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
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Lauren Paulos
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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. Peter Marks, Director, Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Contents

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 **The January 2023 draft guidance on dose optimization in oncology drug development does not address recommendations on dose optimization for rare diseases. Many of the dose optimization principles outlined in the draft guidance, such as randomization and having a trial sized for sufficient assessment of dosage, won't work in oncology, particularly for rare cancers.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

- FDA encourages early interaction and regularly meets with sponsors to provide advice about drug development, study design and dosage selection.
- FDA provides 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]
- FDA encourages modeling tool developers to discuss potential modeling tools

[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

that can be applied to inform dose selection/optimization through the Fit-for-Purpose program.[3]

- FDA established the CDER Quantitative Medicine Center of Excellence, CDER Center for Clinical Trial Innovation, and CDER's Accelerating Rare disease Cures (ARC) Program[4] 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. 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 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.

[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

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 tech 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, X, 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.

The Food and Drug Administration (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 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?**

[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

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 (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.

[11] https://www.fda.gov/media/151712/download?attachment
[12] https://www.fda.gov/media/152279/download?attachment
[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 percent of those meetings were granted as in-person. No meetings were delayed or denied due to conference room availability.

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 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.

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 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.

[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.

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 to provide input to sponsors on these complex and challenging programs.

In May, CDER and CBER announced a plan to establish 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 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 percent 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 ten, 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

[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

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 its risks, including the spread of AMR. As noted in response to 4), we anticipate that only a small minority of these products (< 1 %) 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) notification. 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 "medical 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 would classify 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.

AMR Reclassification

12. How does the FDA intend to take patient access into consideration when it comes to reclassification?

As stated in the response to question ten, the cited action is an initial classification rather than a reclassification. FDA is carefully reviewing and responding to public comments submitted in response to the proposed rule, including those related to patient access. The Agency takes a least burdensome approach for addressing risk to patients and the approach in the proposed rule is based on feedback from multiple FDA advisory committee meetings. Moreover, the testing requirements proposed in the rule are largely consistent with the typical data requests for wound dressings cleared in the last decade. Out of the several hundred products impacted by this proposed rule, if finalized as currently proposed, the majority would remain as 510(k)s and only a small minority (less than one percent) would be subject to PMA. Because less than one percent of currently cleared dressings that are within the scope of this proposed rule, if finalized, would be subject to PMA, and testing requirements and special controls for class II are largely reflective of typical data needs for cleared wound dressings, the proposed rule did not anticipate disruption to patient access if finalized as proposed.

The Honorable Brett Guthrie

Advanced Manufacturing for CGT

1. **Manufacturing processes for cell and gene therapies have been a bottle neck in the development and review process. FDAs new advanced manufacturing technologies (AMT) pathway is intended to create more certainty and standardization in adopting new technologies. The draft guidance to implement this pathway is unclear regarding the circumstances when a cell and gene therapy applicant can cross reference data for a designated AMT. For instance, how would entities that produce cell lines and contract with several different developers be able to provide information to cross reference?**

A Biologics License Application (BLA) holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license, therefore, FDA generally expects such information to be submitted directly to the BLA. For this reason, the BLA applicant should have access to the supportive data and information for drug substance, drug substance intermediate, and drug product (DS/DSI/DP) manufacturing relevant to the AMT. The BLA applicant should not incorporate by reference DS/DSI/DP information from a designated AMT if it does not have access to this information, including by referencing a drug master file (DMF) that contains a designated AMT.

The exclusion for incorporating by reference information contained in a DMF in a BLA is limited to DS/DSI/DP information per 21 CFR 601.2(g) and as described in the FDA's Final Rule regarding Biologics Applications and Master Files (89 FR 9743). This is because DS/DSI/DP information, including the control and validation of the manufacturing process, is critical to evaluating the BLA sponsor's control over product quality.

Sponsors may cross-reference DMFs in a BLA for other kinds of information. We are still considering comments regarding the draft guidance on Advanced Manufacturing Technologies Designation Program. However, we anticipate that some AMT information could be appropriate for incorporating into a BLA by reference to a DMF. For example, an AMT may be equipment that is used in the DS/DSI/DP manufacturing process; in this case, some information related to the manufacturing equipment may be provided by cross-reference to a DMF.

While a BLA may not incorporate by reference DS/DSI/DP AMT information contained in a DMF, we have provided alternative options in certain circumstances for an applicant to provide information when they do not intend to manufacture all aspects of the product for licensure. These options are explained in FDA's guidance for industry regarding cooperative manufacturing arrangements, which allows flexibility in manufacturing strategies while still assuming responsibility for meeting the applicable product and establishment standards.[20] This includes options for divided manufacturing arrangements and shared manufacturing arrangements.

a. As the upcoming guidance is revised, can the Agency commit to offering additional examples and clarification of when it is and is not appropriate for cell and gene therapy manufacturing technologies to cross reference AMT designations so that the pathway is utilized in accordance with its legislative intent?

As the Agency finalizes the draft guidance, it will address comments from stakeholders, including questions specific to cell and gene therapy products.

Potency Assays

2. Dr. Marks – one of the big issues in cell and gene therapy development is the issue of being able link tests in the lab to how well the product will work in people – known as potency assays. As I understand, this is challenging because the scientific link between product characteristics and clinical performance is still evolving – and FDA has held dozens of learning sessions with experts. FDA released a guidance document earlier this year on potency assays which will be critical to the field. Can you commit to ensuring that any final document will be

[20] https://www.fda.gov/media/70712/download

responsive to calls for regulatory clarify, flexibility in the early stages of drug development, and consistency with international standards?

CBER has worked extensively, both in public meetings, and with sponsors directly, to provide additional clarity regarding potency related considerations for development of cell and gene therapy products. In addition, CBER already employs flexible approaches in all aspects of its regulatory decision making, and will continue to do so. CBER commits to ensuring our final guidance will be responsive to calls for clarity, flexibility, and consistency with international standards, as appropriate.

OTP Hiring

3. **CBER is charged with filling vacancies across the Office of Tissue Products to ensure adequate staffing to address the anticipated workload. During this matriculation, how have senior level staff been maintained and new staff trained and mentored to ensure continuity in product development and review?**

The recent reorganization of the Office of Therapeutic Products (OTP) created new offices within the super office structure that align disciplines and product types, allowing our workforce to address the exponential growth in cell and gene therapies. This updated structure will enable OTP to provide oversight and coordination across programs, enhance expertise in highly specialized disciplines, and meet our review and workload needs.

Once fully hired and trained, new staff throughout CBER supporting cell and gene therapy development and review will substantially increase capacity to provide additional time on meetings and submission reviews, expand stakeholder outreach, invest in new policy and guidance, and facilitate development of regulatory tools.

Approximately 75-80 percent of OTP positions have been filled. This allows our workforce to better address the exponential growth in cell and gene therapies.

Clinical Holds

4. **Too often we hear that drug developers are put on clinical hold for an initial IND review for reasons that are most likely related to the mandated 30-day review period not being sufficient time for the limited FDA staff to complete their review. Clinical holds can have a significantly negative impact on a company's ability to efficiently move development programs forward and reduce confidence in the physician and patient communities and their interest or ability to participate in clinical trials. If the FDA could be given 60 days to review an initial IND, what would it take for the agency to adapt their staffing priorities accordingly to consistently complete their review on time?**

By statute, if FDA does not place an IND on clinical hold within 30 days, the clinical

investigations described in the IND may automatically proceed. Whether FDA places the clinical investigations described in an IND application on hold is related to several factors, including the quality and completeness of each IND section (e.g., Clinical, Chemistry, Manufacturing and Controls (CMC), and Pharmacology and Toxicology (P/T)) and whether all the identified safety risks are adequately addressed. FDA supports submission of quality IND submissions through outreach, guidance and the PDUFA meetings process, where specific topics and issues can be discussed prior to submitting an IND.

In many cases, it is challenging for FDA to thoroughly assess the potential safety risks to individuals participating in a clinical trial in an original IND within 30 days of IND receipt. INDs that contain novel or complex biological products, utilize advanced or novel manufacturing technologies, are combination products (e.g., drug-device combination products), or use AI/ML in some aspect of manufacturing or in the clinical study also present challenges, in addition to the quality of the IND submission.

In response to FDA questions, the sponsor may submit additional information to address safety concerns. However, it may not be possible for the sponsor to provide the requested information, or for FDA to assess this information within the current 30 days review timeframe. These timing pressures can result in more INDs being put on hold when issues cannot be resolved within the 30-day timeframe. We continue to work on overcoming this challenge and responding to submissions in a timely and efficient manner.

The Honorable Michael Burgess, M.D.

Platforms

1. **We appreciate the work the FDA is doing on platform technology designations and are looking forward to the soon to be released guidance. How many platform technology designation requests have been approved by the FDA?**

    a. **Which centers have approved requests thus far and for which specific therapeutic areas?**

        i. **If none, why is that? And how many applications have been received?**

        ii. **For what kinds of products? And what kind of efficiencies have you seen?**

        iii. **Can you please also let us know which centers have received granted requests and for which specific technologies and therapeutic areas?**

    FDA issued a draft guidance in May 2024, entitled *Platform Technology Designation Program for Drug Development*.[21] This guidance outlines eligibility factors for receiving a platform technology designation, potential benefits of receiving a designation, how to leverage data from designated platform technologies, how to discuss a planned designation request as part of a milestone

[21] https://www.fda.gov/media/178938/download

meeting, the recommended content of a designation request submission, and the review timelines for a designation request. This program is intended to result in efficiencies in drug development, manufacturing, and review processes for drug product applications that incorporate designated platform technologies.

Given the potential of platform technologies in products incorporating human genome editing technology—such as CRISPR—CBER announced its intent to issue draft guidance on the use of platform technologies in human gene therapy products incorporating human genome editing (see 2024 guidance agenda)[22] in order to provide additional clarity specific to these types of products. CBER has not yet received any requests for platform technology designation. To date, CDER has received and is currently reviewing one request.

The Honorable Robert Latta

Exclusivity

1. **The FDA Commissioner commented on the Agency's unapproved drug guidance at a hearing in July 2017 before the House Judiciary Subcommittee on Regulatory Reform, Commercial and Antitrust Law. The Commissioner explained that "if you want these unapproved drugs to come through a regulatory process and develop the data to demonstrate safety and effectiveness and go through the manufacturing requirements, you have to provide an incentive"— the incentive being that "if [manufacturers] go through that process and spend the money to do it, they're going to get a short period of exclusivity, and the FDA is going to make an attempt to clear the market of potential competitors. What is the FDA doing on guidance to industry regarding a period of exclusivity to companies that invest in the regulatory process to prove safety and efficacy?**

Unapproved prescription drugs can pose significant risks to patients because they have not been reviewed by FDA before marketing for safety, effectiveness, or quality. Unapproved new drugs have resulted in patient harm, and the Agency works to protect patients from the risks posed by these drugs. The Agency has a two-pronged approach to help assure patient safety. First, the Agency encourages manufacturers of unapproved new drugs that are subject to approval requirements to obtain approval for those drugs to be legally marketed in the United States. Upon approval, drugs may qualify for 3- year or 5-year exclusivities under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 7-year orphan drug exclusivity under the Orphan Drug Act if they meet eligibility requirements. See the Agency's implementing regulations in 21 CFR 314.108 for 3- and 5-year exclusivity requirements, and 21 CFR 316 orphan drug exclusivity requirements. Regarding eligibility for exclusivity, those determinations are made upon approval and necessitate a review of the data and information submitted in the NDA.

[22] https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/guidance-agenda-guidance-documents-cber-planning-publish-during-calendar-year-2024

Second, FDA has worked to remove unapproved drugs from the market. While FDA plans to issue guidance, consistent with FDA's good guidance practices (21 CFR 10.115), to provide appropriate updates regarding its enforcement priorities for marketed unapproved new drugs, the Agency's current risk-based enforcement approach involves prioritization in light of the facts of a given circumstance, including those drugs that pose the highest risk to public health. This risk-based enforcement approach best supports FDA's public health priorities.

Efficiencies

2. **You speak often about the importance of early engagement with the agency and working collaboratively with drug developers. However, FDA seems to be addressing more and more requests to meet with what is called 'Written-Response-Only' essentially having developers wait months to get notes back rather than engage in a discussion. At the same time, you have discussed a pilot CBER is running to assess if real-time communication to address development questions will smooth and speed the road to market. How can we move to deploy a streamlined approach now with the existing resources of the agency?**

CBER uses Written Response Only (WRO) to provide written responses that sufficiently address the questions posed by a sponsor. Sponsors also recognize the value of WROs and request a WRO when a written response will provide the information they seek. (Currently, about 35 percent of all requests from sponsors to address questions (meeting and WRO requests) are requested as WROs). Written responses are governed by the same user fee timelines as when a live (e.g., in-person, virtual, or teleconference) sponsor meeting is held. In Fiscal Year (FY) 2024 year to date, CBER has converted some meeting requests (less than 25 percent) to WROs when a written response appropriately address the sponsor's questions. In FY24 year to date, CDER has converted approximately 50 percent of meeting requests that qualify for WRO, when a written response can effectively address the sponsor's questions. Such conversions are appropriate when questions are straightforward and the written answer can be clearly and readily understood, without the need to explain or expand on the answer in a meeting. Other examples of situations where a written response is appropriate include answers to questions that are found in FDA guidances (so clearly explained in the guidance) or where the sponsor has been provided answers to similar questions or similar approaches for products previously discussed. Judicious use of meetings and WRO's allows CBER and CDER to maximize resources for sponsor inquiries, and other regulatory activities.

In terms of the START Pilot Program, CBER and CDER hope that the insight gained through this pilot program will 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. 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.[23] 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 resources were required to support 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 whether expanding the communication timelines in the pilot to other sponsors is feasible with our current resources.

3. **FDA has noted that data packages are increasingly complex and time consuming to address. Has FDA considered what efficiencies they might pursue to aid engagement?**

    a. **Are there activities FDA could consider pulling back from or areas where a lighter touch might be valuable?**

    FDA is always looking to achieve its mission in the most efficient and effective way possible. The Agency has a long history of exploring and adopting innovative ways to enhance medical product development and review. This includes, among other things, early engagement with developers, and the use of real-world data (RWD) and real-world evidence (RWE) to inform and support FDA regulatory decisions. The most recent user fee authorization provided support to FDA to manage the increase in advanced biological therapies such as cell and gene therapies, advance drug development tools, modernize FDA data and information technology, expand capacity in digital health technologies, and improve efficiency and expand communication in the human drugs review program. One such effort, the START Pilot program mentioned above, is intended to 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.

RWD

4. **As our health care system becomes more and more digitized, increased information and data are available to researchers and clinicians which can help shorten timelines to diagnosis, reduce costs to patients and our health care system, and have a profound impact on patient outcomes. Today, the cost of studying and monitoring new interventions is staggering and sometimes unrepresentative of real-world care, yet a necessary and lifesaving investment for life sciences companies and patients alike. Leveraging real-world data in conjunction with clinical development programs can reduce these costs, provide a more complete picture of trial patients and care in real- world settings, while transforming the R&D process and accelerating the pipeline for life- changing**

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

and life-saving therapies. This is particularly the case for rare and hard-to-treat diseases. In what ways is the FDA encouraging the research community to utilize real- world clinical data?

FDA has used what is now called real-world data (RWD) to generate real-world evidence (RWE) for many years, originally to monitor and evaluate the postmarket safety of approved drugs. Along with the availability of big data, legislation has contributed to the growth of RWE. Specifically, the 21st Century Cures Act included a mandate for the FDA to evaluate the potential use of RWE to support a new indication for an already approved drug (i.e., to evaluate RWE's potential use for effectiveness). In 2018, FDA published a framework[24] describing a Real-World Evidence Program for drug and biological products. The Program has evolved to encompass internal Agency processes, external stakeholder engagement, demonstration (research) projects, and guidance development.

FDA created a Real-World Evidence Subcommittee comprised of FDA staff from multiple centers and offices. This Subcommittee provides oversight of policy development on RWE and offers resources as well as leadership, including with discussions of applications containing RWE. The Subcommittee also holds "listening sessions" to learn about innovative perspectives and technologies involving the creation, collection, linkage, and/or analysis of RWD. Beyond Subcommittee activities, RWE experts present and speak at scientific and industry conferences, and FDA experts generate publications to address ongoing issues related to RWE.

As a prominent component of FDA's RWE Program, FDA has published a series of guidance documents to promote the appropriate use of RWD and RWE for regulatory decision-making.[25] For example, FDA has provided recommendations in guidance on topics including evaluating sources of RWD (electronic health records/claims and registries), data standards, and types of study design (externally controlled trials and non-interventional studies), with a draft guidance on clinical trials in routine clinical practice settings in development, regulatory considerations, and procedural issues. To help identify and promote awareness of RWE-based approaches that can meet regulatory requirements, FDA has established additional initiatives, including demonstration (i.e., research) projects that seek to improve the quality of RWD and RWE. For example, FDA announced four Cooperative Agreement Awards (U01)[26] in 2023 to encourage innovative approaches to generate RWE. Other ongoing Agency initiatives continue to promote awareness of, and consistency in, reviewing submissions with RWD.

As part of the FDA User Fee Reauthorization Act of 2022 process, FDA committed to establish an Advancing RWE Program[27] to identify approaches for RWE that can meet regulatory requirements, develop Agency processes that promote consistent decision-

[24] https://www.fda.gov/media/120060/download?attachment
[25] https://www.fda.gov/science-research/real-world-evidence/center-biologics-evaluation-and-research-center-drug-evaluation-and-research-real-world-evidence#Guidance
[26] Cooperative Agreement Awards (U01) support a discrete, specified, circumscribed research project
[27] https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program

making, and increase awareness of RWE characteristics that support regulatory decisions. The Advancing RWE Program launched in 2023 and has provided additional opportunities for sponsors to meet with FDA staff to discuss the use of RWE early during medical product development. Also, FDA released the first annual public report on RWE in June of 2024.[28]

b. Are there ways in which the FDA can better prioritize and standardize specifications for the use of this data in drug approval and surveillance processes?

FDA is committed to realizing the full potential of fit-for-purpose RWD to generate RWE that will advance the development of therapeutic products and strengthen regulatory oversight of medical product across their lifecycle. As mentioned above, FDA is already using RWE to support regulatory decisions, and the Agency will continue to consider how to optimally incorporate RWD/RWE about the safety and effectiveness of medical products. FDA is also currently engaging with standards development organizations to update standards designed to more optimally address RWD sources.

The Honorable Gus Bilirakis

PRVs

1. The Priority Review Voucher Program has been a critical incentive for sponsors to pursue treatments in rare disease 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 help 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 of factors, while one sponsor said they were pivotal in its development of a drug.[29]

Advisory Committees

2. 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

[28] https://www.fda.gov/science-research/real-world-evidence/real-world-evidence-submissions-center-biologics-evaluation-and-research-center-drug-evaluation-and
[29] https://www.gao.gov/products/gao-20-251

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.

Rare Disease Therapies

3. **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 Program 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 at https://www.fda.gov/news-events/fda-voices/fda-rare-disease-innovation-hub-enhance-and-advance-outcomes-patients.

4. 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

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

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.

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

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

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,

[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.

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

we can then determine the best approach to potentially expanding the communication timelines in the pilot to other sponsors.

The Honorable Earl "Buddy" Carter

Advanced Manufacturing for CGT

1. **You have noted on numerous occasions that manufacturing processes for cell and gene therapies have been a bottle neck in the development and review process. I authored legislation passed as part of the last user fee reauthorization that setting up a new pathway for you to review new advanced manufacturing technologies before they are used in drug and biological products to create more certainty and standardization. However, FDAs draft guidance to implement the pathway undercuts the intent of the law and runs contrary to the letter of the law that I wrote. How is CBER working with stakeholders to ensure that this new pathway helps to deliver on the promise of advanced manufacturing technology for cell and gene therapy and encourage onshoring?**

Facilitating advanced manufacturing remains a high priority for FDA as it may help limit manufacturing interruptions as well as help prevent drug shortages and address significant challenges in certain circumstances related to drug manufacturing and maintaining robust supply chains.

As you note, use of advanced manufacturing technologies may also expedite the development of novel therapies such as cell and gene therapies.

The Agency published the Advanced Manufacturing Technologies Designation Program draft guidance in the *Federal Register* on December 13, 2023, with a 60-day period for public commenting. The comment period was later extended from February 12, 2024 to March 13, 2024, to allow stakeholders additional time to provide comments on the draft guidance. Currently, the Agency is revising the draft guidance to address the comments received, including those from cell and gene therapy manufacturers.

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 or 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 planned 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 to provide advice on scientific, technical, and policy questions and share their perspectives on patient and consumer experience issues, to help FDA make decisions based on the best science available. The topics FDA takes to advisory committees are often intricate. Because of 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 better understand the needs of our broad population. FDA's advisory committees include committee members from a wide variety of backgrounds, often including patient or consumer representatives, whose role is to provide a voice for those most impacted by our decisions. We have made it a priority to evaluate our advisory committee process and to explore ways to optimize their use. As advances in science and technology continue to expand, and the opportunities for new treatments and approaches grow, it is increasingly important for all stakeholders 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.

HCTPs

2. **FDA appears to have departed from the preamble in the final rule outlining the requirements for 361 HCT/P classification, in which FDA stated that cutting, grinding, and shaping of HCT/Ps constitute minimal manipulation. (*See* 66 Fed. Reg. 5447, 5447) How does FDA approach "minimally manipulated" standard in human bone powder versus other types of human tissue manufactured in powder form (e.g., dermis, amniotic membrane, placental disc)?**

The 1271.10(a) criteria, including the minimal manipulation criterion, were intended to serve as the dividing line between HCT/Ps that present a lower degree of clinical safety and effectiveness risk and that are appropriately regulated solely under the communicable disease provisions of section 361 of the Public Health Service (PHS) Act and part 1271, and HCT/Ps that may present a greater degree of clinical safety and effectiveness risk and that therefore should be subject to premarket review requirements to help ensure safety and effectiveness. FDA has explained that clinical safety and effectiveness concerns depend in part on the extent of manipulation of the cells or tissues.

As defined in 21 CFR 1271.3(f), minimal manipulation for structural tissue means "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair or replacement" and is a product/tissue specific evaluation. Different tissue types possess different original relevant characteristics relating to the tissue's utility for reconstruction, repair or replacement, which is integral to the assessment of the minimal manipulation criterion. Original relevant characteristics of bone relate to its utility to support the body and protect internal structures. These characteristics include strength and resistance to compression. Milling, grinding, and other methods for shaping and sizing bone may generally be considered minimal manipulation when they do not alter bone's original relevant characteristics

relating to its utility to support the body or protect internal structures.[33] In contrast, the original relevant characteristics of other tissues are specific to those tissue types. If you have questions about FDA's policies and views on the application of the minimal manipulation criterion to these tissue types, please see the guidance document, *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*.[34]

3. **From each of your respective standpoints, what are the criteria applied by the Device Center and the Biologic Center to determine whether product powdered wound dressing derived solely from human tissue should be classified as a device versus a biologic?**

    a. **Please explain how you apply these criteria to powdered wound dressing and other types of human tissue products that fall short of 361 HCT/P classification due to more than minimal manipulation.**

    For HCT/Ps that do not qualify for regulation solely under Section 361 of the PHS Act and 21 CFR Part 1271 (for example because the HCT/P does not meet the minimal manipulation criterion in 21 CFR 1271.10(a)(1)), FDA reviews on a case-by-case basis how to appropriately classify such products. As appropriate to the specific product at issue, FDA considers whether the product meets the definition of a biological product, drug, or device. FDA's 2017 Guidance for Industry and FDA Staff entitled *Classification of Products as Drugs and Devices and Additional Product Classification Issues* addresses FDA's thinking on many classification questions.[35]

The Honorable Neal Dunn, M.D.

Cloud Services

1. **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?**

[33] https://www.fda.gov/media/109176/download
[34] ibid
[35] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/classification-products-drugs-and-devices-and-additional-product-classification-issues

FDA shares the goal of maximizing the potential of technological advances, including clearer communications and digital experiences via modern platforms, streamlining data storage, ensuring data security, and promoting innovation to protect the public health.

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. 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. The Agency strives for alignment in the application of our regulations and policies across regulatory review programs, recognizing that differences in diseases, clinical endpoints, and the evidence submitted to support effectiveness may warrant an approach that is appropriately tailored to each application.

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.

Platforms

2. 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 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.

Rh Immunoglobin Supply

2. We are aware from the CBER website that there may be supply issues related to Rh Immunoglobulin – a plasma medicine. Many of these manufacturers are facing capital issues as a result of increased Medicare Part D rebates under the Inflation Reduction Act. How is CBER working with manufacturers on these supply chain issues?

CBER recognizes that it is important to patients and healthcare professionals to have access to the CBER-regulated products they need, when they need them, and works with all stakeholders on strategies to prevent and mitigate shortages of these products. With the ongoing shortage of some Rho(D) Immune Globulin (Human) products, CBER, working within its legal authority, has expedited BLA supplement reviews and has expedited lot releases to facilitate the availability of more Rho(D) Immune Globulin (Human) products for patients. Some Rho(D) Immune Globulin (Human) products are available and not currently in shortage.

We refer to CMS for any questions associated with implementation of the Inflation Reduction Act.

The Honorable Troy Balderson

For CMS, not an FDA issue

1. Both the nursing home staffing rule and the part of the access rule that is under scrutiny contain reporting requirements for providers to tell their states what percentage of payment they spend on the direct care workforce. How does CMS plan to support states in creating these reporting templates?

    a. How will CMS ensure any consistency in what is reported?

    b. How will CMS compare data across states if there isn't consistency in how it is defined and reported?

2. How is CMS going to know and distinguish if the non-workforce costs are, in fact, essential to running a business – such as making needed repairs on a nursing home or ensuring staff in people's homes have appropriate technology to do their jobs?
3. In the case of the HCBS Access rule 80/20 threshold, why is CMS mandating a threshold before gathering this data?

4. What data did CMS use to calculate an 80 percent threshold? The rule cites high level examples of ARPA projects but provides no actual data used. Please share all relevant data sources.

5. The ARPA projects referenced were never formally evaluated – does CMS have any plans to evaluate the effectiveness of the ARPA interventions?

6. Did CMS consider other ways in which the effects of this rule would not be unduly born on small providers? The small provider exemption is highly burdensome to states and still requires a plan for exempt providers to comply which undermines its effectiveness.

The Honorable Dianna Harshbarger

Rare Disease Efforts

1. **FDA has initiated several initiatives to facilitate and improve rare disease development, such as the CDER Rare Disease 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. 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 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 and consistency related to product review.

AMR

5. **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 must find substantial evidence of effectiveness and a demonstration of safety at the time of approval, which includes 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/10.7326/M16-0291?journalCode=aim**

Please refer to the above response.

Drug Trials and Approvals

6. 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 new drugs based on in-vitro and pre-clinical studies alone. Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), new 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 FDA's 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 FDA regulations at 21 CFR 300.50 and Agency guidance.

7. 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."

8. 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 Federal Food, Drug, and Cosmetic Act (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).

9. **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?**

10. **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.

Bone Marrow Concentrate

11. **I have heard from several physicians in Tennessee who use bone marrow concentrate (BMC) for appropriate uses in spine and musculoskeletal conditions in chronic pain patients. They believe BMC holds the promise to relieve a**

number of ailments while minimizing the need to utilize more opioids — something we can all agree is a good thing. My understanding is the agency has not yet updated its guidance for use of bone marrow concentrate. Can you tell me if the agency has or is planning to do so?

The Agency has not issued guidance, and is not currently planning to issue guidance, specific to use of bone marrow, or bone marrow concentrate. However, we believe that FDA's regulations and guidance documents provide clarity to help practitioners understand how the bone marrow they are using is regulated by FDA.

Under FDA's regulations, under certain circumstances, the use of autologous bone marrow may meet the same surgical procedure exception under 21 CFR 1271.15(b), which provide exceptions from the requirements in 21 CFR Part 1271. Even if the use of autologous bone marrow does not meet the same surgical procedure exception, the autologous bone marrow may meet the criteria in 21 CFR 1271.10 and be regulated solely under section 361 of the Public Health Service Act and the regulations in 21 CFR part 1271 under certain circumstances. Autologous bone marrow would not meet the criteria in 21 CFR 1271.10, for example, if it is more than minimally manipulated, is intended for nonhomologous use, or is combined with another article except for water, crystalloids, or a sterilizing, preserving or storage agent, and would generally be regulated as a drug and biological product that requires FDA's premarket review and approval. Allogeneic bone marrow for spine and musculoskeletal conditions in chronic pain patients would likely be regulated as a drug and biological product that requires FDA's premarket review and approval.

The Honorable John Sarbanes

AACC

1. **The Accelerated Approval Coordinating Council (AACC) was established to maintain the consistent and appropriate use of the accelerated approval pathway across FDA. How is AACC working to achieve this mission and promote consistency both across and within all Centers, and what are your expectations for the functioning of the Council and its deliverables?**

As required by FDORA, FDA has established an accelerated approval council, the Accelerated Approval Coordinating Council. The membership of the AACC includes the Directors (or designees) of the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER) and the Oncology Center of Excellence, as well as other senior officials as required by FDORA. The AACC has held meetings during both the 2023 and 2024 calendar year. The meetings included discussion of policy issues, including issues related to the new accelerated approval authorities contained in FDORA. As required by FDORA, FDA published a report on our website regarding the Council's activities in 2023.[36] We anticipate that the Council will continue to provide a senior-level forum to address policy issues related to accelerated approval

[36] https://www.fda.gov/media/174154/download

and help ensure that accelerated approval program is applied consistently and appropriately across FDA. The Agency will continue to publish an annual report on the activities of the Council.

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 insight gained through 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 it has been fully operationalized. FDA plans to develop metrics to assess both the outcomes of, and resources used, 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."[37]

2. **What additional measures can be taken by CBER/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

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

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 the Agenda 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 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 Lori Trahan

MDUFA

FDA Clarification: FDA's Center for Devices and Radiological Health is funded by MDUFA, as such Dr. Shuren responded to this question.

1. **For MDUFA V, Congress authorized the collection of nearly $2 Billion over the 5 year term of MDUFA. Please provide the following financial information:**

   a. **Number of CDRH employees whose salaries are paid by MDUFA funds.**

   In FY 2023, CDRH paid for 1,008 FTEs with MDUFA user fees. This includes CDRH's portion of shared service staff. "FTE employment," as defined by section 85 of the Office of Management and Budget (OMB) Circular A-11, reflects the total number of regular straight-time hours—not including overtime or holiday hours—worked by employees, divided by the number of compensable hours applicable to each fiscal year. Annual leave, sick leave, compensatory time off, and other approved leave categories are considered "hours worked" for purposes of defining FTE employment.

   b. **Amount of MDUFA funds spent on IT systems and digital transformation for the last 3 years.**

   Within CDRH, $107,735,800 in MDUFA user fees was spent on IT systems and digital transformation from FY 2021 through FY 2023.

   c. **Amount of MDUFA funds that pay for each of the covered activities (review process) listed in Section 737(9)(A) thru (k) and Section 737 (10).**

In FY 2023, **CDRH** spent a total of $282,643,476 in MDUFA user fees on costs to support the process for the review of device applications as defined in section 737(9)(A) through (K) and section 737(10) of the Federal Food, Drug, and Cosmetic Act.

IT Modernization

2. **FDA has shared multiple action plans to update its IT infrastructure to improve efficiency. This is important because we all saw the challenges the agency went through during Covid because of outdated IT. We also know industry has prioritized IT in the last PDUFA agreement and provided funding so FDA can accept submissions in the cloud. Given all the investment, FDA's own efforts via technology modernization action plan (TMAP) as well as Industry support, where is FDA today?**

   a. What progress has the Agency made?

   FDA has made substantial progress implementing its FDA Information Technology (IT) Strategy,[38] IT Operating Plan,[39] and improving industry collaboration. Key developments include executing the Department of Health and Human Services' procurement consolidation, which improves efficiency and reduces duplication, and the upcoming Electronic Submissions Gateway (ESG) Next Generation "NextGen" directive, which consolidates multiple gateways into a unified system aligned with PDUFA plans for cloud modernization. ESG NextGen replaces legacy systems with a modern, unified platform that ensures secure and efficient submission transfers and provides real-time status tracking. Also, FDA has and continues to modernize and strengthen our network and cloud environments, identity capabilities, Zero Trust focus, and data protections while deploying new digital services to facilitate more seamless data sharing across its global regulatory environment. Specifically, FDA has authorized 133 cloud service providers and applications. We will continue to adopt innovative tools and technologies like Artificial Intelligence, Machine Learning, data sharing, collaboration platforms, and High-Performance Computing to advance FDA's public health mission. FDA has made significant progress improving its IT Governance posture. We recently completed a comprehensive analysis of FDA's IT portfolio. This initiative vetted 350 projects and revealed the presence of over $140M of shadow IT—IT spend that were not traceable to enterprise-level governance processes. FDA has ensured that most of these projects (representing $110M) became compliant with Dept of Health and Human Services, Office of Management and Budget, and Federal Information Technology Acquisition Reform Act laws and governance policies. The remaining projects are expected to be closed out by Q2 of FY 2025.

   Additionally, Data as a Service (DaaS) initiatives have enhanced our ability to address supply chain challenges effectively. FDA is also refreshing and will publish

[38] https://www.fda.gov/about-fda/office-digital-transformation/fda-information-technology-strategy-fy-2024-fy-2027
[39] https://www.fda.gov/media/177127/download?attachment

its updated IT Strategy and IT Operating Plan by September 30, 2024. The updated IT Operating Plan will include a Customer Experience Strategy aimed at continuing our efforts to enhance user satisfaction across regulatory processes and applications. These documents will outline our latest goals, objectives, and strategic initiatives for further advancing our IT capabilities.

b. How is this progress helping improve the efficiency of drug review?

The modernization efforts have streamlined drug review processes by transitioning to cloud-based systems, which enhance data security and processing speed. ESG NextGen will play a crucial role in this transformation by replacing outdated systems with a unified user interface, secure submission capabilities, and real-time status tracking. These upgrades will contribute to faster review cycles and more efficient data management. The updated IT Strategy and IT Operating Plan will further support these improvements by detailing new initiatives and performance metrics designed to enhance review efficiency.

c. What details and metrics can you provide?

ESG NextGen has 10x times faster submission transfer speed and bandwidth, compared to legacy ESG. Additionally, account onboarding times will be significantly reduced from days to, in some instances, minutes. During our user acceptance testing, we are seeing and anticipating approximately 75 percent reduction in new account onboarding duration. We are also anticipating a 35 percent reduction in support and helpdesk tickets. The Unified Submission Portal (USP), meanwhile, provides real-time tracking and historical data. Similarly, as of the end of FY24 we have achieved significant progress in addressing our legacy hardware and technical debt with 87.24 percent of the combined total device scope completed, including 91.60 percent of physical servers decommissioned and 78.46 percent of End-of-Life (EoL) equipment fully decommissioned, reflecting strong advancements towards our strategic goals. The refreshed IT Strategy and IT Operating Plan will include updated metrics and clearer objectives. These plans reflect our ongoing commitment to technology advancement, global health standards, and enhancing the customer experience with a focus on accessibility and service efficiency.

Dose Optimization

3. **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)[40] 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[41] 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"[42] 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 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.

The Honorable Kathy Castor

Inclusion of Pregnant Women in Trials

1. **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

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

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.

What is your Center currently doing to advance the inclusion of pregnant and lactating women in clinical studies?

FDA Clarification: Response below written to address FDA activities across FDA offices and product centers.

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 (October 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.[43] Additionally, OWH maintains a searchable list of funded research projects by topic area.[44]

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.[45] The webpage currently lists 172 studies.[46] 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 a 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 the inclusion of pregnant women and lactating women in clinical studies.

- Upcoming: Workshop to be held July 2024 on Evaluating immunosuppressive effects of in utero exposure to drug and biologic products;
- September 2023 FDA Public Workshop on Optimizing postapproval pregnancy safety studies;
- May 2022 FDA Public Workshop on pharmacokinetic evaluation in pregnancy;
- June 2022 National Academies of Sciences, Engineering, and Medicine (NASEM) public workshop on Inclusion of pregnant and lactating persons in clinical trials
- May 2022 OWH/DPMH Webinar #1: Pregnancy and Lactation Medication Information for the Healthcare Provider
- October 2022 OWH/DPMH Webinar #2: Engaging Providers to Address Knowledge Gaps on Medication Use in Pregnancy and Lactation
- May 2022 OWH Public Meeting on Leveraging real world data to understand

[43] https://www.fda.gov/about-fda/nctr-research-focus-areas/perinatal-and-maternal-research
[44] https://www.fda.gov/consumers/owh-funded-research/project-areas-topic
[45] https://www.fda.gov/consumers/womens-health-topics/pregnancy-exposure-registries
[46] https://www.fda.gov/consumers/owh-funded-research/project-areas-topic

medication use in pregnancy and lactation;

- February 2021 Public workshop in collaboration with the Duke Margolis Center for Health Policy on scientific and ethical considerations for the inclusion of pregnant women in clinical trials.