduce the death toll from what remains the leading cause of preventable deaths in our country?**

   As tobacco dependence results in many serious or life-threatening conditions (e.g., heart and lung disease and cancer), FDA recognizes there is an unmet need for novel therapies particularly for individuals who have not been able to quit despite available therapies.

   Because we consider nicotine dependence to be a serious or life-threatening condition with an unmet medical need, in the 2023 final NRT guidance, we are encouraging development of novel smoking cessation drug therapies that show benefit over existing products by ensuring manufacturers are aware of the expedited development pathways such as fast track, breakthrough, and priority review and encouraging them to discuss eligibility with the agency.

[44] https://dps.fda.gov/omuf/ordersearch/order_otc000027
[45] https://dps.fda.gov/omuf/forecast

In addition, because the data are so strong in demonstrating that quitting smoking can lower a person's chance of having lung disease, heart disease, and certain types of cancer, our guidance for industry, *Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy [NRT] Drug Products,* published in May 2023, states that for NRT drug products that have demonstrated effectiveness for cessation or reduction in risk of relapse, sponsors do not need to provide additional data to include information in the labeling about the therapeutic benefits of smoking cessation or maintaining abstinence from cigarettes. Labeling of this nature without the requirement of a large outcomes trial still allows the sponsor to promote the long-term benefits of quitting with its specific drug product. Including this in a guidance is a very unusual step for FDA to take to further drug development in an area and is another indicator of how important we think this is.

To support the majority of smokers who wish to quit and to increase utilization of cessation products and interventions, FDA and NIH are collaborating to identify treatment gaps and opportunities for the development of novel therapies, support innovative trial designs, and facilitate product development for smoking cessation therapies. Opportunities for innovation exist in many areas including collaboration with researchers to help identify novel targets, use of innovative clinical trial design and conduct, inclusion of individuals underrepresented in research, developing a better understanding of quit failures and relapse, and utilizing FDA's expedited programs for medical product development.

AMR

7. **It is my understanding that recent studies show ***none*** of the new antimicrobials approved over the last decade by the FDA improve patient outcomes for those who are enrolled in those studies. Can you please explain why FDA is not requiring studies that evaluate whether new drugs are actually ***better*** for those enrolled in the studies and patients like them?**

   For approval of all new drug applications, FDA approves a drug based on a finding of substantial evidence of effectiveness and a demonstration of safety at the time of approval, which collectively, must support a determination that the benefits of using the drug outweigh its risks for the drug's proposed use(s). Generally, substantial evidence comes from two or more adequate and well-controlled clinical investigations or one adequate and well-controlled clinical investigation plus confirmatory evidence when the Agency deems such an approach is appropriate.

   Clinical trials conducted for approval of new antimicrobial drugs, including antibacterial and antifungal drugs, are designed to demonstrate clinical benefit to the patient. Primary endpoints recommended by FDA for trials of new drugs to treat serious or life-threatening infectious

diseases include: improvement or resolution of symptoms, improvement or resolution of symptoms and a negative culture, or survival.

We will always have to address the issue of antimicrobial resistance. By nature, pathogens evolve and adapt and eventually develop resistance to antimicrobial agents. While approved antimicrobials are highly effective at treating susceptible pathogens, we need new therapeutic options to treat antimicrobial resistant pathogens for which we have few or no effective therapies, and we will continue to need new therapeutic options in the future. FDA is dedicated to addressing the challenges of antimicrobial resistance by helping to preserve the effectiveness of currently available antimicrobial products and promoting the development of new medical products that can help reduce the emergence and spread of antimicrobial resistant pathogens.

Non-inferiority trials are an appropriate trial design to study new antimicrobial drugs for the treatment of serious diseases for which a treatment effect for a clinically meaningful endpoint can be established, and no treatment (or a delay in treatment) would be neither safe nor ethical. Non-inferiority trials are active-controlled trials designed to demonstrate that a new drug is not materially worse than the drug(s) used in the control arm. Because approved, standard-of-care antimicrobials are highly effective at treating susceptible pathogens, it may be difficult to statistically demonstrate clinical superiority of a new drug over the standard-of-care unless the trial enrolled only patients with infections resistant to the standard-of-care.

Conducting superiority trials that enroll only patients with serious infections caused by resistant pathogens is often quite challenging and would likely delay the availability of a safe and effective drug for patients with unmet medical need. While antimicrobial drug resistance is an important public health problem, a particular type of resistance that a new drug is developed to address may not currently occur with sufficient frequency for a clinical trial to be feasible. In addition, there can be a delay of a couple of days before culture and resistance testing results are available for a patient. Therefore, the test drug and the active comparator used in a trial should be expected to be effective to treat the patient's infection at the time they are enrolled in the trial. A properly designed non-inferiority trial enrolling patients who have the same disease as those patients with a resistant pathogen can provide evidence of efficacy for a new antimicrobial drug, and the trial can be completed before widespread resistance to the standard-of-care therapy develops.

a. How can we address antimicrobial resistance if the drugs do not improve patient outcomes?

- **The studies to which I refer are the following:**
  - **https://bmjmedicine.bmj.com/content/1/1/e000227**
  - **https://www.acpjournals.org/doi/abs/10.732 6/M16- 0291?journalCode=aim**

See above.

Drug Trials and Approvals

8. **Does the FDA approve drugs based on "test tube" tests and animal studies? If so, please specify on what regulatory basis FDA is empowered to approve drugs on this basis in the absence of substantial evidence.**

    - **I note a recent BMJ investigation showing FDA did not follow its own rules in approving a new antimicrobial called Recarbrio.**
      - **Link: https://www.bmj.com/content/381/bmj.p1048**

    FDA generally does not approve drugs based on in-vitro and pre-clinical studies alone. Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), drug sponsors must provide substantial evidence of effectiveness that the drug will have the effect it purports or is represented to have. Generally, substantial evidence comes from two or more adequate and well-controlled clinical investigations or one adequate and well-controlled clinical investigation plus confirmatory evidence when the Agency deems such approach appropriate. FDA has provided comprehensive considerations regarding the demonstration of substantial evidence in the 1998 guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, and the 2019 draft guidance for industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.*

    Of note, when scientifically justified and legally permissible, an applicant can rely, in part, on its previous finding of safety and/or effectiveness for an approved drug to support a demonstration that a drug will have the effect it purports or is represented to have, thus not requiring additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of evidence provide a way to apply the known finding of effectiveness to a new population or a different dose, regimen, or dosage form. For example, a section 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference or use, including, for example, the Agency's finding of safety and/or effectiveness for a listed drug or

published literature. FDA's determination of the substantial evidence of effectiveness of Recarbrio via a section 505(b)(2) application was supported in part by the previous finding of effectiveness for imipenem/cilastatin for the treatment of complicated urinary tract infections and complicated intra-abdominal infections. Recarbrio includes imipenem, cilastatin, and relebactam as a fixed-combination drug product. Relebactam is a new beta-lactamase inhibitor. Relebactam alone does not have antibacterial activity; it prevents degradation of imipenem by enzymes produced by some resistant bacteria. As relebactam cannot be studied as monotherapy in the clinical condition of interest, the contribution of relebactam was assessed in vitro and in animal models of infection, consistent with 21 CFR 300.50 and Agency guidance.

9. Can you please confirm that "Subpart E" regulatory authority (21 CFR 312.80) provides that "the statutory standards of safety and effectiveness apply to all drugs"?

The language quoted in this question is part of language that appears in FDA regulations at 21 CFR 312.80, included under 21 CFR Part 312, Subpart E (Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses). However, the quote is not complete. The language quoted is included as part of the following language from Sec. 312.80:

> "*while the statutory standards of safety and effectiveness apply to all drugs*, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated." (emphasis added)

10. Current law and FDA regulations usually reserve expedited approvals for drugs which improve patient outcomes over available therapies. Can you explain why this is not being done for new antimicrobials?

FDA's expedited programs – fast track designation, breakthrough therapy

designation, accelerated approval, and priority review designation – are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of serious or life-threatening conditions. Each program has specific qualifying criteria and features. Antimicrobial agents may qualify for fast track, breakthrough, accelerated approval, or priority review, and are held to the same standards as drugs that treat non-infectious conditions. For additional information on these programs, please refer to FDA's guidance for industry, *Expedited Programs for Serious Conditions - Drugs and Biologics* (May 2014).

In addition, there is a streamlined development program specific to certain antimicrobial agents: the limited population pathway for antibacterial and antifungal drugs (LPAD). FDA believes the LPAD pathway will facilitate development and approval of certain antibacterial and antifungal drugs to treat serious or life-threatening infections in limited populations of patients with unmet needs. We expect that development programs for drugs eligible for approval under the LPAD pathway will follow streamlined approaches to clinical development. This may involve smaller, shorter, or fewer clinical trials. For further information, please refer to FDA's final guidance for industry, *Limited Population Pathway for Antibacterial and Antifungal Drugs* (August 2020), available at https://www.fda.gov/media/113729/download.

We note further that many antibacterial and antifungal drugs for serious or life-threatening infections meet the criteria for Qualified Infectious Disease Product (QIDP) designation. The first application or efficacy supplement designated as a QIDP that requires clinical data (other than bioavailability studies) to demonstrate safety or effectiveness is granted priority review pursuant to section 524A of the FD&C Act, regardless of whether the usual criteria for priority review are met. Similarly, QIDPs are eligible for fast track designation pursuant to section 506(b)(1) of the FD&C Act.

FDA has also provided its current thinking about possible development programs and clinical trial designs for antibacterial drugs to treat serious bacterial diseases in patients with unmet medical need. See the guidance for industry, *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases* (August 2017). The agency has also issued a draft guidance that is intended to assist sponsors in the clinical development of new antibacterial drugs, and provide updates to the options for development programs, given the availability of some new therapeutic options. *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers* (Revision 1 – May 2022).

11. Can you explain why current trials that are being done in infections exclude the patients with the greatest unmet needs such as those with immunocompromise and those with infections from resistant organisms to older drugs?

Answer below

a. How does this justify the increased cost of these new drugs if they are not studied in the patients who need them most in practice?

Whether the benefits of enrolling in a study outweigh the potential risks is a primary consideration for determining eligibility criteria, and ethical considerations may lead to the exclusion of certain patients.

There are specific considerations for enrolling patients in clinical trials conducted for new antimicrobial drugs. Superiority trials enrolling only patients with serious infections caused by resistant pathogens are very challenging to conduct. While antimicrobial drug resistance is an important public health problem, a particular type of resistance that a new drug is developed to address may not occur with sufficient frequency for a clinical trial to be feasible. If a superiority trial is feasible that is dependent upon having a less effective comparator because resistance to all existing therapies has developed, then we are in a situation where drug development (despite stewardship and infection control efforts) has not kept up with emerging resistance. This is a situation most would prefer to avoid.

As new treatment options have become available, it is now possible to conduct noninferiority trials that include subjects with infection caused by certain antibacterial drug-resistant phenotypes of interest that are susceptible to both the active comparator and the study drug. FDA has addressed this topic, and the conduct of nested noninferiority/superiority trials when a sufficient number of subjects with infection caused by bacteria resistant to the active comparator are expected to be enrolled in the trial in its draft guidance, *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers* (May 2022).

With respect to patients who are immunocompromised, there are a number of serious infectious diseases that often occur in immunocompromised patients, and immunocompromised patients are the majority of participants in trials of new antimicrobial drugs to treat those diseases, e.g., trials to assess new antifungal drugs for the

treatment of invasive aspergillosis. FDA continues to dialogue with interested parties regarding data needs for the care of immunocompromised patients. For example, this topic was discussed at a recent public workshop sponsored by FDA. See https://www.fda.gov/drugs/news-events-human-drugs/drug-development-considerations-empiric-antibacterial-therapy-febrile-neutropenic-patients-04232024.

Compounded Bioidentical Hormones

12. Compounded bioidentical hormones are preferred by millions of women going through menopause, yet the FDA seems to be considering a ban on these medicines. Will the Agency prioritize women's preferences and consider the ample evidence supporting the safety and efficacy of compounded bioidentical hormones, rather than relying solely on randomized controlled trials — which are required for drug approval, but are NOT required for compounded medicines?

Compounded drug products marketed as "bioidentical hormone replacement therapy" (BHRT) are sometimes used instead of FDA-approved drug products indicated for hormone replacement therapy. Some compounders market compounded BHRT products as superior to FDA-approved drugs by making assertions that they are more natural or safer or better for patients than FDA-approved drug products. However, because compounded BHRT products are not FDA-approved, these products have not undergone an FDA assessment of safety, effectiveness, or quality prior to marketing.

To examine the issues raised by the use of compounded BHRT products, FDA asked the National Academies of Sciences, Engineering, and Medicine (NASEM) to appoint an ad hoc committee to study the clinical utility of treating patients with compounded BHRT products. The committee also reviewed which populations may benefit from the use of these preparations and considered whether the available evidence supports their use to treat patients. The committee issued its report, "The Clinical Utility of Compounded Bioidentical Hormone Therapy," in July 2020.[46]

According to NASEM, their reports aim to provide independent, objective expert advice. NASEM held six open-session meetings for the Committee on Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy. These meetings provided an opportunity for the committee to gather data and contextual information from relevant BHRT compounders and medical professionals.

[46] https://www.nationalacademies.org/our-work/clinical-utility-of-treating-patients-with-compounded-bioidentical-hormone-replacement-therapy

FDA has not issued a "ban" on compounded bioidentical hormones. When developing Agency policies, FDA intends to consider relevant information, which, in relation to BHRT products, would include the NASEM report and stakeholder comments, including ones regarding patient access concerns. Moreover, before implementing a new policy, the Agency generally provides an opportunity for public comment.

The Honorable Mariannette Miller-Meeks, M.D.

Anti-Obesity Drugs

1. **Dr. Cavazzoni, some believe that obesity is a serious chronic disease that affects more than 100 million Americans. The Centers for Disease Control and Prevention (CDC) has stated that obesity is an epidemic in the United States. Since being obese and overweight are major risk factors for a broad range of chronic diseases including diabetes, the increase in their prevalence across the nation has major implications for the health and well-being of the country. In 2007, the Food and Drug Administration (FDA) released draft guidance for industry developing products for weight management, which included recommendations regarding the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research (CDER) for the indication of weight management. In 2023, this draft guidance was listed on the Agency's review list. In light of the changes in the medical community's understanding of obesity and the drugs used to treat those living with obesity, including obesity being designated as a disease in 2013, and the approval of newer, safer, and more effective drugs, does the agency believe it is important to distinguish between weight loss drugs for cosmetic purposes and anti- obesity medications (AOMs)?**

   For decades, FDA has recognized that obesity is a chronic disease characterized by excess body fat (adiposity), and that excess adiposity is associated with an increased risk of death and an increased risk for conditions such as type 2 diabetes mellitus, high blood pressure (hypertension), abnormal cholesterol (dyslipidemia), cardiovascular disease (e.g., heart attack), nonalcoholic steatohepatitis ("fatty liver disease"), gallbladder disease, arthritis of the knee, sleep apnea, and some cancers.

   In individuals with obesity or who are overweight, particularly individuals with hypertension, dyslipidemia, and type 2 diabetes, long-term weight loss greater than or equal to 5% of baseline body weight or body mass index (BMI) following diet, exercise, and, in some cases, drug treatment, is associated with improvement in blood pressure, cholesterol levels, and blood sugar. Furthermore,

pharmacologic induced weight loss with one drug has been associated with a reduced risk of major cardiovascular events. Additionally, some observational studies suggest that modest intentional weight loss in individuals with obesity and overweight can reduce the incidence of some cancers, cardiovascular disease (e.g., heart attack), and death.

Importantly, there are no FDA-approved drugs for cosmetic weight loss. The draft *Guidance for the Clinical Evaluation of Weight-Control Drugs* (1996) and its first revision *Developing Products for Weight Management* (2007) provide recommendations to industry regarding the development of drugs intended to be used for medical weight loss. FDA has only approved weight loss drugs for the purpose of medical weight loss, with a goal of reduced morbidity and mortality, in adults and children with obesity and in adults who are overweight in the presence of at least one weight-related comorbidity. In addition to evaluating changes in body weight or BMI, clinical trials of weight loss drugs have also evaluated blood pressure, cholesterol levels, and blood sugar levels to assess their effects on these risk factors for cardiovascular disease.

Questions on MA Medicaid program mistakenly included, not for Dr. Cavazzoni

2. When you were the Medicaid director of Massachusetts, I am sure you had a lot of people seeking care from out-of-state. Boston Children's is one of the premier children's hospitals, and I know kids from all over the country fly there to get care. I have a bill with Representative Trahan, the Accelerating Kids Access to Care Act, which would reduce burdens associated with providers enrolling in other state Medicaid programs to ensure they can more easily be reimbursed for the out-of-state child's care, increasing the ability to get care in a timelier manner. Can you speak to the burdens that you saw during your time in Massachusetts and whether it was difficult for doctors to deliver care to kids from other states?

Third Party Logistics Providers

3. **As we are discussing how the United States can continue to lead in the development of cutting-edge biomedical innovations, we must address the supply chain that moves medications and health supplies from manufacturers to the patients in need. Third-party logistics providers (3PLs) play a key role in the reliability of medical supply chains by moving healthcare goods safely and quickly across the country, often with temperature and time restrictions. To ensure healthcare goods are moved safely, Congress passed the Drug Supply Chain Security Act (DSCSA) in 2013, requiring the FDA to create national standards for the licensure of 3PLs. However, to date final regulations have yet to be released.**

a. **Can you share insight into when the FDA expects to finalize the pending third- party logistics providers regulations?**

Following an extension to the comment period for the proposed rule 'National Standards for the Licensure of Wholesale Drug Distributors and Third-Party Logistics Providers,' comments were due to the public docket by September 6, 2022. FDA is working to finalize this rule.

The Honorable John Sarbanes

Accelerated Approval and Rare Diseases

1. **The accelerated approval process allows certain promising new treatments to reach patients earlier based on meeting a surrogate endpoint, rather than a full clinical end point. In 2022, Congress passed legislation strengthening transparency and accountability measures related to the accelerated approval process to ensure it can meet its goals of advancing innovative treatments for debilitating diseases and ensuring meaningful clinical gains for patients. Currently, the primary endpoints for ALS drugs are largely measured on the basis of a disease-specific score known as the ALS Functional Rating Scale (ALSFRS-R). Could you speak to the use of the ALSFRS-R in this context and whether any other measures could be the basis for measuring the effectiveness or likely clinical benefit of an ALS drug seeking accelerated approval?**

   In people living with ALS, disease severity and level of function are commonly measured in the clinic using a standardized, 12-item questionnaire known as the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). In 2019 FDA released Guidance for Industry: Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment. This guidance stated that although existing outcome measures that have been developed for ALS may be appropriate, FDA supports the development and use of new outcome measures capable of measuring clinically meaningful effects in patients. FDA encourages the use of patient input and experience in the development of these new measures. Sponsors can also consider novel technologies (e.g., wearable biosensors), as appropriate. In addition, as part of the private-public partnership with NIH under the Act for ALS, which now includes both the Critical Path Institute and the Foundation for the National Institute of Health, the improvement of existing clinical outcome assessments or development of new clinical outcome assessments for ALS will be prioritized.

   Subsequently, FDA approved Qalsody (tofersen) to treat patients with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene (SOD1-ALS). Qalsody is an antisense oligonucleotide that targets SOD1 mRNA to reduce the synthesis of SOD1 protein. The approval was based on a reduction in

plasma neurofilament light (NfL), a blood-based biomarker of axonal (nerve) injury and neurodegeneration in the context of evidence of target engagement demonstrated by a reduction in SOD1 protein. The use of this biomarker as a primary endpoint was novel (never been used to support drug approval).

2. **As you know, CDER holds the important responsibility of ensuring treatments that come to market are safe and effective. How do you believe the Center can best work with other stakeholders to most effectively advance innovative treatments, especially for the rare disease community?**

FDA has numerous ongoing efforts to advance the development of treatments for rare diseases in a structured way. Specifically, ARC is a CDER-wide effort governed by senior leadership from the Office of the Center Director, Office of New Drugs (OND), and Office of Translational Science (OTS). The ARC Program supports the development and approval of safe and effective treatment options for people living with rare diseases through scientific and regulatory engagement. In its first year, ARC focused on engagement and brought together experts across the Center for multiple public workshops to share perspectives. In addition, ARC launched the Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) program to identify knowledge gaps about the regulatory process of rare disease drug development with the goal of creating or expanding educational resources for both internal and external stakeholders. To compliment the LEADER 3D effort, CDER's Patient-Focused Drug Development staff is working with the National Organization for Rare Disorders to develop an advanced drug development education series for patients and patient groups.

Additionally, together, CBER and CDER established the Rare Disease Endpoint Advancement (RDEA) Pilot Program to support novel endpoint efficacy development for drugs that treat rare diseases. The RDEA Pilot Program is designed to:

- Advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process;
- Promote innovation and evolving science by sharing learnings on novel endpoint development through FDA presentations, guidance documents, public workshops, and a public-facing website; and
- Develop FDA staff capacity to enable and facilitate the development and use of novel endpoints to evaluate the efficacy of rare disease therapies.

In 2023 CBER and CDER announced the Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program, where participants will be able to obtain frequent advice and regular informal communication with FDA staff to address product-specific development issues, including, but not limited to, clinical study design, choice of control group and fine-tuning the choice of patient population. The program is open to sponsors of products currently in clinical trials under an active Investigational New Drug application (IND), regulated by CBER or CDER. CBER regulated products must be a gene or cellular therapy intended to address an unmet medical need as a treatment for a serious rare disease or condition, which is likely to lead to significant disability or death within the first decade of life. CDER-regulated products must be intended to treat rare neurodegenerative conditions, including those of rare genetic metabolic type. The Agency has selected pilot participants for each center. The pilot launched recently, and we look forward to seeing whether this type of frequent and informal communication between sponsors and FDA staff can help to move development programs for rare diseases forward more efficiently.

In addition, CDER staff are actively engaged with stakeholders through participation in public-private partnerships through the Critical Path Institute and the Foundation for NIH. This includes the Rare Neurological Disease public-private partnership established in response to the Act for ALS, as well as programs focused on Alpha-1 Antitrypsin deficiency and lysosomal diseases. In addition, FDA supported the development of the Critical Path Institute's Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP®) that provides a centralized and standardized infrastructure to support and accelerate rare disease characterization, with the goal of accelerating the development of treatments and cures for rare diseases, including identification of biomarkers. The RDCA-DAP platform continues to expand since going live September 2021, and now contains data for 34 different rare disease areas.

FDA also continues to work with the rare disease community by hosting and participating in patient-focused meetings and listening sessions on rare disease topics. Further, the Agency awards research grants, cooperative agreements, and contracts in addition to conducting pilot programs and special data analyses to advance the regulatory science for rare diseases.

Hiring

3. **In the 2022 User Fee Reauthorization, Congress authorized an increase in programmatic funding for more support staff to help CDER carry out its mission to bring safe and effective drugs to market. Can you provide an update on the filling of these positions?**

PDUFA VII as shown on Page 59 of the PDUFA VII commitment letter available here: https://www.fda.gov/media/151712/download?attachment authorized 289 new user fee-funded FTE positions between FY23-24 and an additional 63 positions in FY25-27.

As of March 31, 2024, FDA hired 216 new user-fee funded FTE for FY23-24. A current update on our hiring efforts can be found on our website here, which is updated quarterly: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-and-bsufa-quarterly-hiring-updates.

The Honorable Debbie Dingell

Sunscreens

1. **Many stakeholders have expressed concerns about Maximal Usage Trial, or MUsTs – a new test FDA invented that had never before been used for sunscreens – as a testing requirement for sunscreen evaluation. There are numerous internationally recognized absorption testing protocols, all previously used to test sunscreen active ingredients, that the FDA could have adopted with robust experience and scientific evidence. An independent analysis commissioned by one stakeholder group determined the MUsT testing standards were inappropriate for sunscreens – and virtually impossible to meet.**

   Why is the FDA insisting on MUsTs as a testing requirement, rather than implementing any other safety evaluation framework to ensure access to new sunscreens in the U.S. while still upholding FDA's rigorous safety requirements, and how might FDA take steps to address this issue?

   FDA's responsibility as a science-based regulatory agency is to protect public health and ensure that drugs are safe and effective for their intended uses. Understanding whether drugs are absorbed into the body and, if so, what the safety consequences of this absorption are, is a standard first step in assuring the safety and efficacy of all drugs, both prescription and nonprescription. This becomes uniquely important for topical drugs like sunscreen, which the evidence shows may be absorbed through the skin and are intended to be applied on a regular, lifelong basis. This is particularly important given that these products are used on children as young as 6 months old and by pregnant women. Additionally, the request for Maximal Usage Trials (MUsT) data to support evaluations

of whether sunscreen active ingredients are generally recognized as safe and effective (GRAS/E) under their specified conditions of use were unanimously supported by the Nonprescription Drugs Advisory Committee, which is a group comprised of independent experts.

In addition, FDA conducted and published two pilot trials[47] evaluating the absorption of various sunscreen ingredients intended to help industry jump-start their development programs and to address concerns related to study feasibility. Wherever possible, FDA has also taken steps to offer industry tailored study recommendations that take into consideration the specific pharmacological properties of sunscreens and that could reduce testing burdens. To assist industry in providing these data and streamline the process for manufacturers wishing to bring new sunscreen ingredients to market, FDA also published guidance for industry on the safety and effectiveness data needed to determine whether a nonprescription sunscreen active ingredient is generally recognized as safe and effective (GRASE)[48] and on conduct of MUsTs.[49]

FDA continues to encourage sunscreen manufacturers to submit data showing that sunscreens that are not yet available in the United States are GRASE. FDA is committed to working with industry and public health stakeholders to help ensure that the sunscreens consumers use every day are safe and effective for daily, life-long use.

2. **One significant concern with FDA's implementation of over-the-counter monograph reform is its insistence on animal testing for sunscreen filters. Current FDA regulations preclude even the possibility of using non-animal testing methods to bring sunscreens with new filters to American consumers. For sunscreen sponsors – including the many sunscreen sponsors prepared and eager to employ non-animal testing alternatives – this is, in effect, an animal testing mandate.**

   Dr. Cavazzoni, how might FDA begin to modernize its sunscreen ingredient testing protocols with regard to animal testing, such as through developing a path forward for New Approach Methods (NAMs) to gather toxicological information?

   FDA is continuously examining opportunities for the use of new alternative methods (NAMs) in the testing of products regulated by FDA and is actively working with stakeholders to reduce reliance on animal testing wherever possible. FDA facilitates the development and use of NAMs by establishing

[47] https://www.fda.gov/news-events/fda-voices/shedding-more-light-sunscreen-absorption
[48] https://www.fda.gov/media/94513/download
[49] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/maximal-usage-trials-topically-applied-active-ingredients-being-considered-inclusion-over-counter

processes to qualify these new methods for regulatory use (e.g., the CDER Drug Development Tool Qualification Programs[4]), providing guidance to stakeholders developing alternative methods, and by filling information gaps with applied research to advance new policy and guidance development.

While FDA is committed to reducing the reliance on animal-based studies in the broad context of human drug development, there are still many areas where animal toxicology studies are scientifically necessary because current science does not support replacement of all animal studies with non-animal methods. This is because current non-animal methods do not reliably predict effects that occur in highly complex interacting systems (such as the human body). In the case of sunscreens, the safety questions that exist, including whether there could be endocrine or carcinogenic risks with long-term systemic exposure, can currently be answered only with animal studies.

Obesity and Drug Efficacy

I'd like to ask about the interaction between patients with obesity and the efficacy of drugs. Unfortunately, clinical trials often fail to include patients with obesity. Consequently, the pharmacokinetics in this population is often unknown until after a drug is marketed. I worry that for all its proclamations, the agency's actions on this issue suggest it regards drugs as a 'one size fits all' proposition.

3. **What does this inaction state about the FDA and pharmaceutical industry's commitment to personalized medicine?**

Precision medicine, sometimes known as "personalized medicine" is an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles. The goal of precision medicine is to target the right treatments to the right patients at the right time.

Advances in precision medicine have already led to powerful new discoveries and FDA-approved treatments that are tailored to specific characteristics of individuals, such as a person's genetic makeup, or the genetic profile of an individual's tumor.

To realize the promise of precision medicine and individualized therapeutics, FDA sees a critical need for consistent assessment of the impact of genomic variation on drug response, improved manufacturing capabilities, and additional tools. FDA is exploring new technologies (e.g., omics) to advance major breakthroughs in diagnosis, prognosis, and treatment of diseases. FDA created "precisionFDA", a cloud-based portal for community research and development that allows users world-wide to

share data and tools to test, pilot, and validate existing and new bioinformatics approaches to Next Generation Sequencing (NGS) processing.

An important goal during drug development and regulatory assessment is to understand the drivers of response to therapy and its variability. Changes in drug pharmacokinetics (PK) in patients with obesity are highly variable and depend on multiple factors, including drug characteristics, degree of obesity, and specific organ (liver or kidney) function. The impact of intrinsic/extrinsic factors on treatment effects is evaluated in drug development. Population PK and exposure-response approaches are typically utilized to explore the effects of body weight and obesity on drug PK and responses to therapies. When an adequate number of subjects who are overweight or obese are included in clinical studies, the impact on exposure and response are also evaluated. Other approaches such as quantitative systems pharmacology models can be developed to describe the effect of physiological changes in obesity on pharmacodynamics, safety, and efficacy.

Development programs for disease areas where there is higher frequency of patients with obesity such as type 2 diabetes, weight management, cardiovascular disease, etc., do see inclusion of subjects with large body weights in Phase 3 trials. Thus, the adequacy of a dosing regimen can be evaluated. In addition to evaluating the impact of body weight on the PK of drugs, sponsors should conduct Phase 3 trials in a study population representative of the US population. For example, as the effectiveness of some contraceptives may be reduced with increasing body weight, the FDA guidance for establishing the effectiveness and safety of hormonal drug products intended to prevent pregnancy recommends that the trial population include women who are obese (BMI $\geq$ 30 kg/m2), and that the analysis plan should include prespecified subgroup efficacy analysis in this population. Similarly, the FDA guidance for developing drugs for noncirrhotic, nonalcoholic steatohepatitis with liver fibrosis also recommends that a proportion of patients with comorbidities, such as type 2 diabetes and obesity, be included in clinical trials, as that would be more reflective of the target population. In addition, Table 1 from an FDA published manuscript ((https://accp1.onlinelibrary.wiley.com/doi/10.1002/jcph.2327)) shows some of the additional FDA guidances with recommendation for including obese patients in clinical research (The Journal of Clinical Pharmacology 2023, 63(S2) S10–S17).

Table 1. Selected Guidance Issued by the US Food and Drug Administration (FDA) to Provide Recommendations on Concepts Related to Drug Development for Subjects who are Obese

Guidance	Key obesity-related concept
Developing products for weight management (Draft, 2007)	This guidance provides recommendations to industry regarding the development of drugs and therapeutic biologics for the indication of chronic weight management
Coronary Drug-Eluting Stents – Nonclinical and Clinical Studies Companion Document (Draft, 2008)	Factors affecting the poolability of US and non-US studies: patient demographics/clinical characteristics (obesity and others)
Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (Final, 2016)	Additional subheadings representing other specific populations (eg, smokers, patients who are obese, or patients with low body weight) may be included if informative for clinical use of the drug. A description of the studies and the results should be included under these subheadings
Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax (Final, 2018)	Obtaining PK data for specific populations (eg, geriatrics, pregnant women, patients who are obese/morbidly obese, patients with renal or hepatic impairment, and pediatrics, if possible (see section III.C.1., Pediatrics)) is recommended, as well as conducting studies to investigate the potential for drug–drug interactions with medicinal products likely to be co-administered in the clinical scenario
Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment (Draft, 2018)	Given the appreciable overlap of NASH and metabolic conditions (eg, obesity and T2DM), the proportion of patients with these comorbidities to be included in clinical trials should be reflective of the target population and should be discussed with the FDA before the sponsor initiates phase 2/3 trials
Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy (Draft, 2019)	The trial population should include obese women (ie, BMI $\geq$ 30 kg/m^2), and the analysis plan should include a prespecified subgroup efficacy analysis in this population. Insufficient data in the obese population may result in a limitation of use for this population in the labeling. During the trial design phase, sponsors should discuss with the division the adequacy of the number of cycles of drug exposure that will be derived from subjects who are obese
Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs (Final, 2020)	This guidance provides recommendations for approaches that sponsors of clinical trials intended to support a new drug application or a biologics license application can take to increase enrollment of under-represented populations in their clinical trials. This guidance considers both the demographic characteristics of study populations (eg, sex, race, ethnicity, age, location of residency) and the non-demographic characteristics of study populations (eg, patients with organ dysfunction, comorbid conditions, disabilities, patients at the extremes of the weight range, and populations with diseases or conditions with low prevalence). Enrolling participants with a wide range of baseline characteristics may create a study population that more accurately reflects the patients likely to take the drug if it is approved, and allow an assessment of the impact of those characteristics on the safety and effectiveness of the study drug
Development of Anti-Infective Drug Products for the Pediatric Population (Final, 2021)	Cohorts based on age, body weight or body surface area. The sponsor should consider the need to assess the effect of obesity on dose selection
General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products (Draft, 2022)	The impact of the disease state and obesity upon drug disposition and response should be considered

These guidance documents were selected from a manually curated list of guidance identified using keyword search for "obesity" OR "obese" OR "increased body weight" OR "increasing body weight" OR "overweight" OR "weight range." NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic; T2DM, type 2 diabetes mellitus.

Drug Shortages

4. We are seeing a record number of shortages across critical disease areas and populations including patients with cancer and children with mental illness. Dr. Cavazzoni, how much transparency does FDA have on the supply chain and what is needed in terms of mandated reporting to the agency for FDA to be able to act in a timelier manner to better anticipate and address impending shortages?

FDA has visibility into the facilities used to manufacture active pharmaceutical ingredients and finished dosage forms for drugs CDER regulates, although for non-application products, e.g. OTC products, facility information may be submitted upon marketing rather than prior to marketing. FDA is also working on updating our regulation to require all relevant manufacturers in the supply chain to register, regardless of if their products were offered for import directly to the US, as long as it was used as input to a product that was offered for import into the US.

Section 3112(e) of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) added section 510(j)(3) to the Federal Food, Drug, and Cosmetic Act (FD&C Act), which requires drug manufacturers registered under section 510 of the FD&C Act to report annually to FDA the amount of each listed drug they had manufactured, prepared, compounded, or processed ("manufactured") for commercial distribution. Establishing this annual reporting requirement enhanced FDA's visibility into the drug supply chain, as the reports will provide the Agency with information about how much of each listed drug is manufactured at each registered establishment. Through the NextGen Portal, FDA has established a way through which drug registrants and their authorized agents should report the required data. There are guides and videos to provide instructions for how to use the portal. Further information about reporting can be found in the "Reporting Amount of Listed Drugs and Biological Products Under Section 510(j)(3) of the FD&C Act Guidance for Industry"[50] and the "Reporting Amount of Listed Drugs and Biological Products Technical Conformance Guide."[51] However, the manufacturing amount data required to be submitted does not expressly require manufacturers to identify their suppliers (e.g., the manufacturer of the active pharmaceutical ingredient (API) used to manufacture the finished dosage form (FDF)) and how reliant they are on such suppliers (e.g., how much API they used from each supplier to manufacture the amount of FDF product they reported). This lack of a linkage between the amount of API manufactured and its allocation to specific FDF manufacturers limits the utility of the data. FDA's requested authority in the fiscal year (FY) 2025 President's budget to link these data reflect the Agency's effort to be responsive to requests from Congress regarding how these authorities could be enhanced to help address ongoing drug shortages.

The CARES Act also amended the FD&C Act to include a provision requiring each manufacturer of a drug described in section 506C(a) of the FD&C Act or of any active pharmaceutical ingredient (API) or any associated medical device used for preparation or administration included in the drug to develop, maintain, and implement, as appropriate, a redundancy risk management plan that identifies and evaluates risks to the supply of the drug, as applicable, for each establishment in which the drug or API of the drug is manufactured.

[50] https://www.fda.gov/media/175933/download
[51] https://www.fda.gov/media/153612/download

FDA issued a draft guidance for industry titled, "Risk Management Plans to Mitigate the Potential for Drug Shortages"[52] intended to help manufacturers develop, maintain, and implement, as appropriate, risk management plans to proactively assist in the prevention of human drug product and biological product shortages. This draft guidance is relevant to any person or entity who has oversight and control over the manufacture of drugs to ensure quality or owns or operates an establishment that manufactures a drug or biological product.

To further increase transparency into the sources of API, the President's FY25 budget includes a legislative proposal that the labeling of bulk drug substances for use in manufacturing or compounding of a human drug be required to identify the original manufacturer. For compounded drugs, the transparency is important as providers may seek to use them to help meet their needs during a shortage. Under the proposal, a finished product's physical label would be required to identify the finished product manufacturer. For finished products, the name and address of the API sources, an API packer, or distributor would also be required to appear, as appropriate, in the labeling or on another alternate place as designated by the Secretary. This information is critical to rapidly investigating the source and root causes of contaminated or otherwise unsafe drugs in distribution. The lack of sufficient information can compromise the ability of supply chain entities and FDA to contain public health risks associated with defective drugs.

The CARES ACT also included amendments to section 506C(a) of the FD&C Act to expand the requirement for manufacturers of certain drugs to provide information to FDA on permanent discontinuances and interruptions in manufacturing that may lead to a meaningful disruption in supply. However, manufacturers are not required to notify the Agency of an increased demand for a drug that the manufacturer will likely be unable to meet. Because of this, FDA may not become aware of such potential shortages until after they occur, and FDA's ability to respond to shortages due to an increased demand may be delayed. With advanced notice of increases in demand that the manufacturer would likely be unable to meet, FDA may be able to take proactive steps to prevent or mitigate demand-driven drug shortages. Advanced notice gives FDA additional time to work with the manufacturer (and stakeholders) to identify ways to maintain treatment options and prevent a shortage. To address this, FDA's FY 2025 budget request includes a proposal to expand the FD&C Act's notification requirements to include notifying FDA of an increase in demand for drugs described in section 506C(a) that the manufacturer likely will be unable to meet without meaningful shortfall or delay.

Hearing Aids

Nearly 5 years after Congress passed the 2017 FDA Reauthorization Act,

[52] https://www.fda.gov/media/158487/download

which included a provision mandating that FDA establish rules for the sale of over-the-counter hearing aids, the rule finally became effective in October 2022. With this new category, we are seeing an increase of new market participants. With more pathways for individuals with hearing loss to access hearing aids, it is crucial that we ensure companies operating in this space are playing by the rules and that FDA is exercising its appropriate oversight and enforcement authority to ensure the safety and efficacy of these medical devices. To that end, multiple issues have been identified with the potential to create greater consumer confusion or, worse, place consumers at an increased safety risk.

1. **Dr. Cavazzoni, is FDA aware of bad actors that are advertising and selling OTC hearing aids?**

FDA Clarification: CDER does not regulate medical devices, such as hearing aids, rather those fall under CDRH. As such, Dr. Shuren has responded to the questions below.

FDA has received allegations of regulatory misconduct (often called "trade complaints") consistent with the examples listed above. We review allegations submitted to us, whether from consumers, healthcare professionals, industry groups, or others, and take further action as warranted. Such action can include, among others, issuing a public safety communication, issuing a warning letter, holding a regulatory meeting, or initiating a seizure, as appropriate and according to our existing policies. FDA does not comment on pending or ongoing compliance actions or investigations.

2. **Dr. Cavazzoni, is FDA taking or has FDA taken any actions to monitor or ensure compliance with applicable regulations?**

Each allegation submitted by consumers, healthcare professionals, industry groups and others is evaluated, and further action is taken as warranted, according to our existing policies. To help consumers easily find required labeling and other helpful information, we have updated our OTC hearing aid consumer webpage to include consumer information on OTC hearing aids, including the required "outside of the box" (outside package) labeling, and links to report problems with OTC hearing aids and allegations of regulatory misconduct to FDA.

3. **Dr. Cavazzoni, what specific actions has FDA taken on its own, or in conjunction with FTC, to address regulatory violations relating to OTC hearing aids?**

Please see responses to questions 1 and 2 above. As of today, we have not coordinated with FTC on these issues, but expect to do so if

and as appropriate.

4. **Dr. Cavazzoni, what percentage of the OTC hearing aid market in the U.S. is domestic vs. foreign manufacturers?**

   Although FDA maintains information about manufacturing facilities and devices through its device registration and listing database which is publicly available, this information is not intended to capture market-share data. As such, FDA does not have reliable market-share data.

The Honorable Ann Kuster

Rare Disease Therapies

1. **Around 95% of known rare diseases have no FDA-approved treatment options, and drug development for rare disease drugs has its unique challenges compared to trials for more common conditions. This is exacerbated by a somewhat opaque and lengthy regulatory process at FDA.**

   I want to commend FDA for its conception of the Support for Clinical Trials Advancing Rare Disease Therapeutics (START) pilot program, which aims to reduce regulatory hurdles through increased communication between clinical review teams and innovative companies to drive novel therapies across the finish line to attend to the unmet urgent needs of rare disease patients with no treatment options. This increased, intensive communication model will play a pivotal role in ensuring rare disease patients see the results of American innovation.

   What would be necessary to implement the START program on a broader scale for the benefit of rare disease patients?

   FDA hopes that the insights gained from the START Pilot Program will provide information on how to best facilitate more efficient development of potentially life-saving therapies with rare disease indications and help sponsors generate high-quality data sufficient to support a future marketing application. We plan to evaluate the START Pilot Program after the pilot has been fully operationalized. FDA plans to develop metrics to assess both the outcomes of and resources used to in the Pilot Program before expanding or broadening the program. More detailed information can be found on FDA's website: *FDA Opens Doors for*

More Treatments for Rare Diseases through the New START Pilot Program [53]..

2. **What additional measures can be taken by CBER and CDER to address the opaque and lengthy regulatory process that negatively impact rare disease patients access to therapeutics?**

   FDA aims to establish a Rare Disease Innovation Agenda (now known as the Rare Disease Innovation Hub) Among other things, the Agenda will leverage expertise across the Agency to advance regulatory science on key issues critical to rare disease development programs, including novel endpoints, biomarker development, and innovative trial designs, while also enhancing collaboration and consistency across offices and centers related to product review. As discussed at the hearing, under the leadership of the CDER and CBER Center Directors, one of the first undertakings of this effort will be to publish a comprehensive cross-center strategic agenda that sets forth our shared vision for advancing rare disease therapies.

   A Rare Disease Innovation Agenda will provide a forum for enhanced collaboration among scientists, clinicians, and other staff on the use of novel biomarkers across development programs for the same rare disease, as well as consider cross-disciplinary approaches related to product review. In addition, the Agenda will prioritize coordinated engagement with the rare disease community to support enhanced opportunities, as legally permissible, for stakeholders to connect with FDA and for the Agency to learn more about the important perspectives of patients, researchers, and other stakeholders and find common ground.

The Honorable Robin Kelly

Maternal Health

1. **Given the high maternal mortality rates among Black, Latinas, and Indigenous mothers, can you share additional measures the agency is putting in place to ensure this population is included in this research?**

   FDA's Office of Women's Health (OWH) promotes and conducts research initiatives that facilitate FDA regulatory decision-making and advance the understanding of sex differences and health conditions unique to women.[54] OWH is partnering with the National Institutes of

[53] https://www.fda.gov/drugs/our-perspective/fda-opens-doors-more-treatments-rare-diseases-through-new-start-pilot-program
[54] https://www.fda.gov/consumers/womens-health-research/about-owh-research

Health (NIH) Office of Research on Women's Health to raise awareness about clinical trial participation by women of all races, ethnicities, ages, various chronic health conditions and disabilities, as well as those who are pregnant and lactating. The initiative also works to share best practices about clinical research design, recruitment, and demographic analyses.

FDA's Office of Minority Health and Health Equity (OMHHE) works with FDA Centers and external partners to support research studies about minority health and health disparities.[55]

It is important to note that FDA does not require the inclusion of any particular group of individuals in clinical trials for drugs, including pregnant women. That said, helping to ensure that clinical trials reflect the population that will use the drug if it is approved is a priority for FDA and the agency has engaged in numerous efforts in this area that are specific to the inclusion of pregnant women in clinical trials. The Agency provides advice to the pharmaceutical industry regarding the conduct of studies of medical products used by pregnant women and lactating women, including those with preexisting health conditions, through the publication of guidances, speaking engagements at conferences, and FDA public meetings. FDA has published the following draft guidances for industry regarding the conduct of studies in pregnant women and lactating women:

- *Pharmacokinetics in Pregnancy--Study Design, Data Analysis, and Impact on Dosing and Labeling* (2004)
- *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018)
- *Clinical Lactation Studies: Considerations for Study Design* (May 2019)
- *Postapproval Pregnancy Safety Studies* (May 2019)

As part of the Agency's efforts to promote clinical trial diversity, FDA is working to issue draft guidance for industry on diversity action plans to improve enrollment of participants from underrepresented populations in clinical studies.[56] Diversity Action Plans are intended to increase enrollment of participants who are members of historically underrepresented populations in clinical studies to help improve the strength and generalizability of the evidence for the intended use

[55] https://www.fda.gov/science-research/science-and-research-special-topics/minority-health-and-health-equity-research-and-collaboration

[56] This draft guidance describes the form, content, and manner of diversity action plans, the applicable medical products, and clinical studies for which a diversity action plan is required, the timing and process for submitting diversity action plans, and the criteria and process by which FDA will evaluate sponsors' requests for waivers from the requirement to submit a Diversity Action Plan.

population.

Trials

2. Given obesity's prevalence and associated risks, what specific steps is the agency taking to ensure adequate representation in trials?

Helping to ensure that the clinical trial population reflects the diverse population that will use a medical product if approved is a priority for FDA. FDA is engaged in numerous efforts to promote the importance of a diverse clinical trial population to help improve the generalizability of study results to the intended use population. These efforts include publishing guidance documents underscoring the importance of a representative populations and organizing or participating in public workshops about clinical trial inclusion. FDA understands the prevalence of obesity in the United States and therefore the importance of gathering information about the impact of obesity on the safety and effectiveness of medical products, especially the impact of obesity on exposure and response to drugs.

The following are examples about how FDA is working to understand the impact of obesity on drug performance and to help increase representation of obese patients in clinical research:
FDA and University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) in November 2022, convened a workshop to discuss with interested parties the effects of obesity on pharmacokinetics, pharmacodynamics, efficacy, and safety of drugs in adult and pediatric subjects.[57]

On March 19-20, 2024, FDA also participated in a workshop conducted by an external party titled “Medications and obesity: Exploring the landscape and advancing comprehensive care: A workshop.” This workshop explored the relationship between medications and obesity, including medications that are used to treat obesity, state of the science around the safety and efficacy of medications in people who are overweight or obese, medications that may cause changes in body composition and weight status, and medications used to treat obesity and obesity-related comorbidities.[58]

There are several FDA guidance documents that address the impact of obesity and provide considerations for the inclusion of obese individuals in drug development. Some of these include:

[57] https://www.fda.gov/drugs/news-events-human-drugs/bridging-efficacy-and-safety-obese-considerations-and-scientific-approaches-11092022
[58] https://www.nationalacademies.org/event/42135_03-2024_medications-and-obesity-exploring-the-landscape-and-advancing-comprehensive-care-a-workshop.

Guidance	Key obesity-related concept
Developing Products for Weight Management (Draft, 2007)	This guidance provides recommendations to industry regarding the development of drugs and therapeutic biologics for the indication of chronic weight management.
Coronary Drug-Eluting Stents — Nonclinical and Clinical Studies Companion Document (Draft, 2008)	Factors affecting poolability between U.S. and Outside the U.S. studies - Patient Demographics/Clinical Characteristics: *Obesity* and others
Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products —Content and Format (Final, 2016)	Additional subheadings representing other specific populations (e.g., smokers, *obese patients*, or low-body weight patients) may be included if informative for clinical use of the drug. A description of the studies and the results should be included under these subheadings.
Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax (Final, 2018)	Obtaining pharmacokinetic (PK) data for specific populations (e.g., geriatrics, pregnant women, *obese/morbidly obese patients*, patients with renal or hepatic impairment, and pediatrics, if possible (see section III.C.1., Pediatrics)) is recommended, as well as conducting studies to investigate the potential for drug-drug interactions with medicinal products likely to be co-administered in the clinical scenario.
Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment (Draft, 2018)	Given the appreciable overlap of NASH and metabolic conditions (e.g., *obesity*, type 2 diabetes mellitus (T2DM)), the proportion of patients with these comorbidities to be included in clinical trials should be reflective of the target population and should be discussed with the FDA before the sponsor initiates phase 2/3 trials.
Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy (Draft, 2019)	The trial population should *include obese women (i.e., defined as BMI of at least 30 kg/m2)*, and the analysis plan should include a *prespecified subgroup efficacy analysis* in this population. *Insufficient data in the obese population* may result in a limitation of use for this population in labeling. During the trial design phase, sponsors should discuss with the division the adequacy of the number of cycles of drug exposure that will be derived from obese subjects.
Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs (Final, 2020)	This guidance provides recommendations to approaches that sponsors of clinical trials intended to support a new drug application or a biologics license application can take to increase enrollment of underrepresented populations in their clinical trials. This guidance considers both demographic characteristics of study populations (e.g., sex, race, ethnicity, age, location of

	residency) and non-demographic characteristics of populations (e.g., patients with organ dysfunction, comorbid conditions, disabilities, *those at the extremes of the weight range*, and populations with diseases or conditions with low prevalence). Enrolling participants with a wide range of baseline characteristics may create a study population that more accurately reflects the patients likely to take the drug if it is approved and allow assessment of the impact of those characteristics on the safety and effectiveness of the study drug.
Development of Anti-Infective Drug Products for the Pediatric Population (Final, 2021)	Cohorts based on age, body weight or body surface area: The sponsor should consider the need to assess the *effect of obesity on dose selection*.
General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products (Draft, 2022)	The impact of the disease state and *obesity upon drug disposition and response* should be considered.

a. **How does the FDA promptly update drug labels with new dosing data?**

The labeling for human prescription drug and biological products (henceforth referred to as "drug") must contain a summary of the essential scientific information needed for the safe and effective use of the drug.[59] It also must be informative and accurate and neither promotional in tone nor false or misleading in any particular.[60]

Regarding dosing, dosing of drug products is generally designed for the "average patient." Getting the right dose to the right patient at the right time can be a challenge and underscores FDA efforts regarding precision medicine. FDA encourages the robust collection of pharmacokinetic and pharmacodynamic information across a spectrum of characteristics that may be associated with changes in drug performance, for example obesity status, renal/hepatic impairment, older age, and sex. There are sections of the FDA labelling specific to dosing in special populations. Where data indicate dosing adjustments are appropriate, the FDA-approved labelling generally would reflect this information. The labeling must be updated when new information, including use in specific populations, becomes available that causes the labeling to become inaccurate, false, or misleading.[61] Application holders are expected to review a drug's labeling at least annually to ensure it

[59] 21 CFR 201.56(a)(1)
[60] 21 CFR 201.56(a)(2)
[61] 21 CFR 201.56(a)(2)

is accurate and contains up-to-date information.[62]

FDA can also initiate an update to the Warnings and Precautions section of the labeling to adequately warn prescribers upon recognizing "a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug."[63] FDA may also require labeling changes in other situations. For example, under Title IX of the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA may compel changes to previously approved labeling when new safety information becomes available for the drug. Further, when a reference listed drug has been withdrawn, the MODERN Labeling Act of 2020 provides a pathway to update generic drug labels when new scientific evidence is available pertaining to the existing conditions of use, including use in specific populations, that is not reflected in labeling.

3. Can you elaborate on the scientific review that went into approval of this drug for over- the-counter use?

While unclear what drug you are referring to, FDA approves drugs as either prescription or nonprescription drug products under section 505 of the Food Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355). A drug product must be dispensed by prescription when it is not safe for use except under the supervision of a health care practitioner licensed by law to administer such drug product because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use (see section 503(b)(1) of the FD&C Act (21 U.S.C. 353(b)(1)). If the approved drug does not meet the criteria for prescription-only dispensing, it may be marketed as nonprescription.

FDA's regulation at 21 CFR 310.200 sets forth the procedure for exempting a drug product approved for prescription use from the prescription dispensing requirements of section 503(b)(1)(B) of the FD&C Act. A drug product limited to prescription use under section 503(b)(1)(B) is exempt from the prescription dispensing requirements if FDA determines that the prescription dispensing requirements are ''not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and [FDA] finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.'' (See 21 CFR 310.200(b).)

When FDA determines, based on studies submitted by the sponsor, that the original prescription drug product no longer meets the criteria in section 503(b)(1) of the FD&C Act for prescription use, FDA changes the drug product's status from prescription to nonprescription (commonly referred to as

[62] Guidance for industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (February 2013).
[63] 21 CFR 201.57(c)(6)(i)

an ‘‘Rx to OTC switch’’). There are two types of prescription-to-nonprescription switches: *full switch* and *partial switch*. The type of switch a sponsor decides to pursue depends on the circumstances and scope of the proposed switch.

In the case of a full switch, a sponsor switches a *prescription* drug product covered under the NDA to *nonprescription* marketing status in its entirety—i.e., for all approved strengths and indications. To initiate a full switch, a sponsor submits an efficacy supplement to its own approved NDA, or a sponsor who does not hold the NDA for the approved prescription drug may pursue a 505(b)(2) application. After a full switch, the drug is only available as a nonprescription drug.

For a partial switch, the sponsor *partially* switches some of the conditions of use (e.g., indications) to *nonprescription* marketing status while retaining other conditions of use within a *prescription* status. To initiate a partial switch, a sponsor submits a new NDA. After a partial switch, the drug is available as a prescription drug for specific conditions of use and a nonprescription drug for other conditions of use.

An application, including an efficacy supplement to an application, for a prescription to nonprescription switch should contain both efficacy and safety data demonstrating that the drug product is safe and effective when used in the nonprescription setting. Efficacy and safety data to support a prescription to nonprescription switch may include data from randomized, controlled clinical trials submitted in the original NDA for the prescription drug or new randomized, controlled clinical trials. Additionally, the applicant must provide data that demonstrate consumers can understand how to use the drug safely and effectively without the supervision of a healthcare professional. The applicant must also provide postmarketing safety surveillance data.

The Honorable Diana DeGette

NRTs

At the recent Energy and Commerce Committee hearing you stated that CDER is interested and willing to work with developers on the issue of new tobacco cessation therapeutics. You also noted that in 2023 the agency issued the Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products Guidance that “streamlined the development” of such products. You also testified that CDER tries to do everything it can as regulators to make drug development easier, efficient and streamlined as a contribution to innovation.

1. **Under the agency’s guidance, the only indications a new NRT product may initially seek are limited to smoking cessation and reduction in risk of relapse. A new NRT product must first be approved as a smoking cessation drug product before being able to seek an indication for reducing the urge to smoke or relief of cue-**

induced cravings. Why is reducing the urge to smoke or the relief of cue-induced cravings not acceptable as an indication for a new NRT product?

FDA's 2023 Nicotine Replacement Therapy (NRT) Guidance provides recommendations to sponsors in the clinical development of NRT drug products intended to help cigarette smokers stop smoking cigarettes or maintain abstinence from smoking. While the guidance reflects FDA's current thinking on the topics it covers, it does not bind sponsors or the FDA. FDA encourages sponsors that wish to discuss their drug development program to request a meeting with the appropriate review division. Each year, FDA review staff participate in many meetings with requesters who seek advice relating to the development and review of investigational new drugs and biologics, and drug or biological product marketing applications. FDA reviews New Drug Applications (NDAs) based on the best available science as applied to the data submitted in the NDA.

2. **Does not allowing a broader set of indications for a new NRT product hinder the range of therapies available to be studied as combination therapies?**

See response to Question 1 above. In addition, FDA recognizes the importance of developing new NRT products, which could include combination therapies. The FDA guidance titled, Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Products (May 2023), specifically addresses combination therapies. The guidance recommends that clinical trials intended to demonstrate effectiveness of a particular combination of NRT drug products should employ a randomized, double-blind, double-dummy, factorial design and that the contribution of each component to the effectiveness claim should be demonstrated.

The Honorable Jan Schakowsky

ILE

Local Anesthetic Systemic Toxicity (LAST) is a critical health issue that can occur when local anesthetics enter the bloodstream and trigger severe cardiac and neurological adverse events such as seizures, cardiovascular instability, and cardiac arrest. The off-label use of intravenous lipid emulsion (ILE) has been the standard of care to treat LAST for over a decade and is widely endorsed by professional societies such as the American Society of Regional Anesthesia and Pain Medicine (ASRA) and the American Heart Association (AHA). Despite its life-saving potential and extensive off-label use, ILE remains unapproved and unregulated by the FDA.

1. **In light of the fact that ILE therapy to treat LAST is the long-time standard of care, what long-term safety risks does the FDA expect to identify that will change physicians' medical decision-making when faced with a LAST-induced life or death decision?**

   FDA is aware that ILE therapy is used off-label for the treatment of LAST and is endorsed by several professional societies in clinical guidelines. However, FDA cannot approve drugs absent the submission of a market application and careful review of the data and information presented to ensure that legal and regulatory standards are met. Similarly, FDA cannot approve additional indications for approved drugs absent a supplemental marketing application for a new indication and careful review of the data and information. For FDA to approve a new indication for an approved drug, a sponsor would have to meet the same standards for approval that apply to any new drug, which means that, among other things, a sponsor would need to provide substantial evidence of effectiveness as defined in section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the new indication. FDA provides recommendations regarding the provision of substantial evidence of effectiveness in several guidance documents, including, most recently, a December 2019 draft guidance titled *Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products* and a September 2023 draft guidance titled *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*. Sponsors would also need to provide evidence that the benefits of their product for the proposed use under the conditions prescribed, recommended, or suggested in the FDA labeling outweigh its risks.

   All currently-approved ILE products are approved for parenteral nutrition indications, not for use in treating LAST. Moreover, the dose, duration, and method of administration (e.g., fast bolus versus slow continuous infusion) of ILE products for parenteral nutrition described in FDA-approved labeling is vastly different than what is currently used off-label for the intention of treating LAST. In addition to clinical evidence of its effectiveness for each intended use, nonclinical data may be necessary to support other changes in labeling from that currently approved for ILE products' use in parenteral nutrition, including any difference in the dosing regimen proposed for the treatment of LAST, to ensure that there is sufficient evidence of the drug's safety for such use.

2. **If the FDA cannot articulate a specific long-term safety risk that outweighs the medical decision to save a life at immediate risk due to LAST, then why is a warning label not sufficient?**

   Refer to our response to Question 1, as labeling can only be considered after FDA has determined that substantial evidence of effectiveness, as well as a favorable benefit/risk profile, has been established. Any updates to FDA-approved labeling pertaining to efficacy and/or safety requires review of appropriate data submitted to FDA that meets the legal and scientific criteria for approval. ILE products are

not approved for the treatment of LAST. And while FDA may require inclusion in the labeling of an adverse reaction associated with an unapproved use, as noted above, efficacy claims must be supported by substantial evidence of effectiveness.

3. **If the FDA can articulate a specific long-term safety risk that outweighs the medical decision to save a life at immediate risk due to LAST, then please do so, and frame it with a clear working hypothesis to ensure that the non-clinical safety study is well-designed and focused on evaluating the identified risk.**

   Refer to responses to Questions 1 & 2. In addition, nonclinical studies are intended to test the drug product at both clinically relevant exposures and to characterize the potential toxicity at higher levels in order to inform safety monitoring and predict potential adverse effects in patients. They are conducted to identify previously unknown safety concerns when the existing data are lacking. Current medical practices to treat LAST propose dosing lipid emulsions at higher exposures and at faster rates of intravenous infusions than those approved for use in parenteral nutrition products. Whether animal models are needed would depend upon the adequacy of the existing human data (i.e., from adequate and well-controlled clinical investigations) to support the proposed dose and dosing regimen for LAST.

4. **Given that physicians will continue to use ILE off-label until there is an approved version, please explain why a study framed with a clear working hypothesis cannot be conducted post-approval.**

   Refer to response to Question 1 describing the requirements to support approval of an ILE product for the treatment of LAST. FDA is willing to work with sponsors to discuss how they may meet the evidentiary standard for approval.

The Honorable Kathy Castor

Inclusion of Pregnant Women in Trials

I have worked for many years to improve the health of pregnant and lactating women, who have historically been excluded from research and clinical trials. This exclusion has led to significant evidence gaps that negatively impact health outcomes of mothers and infants.

Of the more than 3.5 million women in the US who give birth each year, 89% take at least one prescription medication during pregnancy. Yet, 70% of FDA-approved medications have no human pregnancy data, and 98% have insufficient data to determine risk to an infant.

Lack of data creates challenges for families and providers: excluding pregnant and lactating women from research doesn't make them any safer—it just means that medical decisions will be made without sufficient information on safety and effectiveness.

Last month, the National Academies released a congressionally requested report called Advancing Clinical Research with Pregnant and Lactating Populations: Overcoming Real and Perceived Liability Risks. In it, the Academies recommends that FDA release guidance making clear that pregnant and lactating women should be included as early as possible in studies.

1. **Dr. Cavazzoni: HHS removed pregnant women as "vulnerable populations" in 2018. FDA put out a proposed rule in 2022 to finally harmonize with the rest of the Department, as directed by the 21st Century Cures Act, but we have now been waiting almost 2 years for a final rule. What remaining steps does FDA have to take to publish the final rule?**

   Section 3023 of the CURES Act required HHS and FDA to harmonize differences between the HHS Human Subject Regulations ("the Common Rule") and the FDA Human Subject Regulations, to the extent practicable and consistent with other statutory provisions. Among other harmonization efforts in response to this mandate, FDA published a proposed rule on September 28, 2022, that would harmonize certain sections of FDA's regulations on human subject protection at 21 CFR part 50 and institutional review boards at 21 CFR part 56 with the revised Common Rule, in accordance with the CURES Act. The Common Rule does not include pregnant women in the categories of subjects who are considered vulnerable to coercion or undue influence. In this proposed rule, we propose to adopt the Common Rule language regarding the categories of participants who are considered vulnerable to coercion or undue influence, which would not include pregnant women. Thus, if finalized as proposed, this rule would remove pregnant women from categories of participants who are considered vulnerable.

   This proposal is consistent with our contemporary understanding that pregnant women are individuals with full autonomy and the capacity to make informed decisions for themselves. FDA believes this proposal will eliminate a significant barrier to the participation of pregnant women in clinical research and will enable the Agency to address a significant public health gap in our knowledge of the safety and efficacy of FDA regulated products in pregnant women.

   a. Is there an expected timeframe for when it will be published?

At this time, FDA is unable to comment on the issuance of the final rule but it remains a priority for the agency.

2. **Dr. Cavazzoni: What is your Center currently doing to advance the inclusion of pregnant and lactating women in clinical studies?**

Helping to ensure that clinical trials reflect the population that will use the drug if it is approved is a priority for FDA and the agency has engaged in numerous efforts in this area that are specific to the inclusion of pregnant women in clinical trials. The Agency provides advice to the pharmaceutical industry regarding the conduct of studies of medications and treatments used by pregnant women and lactating women, including those with preexisting health conditions, through the publication of guidances, speaking engagements at conferences, and FDA public meetings. FDA has published the following draft guidances for industry regarding the conduct of studies in pregnant women and lactating women:

- Pharmacokinetics in Pregnancy-Study Design, Data Analysis, and Impact on Dosing and Labeling (2004)
- Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials (April 2018)
- Clinical Lactation Studies: Considerations for Study Design (May 2019)
- Postapproval Pregnancy Safety Studies (May 2019)

Additionally, FDA is actively engaged with The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which aims to bring together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. ICH E21: Inclusion of Pregnant and Breast-feeding Individuals in Clinical Trials, is a new Efficacy guideline in development, which aims to provide recommendations to facilitate inclusion and/or retention of pregnant and breast-feeding individuals in clinical trials.

The 21st Century Cures Act (CURES Act) (P.L. 114-255) established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to advise the Secretary of HHS on gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women. FDA Office of Women's Health (OWH) is a member of the PRGLAC Task Force, and works closely with FDA centers to support policy, research, education, outreach, and other efforts to help bridge knowledge gaps and increase available safety information on FDA-regulated products used during pregnancy or lactation.

FDA is actively engaged in supporting research to bridge important data gaps in our understanding of medication use and safety in pregnancy and lactation. Many of these studies support leveraging cutting-edge technology such as artificial intelligence and real-world data. As part of the National Center for Toxicological Research (NCTR), FDA manages the Perinatal Health Center of Excellence

(PHCE), which reviews and funds research related to perinatal populations.[64] Additionally, OWH maintains a searchable list of funded research projects by topic area.[65]

OWH provides a public listing of active pregnancy exposure registries to bring awareness to opportunities to participate in research for pregnant women who are taking or have taken certain medicines or have received certain vaccines while pregnant.[66] The webpage currently lists 172 studies.[67] FDA is also continuing our efforts to enhance post-approval pregnancy safety studies.

It is also critically important for us to continue the dialogue with multidisciplinary group of experts and stakeholders. With that in mind, FDA in the past few years has developed and engaged in several workshops and webinars on this critically important topic.

- Upcoming: Evaluating Immunosuppressive Effects of In Utero Exposure to Drug and Biologic Products workshop July 2024;
- Optimizing postapproval pregnancy safety studies workshop September 2023;
- May 2022 FDA Public Workshop on PK Evaluation in Pregnancy; https://www.fda.gov/drugs/news-events-human-drugs/pharmacokinetic-evaluation-pregnancy-virtual-public-workshop-05162022Drug Information Association (DIA)
- June 2022 National Academies of Sciences, Engineering, and Medicine (NASEM) public workshop on Clinical Trials in Pregnant and Lactating Persons: https://www.nationalacademies.org/event/06-16-2022/inclusion-of-pregnant-and-lactating-persons-in-clinical-trials-a-workshop
- OWH/DPMH Webinar #1: Pregnancy and Lactation Medication Information for the Healthcare Provider (held May 11, 2022)
- OWH/DPMH Webinar #2: Engaging Providers to Address Knowledge Gaps on Medication Use in Pregnancy and Lactation (held October 27, 2022)
- 2021 OWH Public Meeting on Leveraging Real world data to understand medication use in pregnancy and lactation;
- 2021 Public workshop in collaboration with the Duke Margolis Center for Public Health Policy Scientific and Ethical Considerations for the Inclusion of Pregnant Women in Clinical Trials.

The Honorable Lori Trahan

[64] https://www.fda.gov/about-fda/nctr-research-focus-areas/perinatal-and-maternal-research
[65] https://www.fda.gov/consumers/owh-funded-research/project-areas-topic
[66] https://www.fda.gov/consumers/owh-funded-research/project-areas-topic
[67] https://www.fda.gov/consumers/owh-funded-research/project-areas-topic

Dose Optimization

1. **I am glad to see FDA's efforts to change oncology clinical trials in the hopes of optimizing dosages and lowering potential toxicities, but I'm particularly concerned with how these changes will be felt for pediatric and rare disease trials, which could be much more difficult to execute due to their smaller patient population. In Project Optimus' 2023 draft guidance, there is a lack of clarity for sponsors on critical issues when initiating pediatric oncology trials such as descriptions of the types of trial approaches FDA considers appropriate for dose optimization in pediatric drug development, and what factors FDA would consider when considering dosage optimization in early phase vs post-market studies for smaller populations, such as pediatric trials. Would FDA commit to providing additional clarity to pediatric trial sponsors in the final guidance?**

   Thank you for reaching out regarding this important topic. FDA considers dosage optimization critical to providing new effective treatments to pediatric patients that have less risk of chronic toxicities or late effects. Although the final FDA guidance on dosage optimization (posted August 8, 2024)[68] does not specifically address pediatric drug development, it notes there are unique considerations associated with pediatric drug development and states that some of the general principles outlined may be applicable to dosage optimization for pediatric patients. FDA also acknowledges that there is no one-size-fits-all approach to dosage optimization; the final guidance emphasizes that "the best approach to determining the optimized dosage(s) for a specific drug development program depends upon a variety of factors including but not limited to drug class, proposed indicated patient population, and prior knowledge about the drug that is pertinent to dosing." Additionally, the May 2021 FDA Guidance on FDARA implementation[69] includes recommendations for use of model informed drug development (MIDD) approaches to optimize dosing in pediatric patients. The December 2023 FDA Guidance "Rare Diseases: Considerations for the Development of Drugs and Biological Products"[70] also provides recommendations regarding dose selection for products intended to treat rare diseases, which may be applicable to pediatric cancer drug development.

   FDA shares the sense of urgency for expeditious drug development within the pediatric oncology community and believes that it may be feasible to seamlessly integrate dosage optimization in pediatric drug development

[68] See: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases
[69] See: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdara-implementation-guidance-pediatric-studies-molecularly-targeted-oncology-drugs-amendments-sec
[70] See: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-considerations-development-drugs-and-biological-products

without impeding drug development. To that end, FDA encourages drug developers to engage early with the Agency for guidance that is specific to their development plan.