CATHY McMORRIS RODGERS, WASHINGTON
CHAIR

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED EIGHTEENTH CONGRESS

Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202) 225-3641
Minority (202) 225-2927

June 14, 2024

Dr. Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Marks:

Thank you for appearing before the Subcommittee on Health on Wednesday, May 22, 2024, to testify at the hearing entitled "Check Up: Examining FDA Regulation of Drugs, Biologics, and Devices."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, July 31, 2024. Your responses should be mailed to Emma Schultheis, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to Emma.Schultheis@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Brett Guthrie
Chair
Subcommittee on Health

cc: Anna Eshoo, Ranking Member, Subcommittee on Health

Attachment

Attachment — Additional Questions for the Record

The Honorable Cathy McMorris Rodgers

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 The January 2023 draft guidance on dose optimization in oncology drug development does not address recommendations on dose optimization for rare diseases. Many of the dose optimization principles outlined in the draft guidance, such as randomization and having a trial sized for sufficient assessment of dosage, won't work in oncology, particularly for rare cancers.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

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

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

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?

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

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?

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

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?

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

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

    a. What is the range of approved numbers of days each work period?

    b. What is the most typical number of approved numbers of days each work period?

    c. How is the specified number of days enforced?

    d. Within each center, what percentage of employees are fully remote?

    e. Can FDA provide a summary of actions it is taking to increase the frequency and quality of interactions with sponsors?

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?

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.

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?

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

The Honorable Brett Guthrie

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. 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?

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

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?

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?

The Honorable Michael Burgess, M.D.

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?

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

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

The Honorable Robert Latta

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?

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?

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?

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 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?

    a. 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?

The Honorable Gus Bilirakis

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

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 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?

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

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?

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?

The Honorable Earl "Buddy" Carter

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?

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?

3. 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)?

4. 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.

The Honorable Neal Dunn, M.D.

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?

    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?

The Honorable Dan Crenshaw

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 rare diseases?

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

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?

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

3. 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?

The Honorable Troy Balderson

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

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?

2. 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?

    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

3. 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

4. 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"?

5. 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?

6. 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?

7. 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?

8. 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 Honorable John Sarbanes

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?

The Honorable Ann Kuster

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?

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?

The Honorable Lori Trahan

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.

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

    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).

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?

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

    c. What details and metrics can you provide?

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?

The Honorable Kathy Castor

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 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?