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ONE HUNDRED EIGHTEENTH CONGRESS

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June 14, 2024

Dr. Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10001 New Hampshire Avenue
Silver Spring, MD 20903

Dear Dr. Cavazzoni:

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 The January 2023 draft guidance on dose optimization in oncology drug development does not address recommendations on dose optimization for rare diseases. Many of the dose optimization principles outlined in the draft guidance, such as randomization and having a trial sized for sufficient assessment of dosage, won't work in oncology, particularly for rare cancers.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 The January 2023 draft guidance on dose optimization in oncology drug development outlines the risks of the maximum tolerated dose (MTD) strategy but doesn't discuss the risks of potentially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. The FDA is tasked with applying rigorous safety and efficacy standards to many new and emerging treatment types including cell and gene therapies and antisense oligonucleotides (ASOs). These therapies have the potential to deliver unprecedented

positive outcomes for patients. How, if at all, is the FDA educating its review staff and the agency more broadly on the unique nature of ASOs and other therapies?

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

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

The Honorable Michael Burgess, M.D.

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

2. The Pediatric Priority Review Voucher represents one of the great partnerships and collaborations between FDA and industry. It has come to our attention that FDA may be interpreting the "active ingredient" requirements in a broader way than Congress intended. This is particularly concerning regarding some of the transformative gene therapies coming through the agency. Many of these therapies may use the same delivery system – viral vectors – despite there being significant differences between the drugs themselves. Is there a statutory requirement that mandates FDA treat these viral vector delivery systems as the same "active ingredients" for purposes of awarding PRVs?

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

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

The Honorable Robert Latta

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

law, included report language that directs FDA "to maintain the necessary resources to evaluate PRV candidates in a timely manner." Does FDA anticipate making a decision on if these diseases qualify for the PRV this year?

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

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

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

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

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

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

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

5. As the fight against opioids, synthetics, and analogues continues to evolve, the FDA must remain vigilant to emerging threats like Tianeptine commonly referred to as "gas station heroin." According to the FDA, Tianeptine is not a dietary supplement. Executive and Medical Director of New Jersey's Poison Center, Dr. Diane Calello stated earlier this year, "If it [Tianeptine] got scheduled as a drug it would need to be clearly labeled. And right now, it's not scheduled at all. That's when we get into trouble because that's when the compounds can literally contain anything." Ohio's Board of Pharmacy has already classified Tianeptine as a Schedule I controlled substance banning its sale in my state.

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

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

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

The Honorable Gus Bilirakis

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

2. I strongly believe that patients' perspectives and real-world experience must be front and center when it comes to FDA weighing what benefits truly matter to patients and what risks they are willing to accept in taking a new drug product. I know that you have

several patient-focused drug development meetings coming up, including some for rare diseases with limited treatment options, and I hope you and your staff will listen carefully to what those patients have to say and apply those critical insights to your work. Can you speak to how FDA utilizes information gathered from such meetings, particularly around disease burden and current treatment options, in the agency's approval and labeling decisions?

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

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

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

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

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

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

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

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

The Honorable Richard Hudson

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

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

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

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

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

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

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

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

    a. Please explain how the agency sees the public health impact of the additional time it will take to develop new safe and effective smoking cessation drug products with the continued staggering mortality and morbidity resulting from the inability

of smokers seeking to quit to be more successful in their quit attempts with the current products available to them and how the agency's current posture on this issue will result in net public health benefit (if any)?

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

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

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

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

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

The Honorable Earl "Buddy" Carter

1. In 2016, Congress established the Drug Development Tools (DDT) Qualification Program through the passage of the 21st Century Cures Act. The DDT Qualification Program aimed to expedite drug development by qualifying novel tools, such as biomarkers, clinical outcome assessments, and other scientific methods. Congress intended for the program to provide clarity and predictability to stakeholders, including drug developers, academic researchers, and non-profits regarding the acceptance and utilization of such tools in the regulatory review process. Director Cavazzoni - It has been almost 8 years since the passage of 21st Century Cures, could you give us an update on the performance of the FDA DDT Qualification Program since its enactment?

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

    b. Do you think this program is a success?

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

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

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

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

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

3. In May 2023, FDA released its draft guidance titled, "Decentralized Clinical Trials for Drugs, Biological Products, and Devices" which displays the current thinking of the Agency on the implementation of decentralized trials (DCTs). This would mean that clinical trials could occur in places beyond a traditional clinical trial site, like homes or local health care facilities. For many patients, especially those with rare diseases or other comorbidities, leveraging telehealth with decentralized trials would help reach those who previously could not gain access to clinical trials. How has adoption of decentralized trials gone to date and what if any additional efforts from FDA are needed to ensure robust implementation of decentralized trials?

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

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

6. You are a physician, and I am a pharmacist. We are clinically-oriented people and yet today I know that the farther we get from clinical practice the more we lose some of that

pragmatic know-how of the challenges that patients face. What percentage of your front-line clinical reviewers in the Office of New Drugs are actively practicing clinically?

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

8. At the recent hearing, you testified that CDER tries to do everything it can as regulators to make drug development easier, efficient and streamlined as a contribution to innovation but actions speak louder than words. More than 8.6 million Americans have died from smoking since the last new product was authorized by CDER for smoking cessation. The bottom line is that CDER has set up a bifurcated approach to products for smoking cessation in your 2023 guidance. The products that are eligible to benefit from the modest provisions in that guidance are almost exclusively currently approved products that, as you know, are remarkably ineffective in the real world. Why has CDER taken such a bifurcated approach knowing the very limited real-world effectiveness of the handful of currently approved products and what more can and should CDER do to stimulate the interest of sponsors to come to you with truly innovative products so that new, safe and effective smoking cessation therapies reach patients in as timely a manner as possible?

The Honorable Neal Dunn, M.D.

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

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

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

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

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

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

4. 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/or rare diseases?

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

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

3. In May of 2024 the agency issued the Platform Technology Designation Program for Drug Development. How does FDA expect to staff the platform technology designation

process to ensure capacity for review and approval of platform designation applications – in addition to current workflow of review requirements?

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

   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?

4. At the recent Energy and Commerce Committee hearing you stated that CDER is interested and willing to work with developers on the issue of new tobacco cessation therapeutics. The agency's guidance sets forth that a trial is considered to demonstrate effectiveness if significantly more subjects achieve abstinence when treated with the investigational nicotine replacement therapy (NRT) drug product as compared to subjects treated with the placebo. The agency is defining abstinence as no cigarette use over the entire course of the efficacy ascertainment period, which depending on the product, may be many months long. The agency has repeatedly acknowledged how hard it can be to quit because of the addictive qualities of nicotine and that often smokers seeking to quit relapse. Yet, under the agency's guidance, if a clinical trial participant relapses, even if just one time, and smokes just one cigarette they would be considered a non-responder in the trial even if over the course of the entire trial they were able to reach the cessation endpoint despite a relapse.

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

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

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

5. On September 6th of last year, I wrote to you, along with Congressman Latta and Congresswoman Dingell, about your proposed rule on ACNU, Nonprescription Drug Product with an Additional Condition for Nonprescription Use. Particularly, the proposed concept of simultaneous marketing of both prescription and nonprescription versions of the same drug. There are concerns that this interpretation contravenes previous law. Can you commit to addressing these concerns in the final rule?

The Honorable Troy Balderson

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

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

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

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

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

4. Approving a new drug requires both "substantial evidence of effectiveness" and a conclusion that a drug's benefits outweigh its risk. Do you believe that the FDA should have the authority to approve drugs which have a positive benefit or risk profile even if

there is not substantial evidence of effectiveness, especially for life-threatening diseases where there is no other option for the patient?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The Honorable Mariannette Miller-Meeks, M.D.

1. Dr. Cavazzoni, some believe that obesity is a serious chronic disease that affects more than 100 million Americans. The Centers for Disease Control and Prevention (CDC) has stated that obesity is an epidemic in the United States. Since being obese and overweight are major risk factors for a broad range of chronic diseases including diabetes, the increase in their prevalence across the nation has major implications for the health and well-being of the country. In 2007, the Food and Drug Administration (FDA) released

draft guidance for industry developing products for weight management, which included recommendations regarding the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research (CDER) for the indication of weight management. In 2023, this draft guidance was listed on the Agency's review list. In light of the changes in the medical community's understanding of obesity and the drugs used to treat those living with obesity, including obesity being designated as a disease in 2013, and the approval of newer, safer, and more effective drugs, does the agency believe it is important to distinguish between weight loss drugs for cosmetic purposes and anti-obesity medications (AOMs)?

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

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

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

The Honorable John Sarbanes

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

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

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

The Honorable Debbie Dingell

Sunscreens

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

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

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

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

Obesity and Drug Efficacy

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

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

Drug Shortages

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

Hearing Aids

Nearly 5 years after Congress passed the 2017 FDA Reauthorization Act, which included a provision mandating that FDA establish rules for the sale of over-the-counter hearing aids, the rule finally became effective in October 2022. With this new category, we are seeing an increase of new market participants. With more pathways for individuals with hearing loss to access hearing aids, it is crucial that we ensure companies operating in this space are playing by the rules and that FDA is exercising its appropriate oversight and enforcement authority to ensure the safety and efficacy of these medical devices. To that end, multiple issues have been identified with the potential to create greater consumer confusion or, worse, place consumers at an increased safety risk.

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

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

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

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

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 and CDER to address the opaque and lengthy regulatory process that negatively impact rare disease patients access to therapeutics?

The Honorable Robin Kelly

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

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

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

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

The Honorable Diana DeGette

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

1. Under the agency's guidance, the only indications a new NRT product may initially seek are limited to smoking cessation and reduction in risk of relapse. A new NRT product must first be approved as a smoking cessation drug product before being able to seek an indication for reducing the urge to smoke or relief of cue-induced cravings. Why is reducing the urge to smoke or the relief of cue-induced cravings not acceptable as an indication for a new NRT product?

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

The Honorable Jan Schakowsky

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

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

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

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

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

The Honorable Kathy Castor

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

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

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

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

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

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

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