June 1, 2023

The Honorable Robert Califf, M.D.
Commissioner
U.S. Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Califf:

Thank you for appearing before the Subcommittee on Health on Thursday, May 11, 2023, to testify at the hearing entitled "Preparing for and Responding to Future Public Health Security Threats."

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 and requests with a transmittal letter by the close of business on Thursday, June 15, 2023. Your responses should be mailed to Jolie Brochin, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to Jolie.Brochin@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 1—Additional Questions for the Record

The Honorable Cathy McMorris Rodgers

1) **In your letter response dated May 9, you indicated that only 44 percent of registered drug manufacturers were providing complete volume data pursuant to those requirements included in the passage of the CARES Act in 2020. What actions have you taken to increase compliance? Please include a list of any specific enforcement actions, such as warning letters, that are publicly available.**

The Agency has taken several steps to implement the FD&C Act section 510(j)(3) amount reporting requirements (as added by the CARES Act), including releasing two guidance documents (i.e., draft guidance and technical conformance guide), expanding our electronic portal to accept drug amount reporting information from registrants, and hosting a day-long webinar with multiple question and answer sessions dedicated to providing manufacturers and the public with information regarding the drug amount reporting requirements.

The Agency has also made clear that while the process is ongoing to finalize the reporting guidance as part of the Agency's implementation efforts, it is manufacturers' legal obligation under the statute to report annually on the amount of each listed drug manufactured, prepared, propagated, compounded, or processed for commercial distribution. The Agency has communicated to drug establishments that FDA expects industry to fulfill their statutory obligation to report the appropriate data. We anticipate increased compliance after the issuance of a final guidance on drug amount reporting. FDA is currently reviewing numerous comments to the draft guidance as part of the ongoing process in finalizing the drug amount reporting guidance.

As of May 21, 2023, the Agency has received reported data associated with 3,493 establishments, or 47 percent of registered drug establishments.

Regarding enforcement and notification actions , the Agency has continued to remind firms of their obligation to provide this data. Since FDA's initial communication to industry in October 2021 announcing the draft guidance and use of the CDER NextGen Portal for amount reporting, we have held two webinars in January and September 2022 to educate firms on how to upload data, notified firms of a March 2022 Portal update, and in January 2023 reminded firms of their obligation to report. We also anticipate that issuance of the final guidance will lead to further reporting.

It is important to note that the Agency is actively working with firms to facilitate their compliance with this reporting provision. The Agency, as part of our general drug shortage efforts, maintains communication with firms to help ensure they are providing the Agency the most up-to-date information and are working with the Agency to resolve shortages when they occur. The Agency takes our responsibility to ensure that we receive the amount reporting information seriously but the agency has not yet taken enforcement actions against firms. The Agency actively works to avoid steps that could potentially cause or exacerbate shortages. Should firms continue to not report the required information under section 510(j)(3) of the FD&C Act (as added by section 3112(e) of the CARES Act), we may consider taking action in the future.

We also note that the drug amounts that manufacturers must report annually under the requirements

of FD&C Act section 510(j)(3) will provide insight into supply chains that could identify products at greater risk of shortage. However, the manufacturing amount data required to be submitted does not require manufacturers to identify their suppliers (e.g., where the sourced the API) and how reliant they are on such suppliers (e.g., how much API they used from each supplier to manufacture the amount of finished dosage form product they reported). This lack of a linkage between the amount of active pharmaceutical ingredient (API) manufactured and its allocation to specific finished dosage form (FDF) manufacturers, limit the utility of the data. The requested authority in the FY 2024 budget to require a link of these data reflect our effort to be responsive to requests from Congress regarding how our authorities could be enhanced to help address ongoing drug shortages. This proposal would greatly enhance the work we do to help address shortages.

2) **FDA's Orphan Drug Grant Program was established to support medical product advancement for diseases with unmet clinical needs. How has the program advanced the development and availability of treatments for rare neurodegenerative diseases?**

The FDA's Orphan Products Grants Program awards grants to clinical investigators to fund clinical and natural history studies to support the development of safe and effective medical products for patients with rare diseases. The program has supported clinical research since 1983 and has funded more than 690 clinical trials including 30 studies for rare neurodegenerative diseases. The program has facilitated the approval of more than 80 products for rare diseases.

Additionally, the FDA has funded 16 natural history studies since 2016 to help enhance our knowledge of the natural history of rare diseases. Nine of these natural history studies are for rare neurodegenerative diseases. Unlike common diseases, there is little existing knowledge on the presentation, major limitations on day-to-day function, core unmet needs and course of most rare diseases which makes drug development challenging.

The Accelerating Access to Critical Therapies for ALS Act (ACT for ALS) was enacted on December 23, 2021 and established the FDA Rare Neurodegenerative Disease Grant Program. This new grant program awards grants and contracts to public and private entities to cover the costs of research and development of interventions intended to prevent, diagnose, mitigate, treat, or cure ALS and other rare neurodegenerative diseases in adults and children.

In fiscal year 2022, FDA's Office of Orphan Products Development (OOPD) funded three natural history studies under the Orphan Products Grants program which serve to meet the intent of the ACT for ALS and are for: (1) ALS; (2) Myotonic Dystrophy Type 1; and (3) Ataxia-Telangiectasia. The study for ALS, co-funded by the National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke, has the potential to advance existing knowledge of the natural history of this disease, inform drug development, and possibly support future regulatory decisions. Key details about these three natural history study grants are provided below:

- University of Minnesota (Minneapolis, Minnesota); David Walk; Retrospective and prospective study in amyotrophic lateral sclerosis of clinic-based multicenter data collection; $1.6 million over four years

- Johns Hopkins University (Baltimore, Maryland); Howard Lederman; Prospective study in ataxia-telangiectasia; $1.6 million over four years
- Virginia Commonwealth University (Richmond, Virginia); Nicholas Johnson; Prospective study in myotonic dystrophy type-1 to establish biomarkers and clinical endpoints; $1.6 million over four years

FDA also awarded two contracts in fiscal year 2022. One contract is to develop and adapt a clinical outcomes assessment tool, called the ALS Functional Ratings Scale-Revised (ALSFRS-R), for remote use. Typically, the ALSFRS-R is an assessment done by a health care professional in the office. This study will adapt the tool to be used at home decreasing the amount of travel for patients and their families to participate in clinical trials. Once the remote-use ALSFRS-R is developed in English, it will be translated and culturally adapted to Spanish.

The second contract awarded in fiscal year 2022 is a landscape analysis of communication-type brain-computer interface (cBCI) devices focused on patient preference information (PPI) studies in ALS patients. FDA is specifically interested in BCI devices that allow a person to communicate when they otherwise cannot speak due to a disease such as ALS. It is possible that by enabling communication, such devices can preserve autonomy and allow patients to interact with their families and health care professionals. The contract will review the literature to determine what is already known about BCI devices and PPI studies in ALS.

In planning for FY 2023 grant funding opportunities for the FDA Rare Neurodegenerative Disease Grant Program, we sought input from patients, researchers, nonprofit organizations, companies, and other stakeholders on regulatory science research gaps that could advance medical product development (Docket FDA-2022-N-2544). Specifically, input was sought for development of regulatory science tools or other research and development needs in the preclinical or clinical space.

In FY 2023, FDA is focusing its efforts on two new funding opportunities:

(1) To support efficient natural history studies and/or biomarker studies that fill unmet needs for rare neurodegenerative diseases for children and adults. Through the support of prospective natural history and/or biomarker studies with high quality and interpretable data elements, FDA expects to address critical knowledge gaps, remove major barriers to progress in the field, exert a significant and broad impact on a specific rare neurodegenerative disease or multiple rare neurodegenerative diseases with similar pathophysiology, and facilitate rare disease product development. (RFA-FD-23-028)

(2) To support and inform the future development and use of clinical outcome assessments (COAs) for cBCIs in patients with ALS. This grant is a cooperative agreement and uses a UH2/UH3 grant funding mechanism involving two milestone driven phases: (1) the UH2 Phase will include a systematic landscape analysis of the available literature, relevant data sources, and interviews with key opinion leaders to document COAs for cBCIs used clinically and identify gaps between current COAs used in cBCI studies and other outcome measures that could demonstrate functional benefits for ALS patients with severe communication limitations; and (2) the UH3 phase will consist of patient and caregiver focus groups to collect information about symptoms, functional status, and perceived benefits/risks of BCIs. (RFA-FD-23-030)

3) **The "Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry" was issued in September of 2019[1]. How has this guidance, and its recommendations for drug development for ALS drugs, been implemented within CDER and CBER? What specific actions have been taken within the centers to ensure full understanding and reliance on this document by review staff?**

The FDA has taken significant steps since the release of the 2019 ALS guidance to encourage the development of ALS therapies. Through engagement with drug developers, emphasis on patient-focused drug development , support for innovative trial designs, expedited review pathways, and collaboration with stakeholders, FDA continues to facilitate the development of safe and effective treatments for ALS. These efforts are crucial in addressing the urgent needs of ALS patients and improving their quality of life.

As an initial matter, we note that FDA guidance documents generally do not establish legally enforceable rights or responsibilities. Rather, guidance documents describe the Agency's interpretation of, or policy on, a regulatory issue. FDA considers the Agency's guidance titled "Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry" in 2019 ("2019 ALS Guidance") to be an integral part of our ongoing efforts to support clinical development programs and clinical trial designs for drugs to treat ALS. Consistent with the request, we are providing updates on our efforts since the release of the guidance.

First, in June 2022, FDA released a five-year action plan for rare disease drug development titled *"Accelerating Access to Critical Therapies for ALS Act – ACT for ALS".*[1] The action plan is a blueprint for how the Agency will move forward in aggressively tackling challenges in drug development for rare neurodegenerative diseases, including ALS, in order to improve patients' health. Specific actions include regulatory science initiatives, enhancements to existing programs and new policy initiatives. The plan was developed in accordance with the provisions of the *Accelerating Access to Critical Therapies for ALS Act ("ACT for ALS")* that President Biden signed into law on December 23, 2021.

Second, the FDA has emphasized the importance of patient-focused drug development in ALS. Our efforts highlight the need to incorporate patient input into clinical trial design and the evaluation of treatment benefit-risk profiles. The FDA continues to encourage sponsors to include patient-reported outcomes and other relevant endpoints that capture meaningful changes in the patient's quality of life and disease progression. By incorporating patient perspectives, the FDA aims to ensure that the development of ALS therapies aligns with patients' needs and priorities. FDA recognizes the importance of stakeholder input when considering what constitutes a meaningful effect in the context of evaluating a drug's effectiveness. The September 2021 draft guidance *"Benefit-Risk Assessment for New Drugs and Biological Products"*[2] describes FDA's proposed perspective and approach to these issues and when finalized will represent FDA's current thinking.

Third, the FDA encourages the use of innovative trial designs and surrogate endpoints in ALS drug

[1] https://www.fda.gov/news-events/public-health-focus/accelerating-access-critical-therapies-als-act-act-als
[2] https://www.fda.gov/media/152544/download

development. Given the challenges associated with conducting traditional clinical trials in ALS, the agency has provided recommendations for alternative trial designs, such as adaptive designs and basket trials. Specifically, FDA has provided recommendations in the design of the Healey ALS Platform Trial,[3] the first platform trial in ALS that tests multiple drugs at once and has the potential to reduce research costs by decreasing the time to conduct clinical trials and increasing patient participation. These innovative approaches allow for more efficient and flexible clinical development, potentially accelerating the availability of safe and effective treatments for ALS patients.

Additionally, biomarkers serve a variety of roles and are valuable in drug development. For example, biomarkers serving as surrogate endpoints that are reasonably likely to predict clinical benefit are important for use in the accelerated approval pathway. As discussed in the 2019 ALS Guidance, FDA values and encourages the incorporation of biomarkers in all phases of clinical development, with the goal that a greater scientific understanding of ALS would provide opportunities for the use of surrogate endpoints that are reasonably likely to predict clinical benefit and that might serve as a basis for accelerated approval. Notably, this goal was reached for the first time on April 25, 2023, with the approval of tofersen for the treatment of ALS in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene under the accelerated approval pathway. This approval was based on reduction of a biomarker of neurodegeneration, plasma neurofilament light chain (NfL), observed in patients treated with tofersen. However, there remain challenges in identifying appropriate biomarkers in many diseases, including ALS and other neurological diseases, because there is very limited understanding of the underlying pathophysiology that leads to disability and other outward manifestations of these diseases. Understanding this is often critical for the successful development of surrogate endpoints. More specifically, even though there may be many different biomarkers that are altered in the disease (such as imaging findings, abnormalities of particular proteins in the cerebrospinal fluid, or altered circulating proteins), whether these measures actually are in the direct sequence of pathogenesis is often unknown. A drug may alter a particular biomarker, but whether that change actually means, or is reasonably likely to predict, that the drug will improve the clinical course of the disease, and therefore lead to a meaningful benefit for patients, may be unclear. FDA actively works with sponsors on the identification and use of potential biomarkers that will facilitate and expedite the development of new safe and effective therapies for ALS and other neurological disorders.

Fourth, the FDA has prioritized the review of ALS therapies through its expedited programs. The Agency has implemented expedited pathways, such as Fast Track designation, Breakthrough Therapy designation, Regenerative Medicine Advanced Therapy designation, and Accelerated Approval, to facilitate the development and review of promising ALS treatments. These pathways provide increased access to regulatory advice, more frequent interactions with the FDA, and expedited review timelines, aiming to bring potentially life-saving therapies to patients in a timely manner.

Finally, the FDA has actively collaborated with other stakeholders, including patient advocacy groups, researchers, and industry, to advance ALS drug development. The Agency has participated in public workshops and meetings to gather input and share scientific knowledge. Examples include:

[3] Paganoni S, et al. Adaptive Platform Trials to Transform Amyotrophic Lateral Sclerosis Therapy Development. Ann Neurol 2022;91:165–175.

- In collaboration with NIH and as part of Critical Path Rare Neurodegenerative Disease Public Private Partnership (PPP), FDA hosted a meeting on March 15, 2023, for patients, patient advocates, and other stakeholders to provide them insight into the initial plans for the PPP and opportunities to be involved.
- FDA organized the FDA Neurodegenerative Disease Task Force, which has met several times to promote research under the grant program that reflects regulatory science priorities and is consistent with FDA's framework.
- FDA worked with NIH on the inaugural meeting of the new Accelerated Medicines Partnership for ALS, an expansion of the ACT for ALS PPP between FDA and NIH. NIH will be promoting data exchange with industry partners with the goal of identifying new biomarkers to drive development of therapeutics.
- FDA funded an effort to explore the use of the ALSFRS-R, a common endpoint for ALS clinical trials, in the home. This effort includes a patient committee, which includes patients with ALS as well as caregivers to provide advice regarding how patients and caregivers use technology in their homes and what would be feasible to complete in a remote setting.
- FDA launched the FDA Rare Neurodegenerative Disease Grant Program under section 5 of the ACT for ALS Act. In fiscal year 2022, FDA's Office of Orphan Products Development (OOPD) awarded two contracts. First, the ALS Functional Rating Scale-Revised Clinical Outcome Assessment Remote-Use Equivalency Study will adapt a trial endpoint, called the ALSFRS, for remote use. Typically, the ALSFRS is an assessment done by a health care professional in the office. This study will determine whether this assessment could be done at home, decreasing the amount of travel for patients and their families to participate in clinical trials. Additionally, the contract will include a Patient Consulting Committee for advice, transparency and oversight and translate the remote tool to Spanish. Second, the Landscape Analysis of Brain-Computer Interface Focused Patient Preference Studies in ALS Patients will perform a landscape analysis of patient preference information (PPI) studies focused on brain-computer interface (BCI). FDA is specifically interested in BCI devices that communicate with the brain providing patients with the ability to interact with their families and health care professionals. The contract will review the literature to determine what is already known about BCI devices and PPI studies in ALS. This perspective will help inform FDA's assessment of the benefit-risk profile for these devices and may lay the foundation for future PPI studies for BCIs in ALS patients.

By fostering collaboration and information sharing, FDA aims to leverage collective expertise and resources to accelerate the development of effective therapies for ALS.

4) **In January of this year, you announced that FDA's Centers for Drugs and Biologics will resume in-person, face-to-face meetings beginning in February. This was welcomed news, given that the agency's reliance on remote engagement and "written responses only" (WRO) has raised concerns from regulated industry over the impact of these practices on new drug development.**

a. **What is the status of FDA's plans to resume in-person operations agency-wide?**
b. **What is the breakdown of meetings granted face-to-face versus WRO across each review center since March 2020?**

CDER,CBER:
Beginning June 12, 2023, CDER and CBER will expand in-person face-to-face (FTF) industry meetings (with a hybrid component), to include requests for Type B End-of-Phase 2 (EOP2), along with the previously announced Type A, BPD Type 1, and Type X meeting requests. FTF meeting requests for other meeting types, if granted, will be held fully virtually (i.e., the in-person format will not be considered). Existing meeting requests received before June 12, 2023, or meetings already scheduled regardless of the scheduled meeting date, will not be converted to the in-person format, to permit fair implementation of the transition.

CDER and CBER will continue to frequently monitor conference room upgrades, and as additional rooms are completed, we will continue the expansion until all formal meeting types that would qualify for FTF can be requested as in-person.

As of June 7th, the metrics on meeting requests are as follows:

CDER PDUFA Face-To-Face Meetings:

- 43 eligible (Type A) Meeting Requests received since we announced we were returning to select in-person FTF meetings.
- Of the 43 meeting requests, 11 requests were for in-person FTF meetings and were granted.

BsUFA Face-To-Face Meetings:

- 4 eligible (BPD1) Meeting Requests received since we announced we were returning to select in-person FTF meetings.
- Of the 4 meeting requests, none were requested in-person.

GDUFA Face-To-Face Meetings:

- 27 meeting requests received since the March 27, 2023 resumption announcement
- Of the 27, 4 requests were for in-person meetings
- Of the 4, 1 was granted *(denials were unrelated to the requested FTF meeting format)*

OMUFA Face-To-Face Meetings:

- No eligible (Type X) Meeting Requests received.

CBER PDUFA Face-To-Face Meetings

- 1 eligible (TypeA) Meeting Request received since we announced we were returning to select in person FTF meetings.
- Of the 1 meeting request, 1 request was for an in-person FTF meeting and was granted.

CDRH:
Beginning June 1, 2023, CDRH will expand in-person meetings with external stakeholders, including industry, to include requests for submission-specific interactions with sponsors. These meetings will include a hybrid component, as do meetings for CDER and CBER.

Since January 2023, CDRH has held 26 in-person meetings with stakeholders, with another 6 meetings scheduled throughout the summer so far. The Center will continue to schedule in-person meetings going forward.

CVM:

ADUFA

- 68 meeting requests received since we announced at the end of January 2023, we were returning to FTF meetings.
- Of the 68, 13 were requested to be in-person and were granted.

AGDUFA

- 14 meeting requests received since we announced at the end of January 2023, we were returning to FTF meetings.
- Of the 14, 3 were requested to be in-person and were granted.

CFSAN:
CFSAN has found through the COVID pandemic the tremendous value that virtual meetings offered in facilitating our ability to respond meaningfully and rapidly to stakeholder meeting requests. However, since the time that COVID community levels declined we have been working with stakeholders to accommodate in-person and hybrid meeting requests. We have also had leadership routinely attend externally hosted meetings in-person.

CTP:
The Center for Tobacco Products (CTP) receives requests for meeting/listening sessions from stakeholders such as industry trade groups and advocacy organizations, as well as formal industry meeting requests to provide feedback and information to tobacco product manufacturers and investigators on questions and concerns pertaining to compliance with regulations and requirements regarding the research, development, and marketing of tobacco products.

CTP's process for evaluating pre-submission meeting requests has been in place since 2015. CTP determines whether a face-to-face meeting, teleconference, or written response is the appropriate course of action for each individual request. CTP may also determine that a written response is unnecessary or inappropriate, and deny a request, for reasons such as the following: the requestor did not provide enough information for FDA to determine the utility of the meeting, the requestor is trying to circumvent the review process, or the requestor is asking questions whose answers have already been made publicly available. During FY 2022, CTP received 14 pre-submission meeting requests for PMTAs. FDA responded in writing to nine of these requests and denied five requests.

This process increases efficiencies while being responsive to industry.

In FY 2023, CTP has increased the number of in-person engagements with stakeholders. This includes participation in more than nine in-person conferences over the last year and an in-person Tobacco Products Scientific Advisory Committee meeting. In terms of individual meetings with stakeholders, whether a stakeholder requests a videoconference or in-person meeting, CTP tries to accommodate that request; CTP has found that many stakeholders prefer video conference.

5) **HHS's leadership and coordination of public health emergencies has been placed on GAO's high-risk list. What are FDA's specific priorities and planned actionable items to address the concerns raised by GAO to ensure our nation is more prepared for future public health emergencies than we were for the COVID-19 pandemic and prior threats?**

In September 2022, FDA formalized a senior-level Integrated Strategic Human Capital Planning Council (ISHCCP) with representatives from FDA's centers and offices to establish updated FDA-wide strategic human capital goals and objectives; evaluate recruitment and retention risks in consultation with subject matter experts; prioritize FDA capability areas and Mission Critical Occupations (MCOs); draft an FDA Strategic Workforce Plan; and monitor progress to ensure alignment with HHS and FDA priorities and to maintain compliance with legislative requirements and Federal regulation. As of June 2023, FDA has a draft of the Plan that is undergoing review and refinement with expected completion by September 30th, 2023.

The plan will demonstrate strategic alignment with related human capital plans, goals, and objectives (such as HHS strategic goals, FDA leadership priorities, and the OPM Human Capital Framework). Elements of the draft plan include: an environmental scan of FDA hiring, retention, and training/development efforts; an overview of major human capital improvement projects; a workforce skills gap analysis and prioritization strategy; its human capital goals with supporting actions; and a roadmap for evaluating progress and future planning, including specific performance measures and key performance indicators.

The Honorable Earl L. "Buddy" Carter

1) **Are there ways FDA can, through rulemaking or guidance for industry, put a more permanent framework in place for compounding pharmacies, both 503A state licensed pharmacies as well as 503B outsourcing facilities, to step up and help mitigate drug shortages while the drug manufacturers take steps to ramp up production?**

Preventing and mitigating drug shortages is a priority for FDA. Throughout our work to address drug shortages, we continue to evaluate factors impacting firms that could help address supply issues, including both traditional drug manufacturers and compounders, while working to address potential risks to patients.

Provisions in sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) address compounders such as pharmacies and outsourcing facilities preparing drug products in

shortage. FDA has issued guidances that describe policies related to compounding drugs that appear on FDA's drug shortages list. These policies include, for example, a period for outsourcing facilities to fill orders for compounded drugs that are identical or nearly identical to approved drugs that were on FDA's drug shortage list at the time that the outsourcing facility received the orders provided the drugs appeared on FDA's drug shortage list within 60 days of the outsourcing facility distributing or dispensing the drugs.

FDA continues to evaluate these and other compounding policies to mitigate drug shortages when appropriate. Given the rapidly evolving nature of the drug shortages landscape, the complexity of this issue, and the variety of tools at FDA's disposal to prevent and mitigate shortages, it is important for FDA to be able to carefully consider and balance the risks to the public from drug shortages against the risks of patients receiving a compounded drug when a shortage has resolved, and an FDA-approved drug is again available. FDA is engaged with drug compounders to understand potential barriers to preparation of drugs during shortages to inform future policy considerations. FDA is actively considering feedback on these matters, including feedback on the guidance documents noted above.

2) **Should Congress provide FDA with more flexibility in the law as it relates to the legal authority for compounding pharmacies and outsourcing facilities to compound drugs in shortage, including those needed for urgent administration to patients in clinical settings like the COVID guidance for industry did?**

As noted above, provisions in sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) address compounders such as pharmacies and outsourcing facilities preparing drug products in shortage. The COVID-19 public health emergency led to unprecedented disruptions to, and demands on, the global pharmaceutical supply chain. FDA published temporary guidances, which have expired, on compounding of certain drugs during the COVID-19 public health emergency to help ensure that treatment options were available when hospitals were unable to obtain FDA-approved drugs used for hospitalized patients with COVID-19. At this time, FDA believes the tools currently at the Agency's disposal allow us to work with drug compounders on shortage issues when necessary and appropriate. FDA has investigated serious adverse events and serious product quality issues associated with certain compounded products and would have concerns if section 503A or 503B of the FD&C Act were amended to provide broader allowances than currently exist for compounding drug products in shortage.

3) **With the upcoming expiration of several authorities and grant programs provided in the Pandemic and All-Hazards Preparedness Act (PAHPA), what adjustments should we consider in order to better encourage and support domestic pharmaceutical and medical product manufacturing within the U.S. to ensure a reliable and sustainable supply chain?**

Reliance on foreign manufacturing is not a new concern for FDA. There are some things we can do to make it easier for manufacturing to be done in the United States, however there are significant economic issues that are out of our purview that have contributed to increased foreign manufacturing, specifically, pricing pressures, labor and regulatory costs. Within FDA the most important thing we can do to help reduce our reliance on foreign manufacturing is to

encourage and facilitate the adoption of advanced manufacturing. Ensuring that both brand drug and generic drug manufacturers will have access to advanced manufacturing technologies is vitally important because advanced manufacturing requires a skilled workforce and can help domestic companies operate with lower costs and fewer quality defects in smaller facilities, improving the global competitiveness of U.S. manufacturing.

The Honorable Gus Bilirakis

1) **Regulatory flexibilities temporarily adopted during the Covid-19 pandemic allowed manufacturers to establish end-to-end domestic production for vaccines and therapeutics. However, it is known that this is not the case for the majority of medical countermeasures or other medicines and it is a concern that regulatory hurdles will lead to greater offshoring of production and disincentivize domestic production of medicines.**
    - **What steps is FDA taking to codify and adopt the regulatory flexibilities for adaptable supply chains, speedier inspections, and expedite the approval of these much needed innovations?**

The last three years of the COVID-19 pandemic underscore the need to continue to optimize our preparedness and response capabilities. The Agency's continued preparedness for, and capabilities to respond to, public health emergencies and disease threats such as COVID-19, mpox, respiratory syncytial virus, and pandemic influenza have been strengthened by Congress' support of our work. Our efforts are in close coordination and collaboration with our partners, both within HHS and across the federal government, to help facilitate the development, authorization, licensure, approval, clearance, and availability of critical, safe, and effective medical products and help ensure the continuity of the food supply to address current and future public health threats.

One of the lessons learned from the COVID-19 pandemic was the importance of a swift and agile response coordinated across all levels of government and in collaboration with the private sector. Through effective communication, dexterity, and innovation, we were able to mitigate the impact of the pandemic and prevent innumerable illnesses and deaths. From the beginning of the COVID-19 public health emergency (PHE), FDA has taken a leadership role in the all-of-government response and continues to focus on facilitating the development and availability of medical countermeasures (MCMs) to diagnose, treat, and prevent COVID-19; surveilling the medical product and food supply chains for potential shortages, disruptions, and contaminated or fraudulent products; and helping to mitigate or prevent such impacts. Looking ahead, FDA is committed to continuing to use every tool in our toolbox to prepare for chemical, biological, radiological, and nuclear (CBRN) response activities, fight future public health emergencies, arm ourselves with the best available MCMs, and support U.S. response efforts.

As I noted in my testimony there are several legislative proposals the Agency would like to work with you and the Committee on to ensure we can learn from the COVID-19 pandemic and ensure

we have the appropriate statutory authorities to be ready for the next pandemic.

2) **To be a global leader, America needs to be able to reinvest in itself , the US needs to be a net exporter of these important medical products and supplies. Does FDA have plans to expand use of mutual reliance agreements to improve regulatory efficiency and ensure there aren't barriers to domestic production because the U.S. system creates barriers for production that may not be present in other countries?**

To enhance regulatory efficiency, FDA has negotiated and implemented several Mutual Recognition Agreements (MRAs) with partnering authorities to share and use each other's good manufacturing practice (GMP) inspection reports. These MRAs reduce duplication and allow the FDA and its partners to reallocate their resources and expand their inspectional reach. FDA signed an amended MRA with the EU in March 2017 and fully implemented this MRA for human drugs in July 2019. Since then, FDA has engaged with the EU and other like-minded authorities to expand the use of the EU MRA. Most recently, FDA and the EU announced on May 31, 2023, the joint decision to expand and implement the U.S.-EU MRA to include veterinary medicines. FDA has also negotiated additional MRAs, including an MRA with the UK which entered into force on January 1, 2021.

The Honorable Angie Craig

The COVID-19 pandemic laid bare many shortcomings in our public health infrastructure. In Minnesota, as in other parts of the country, our economy and medical response systems were hampered by supply-chain constraints from which they have yet to fully recover.

For example, reports out of our state have indicated that there is a critical shortage of liquid albuterol, a medication commonly used to treat breathing problems. As a matter of fact, one of my constituents who has COPD and uses nebulizers three times a day recently had to have a family member drive all the way to North Dakota to retrieve the medication because it wasn't available at any closer pharmacies. Albuterol has been on the FDA's shortage list since October.

As stateside shortages persist, I am growing more concerned by America's increasing reliance on foreign-produced active pharmaceutical ingredients, or APIs. I am proud to serve as a Co-Chair of the bipartisan Congressional Supply Chain Caucus, and as such, I am always searching for ways to improve our domestic supply chains and lower costs for hardworking Americans.

Specifically, I am interested in what we can do to bring more production of APIs back to our shores. As we saw with COVID-19, if one region is shut down due to an outbreak or other disaster, that can impact the entire world's access to lifesaving drugs. One potential avenue for increased domestic production is increased advanced and continuous manufacturing technologies, which can improve efficiency and drug quality, making the process easier to onshore.

1) **Dr. Califf, can you tell us more about how these advanced manufacturing technologies can increase domestic production of pharmaceuticals, and how FDA is**

working to increase available advanced manufacturing technologies?

The need for advanced manufacturing technologies—which hold promise to strengthen the nation's public health infrastructure, strengthen the domestic supply chain, and further renew U.S. jobs and manufacturing—has never been more evident than in the context of COVID-19.

Thanks to the resources Congress has provided in recent years, we have been able to encourage deployment of these technologies by providing greater clarity and confidence for businesses looking to invest in this space.

Our work is far from done. With the most recent funding we received as part of the FY 2021 reconciliation bill, we are continuing to work to improve efforts in this space. The U.S. pharmaceutical and biotechnology industries are moving toward advanced manufacturing technologies such as continuous manufacturing for both small-molecule drugs and biological products (e.g., monoclonal antibodies, cell and gene therapies and vaccines), advanced process monitoring and control, and artificial intelligence/machine learning, to improve the agility, flexibility, cost, and robustness of their manufacturing processes.

FDA encourages the development and adoption of these advanced technologies to modernize manufacturing. This modernization effort aims to create a more flexible, agile and robust manufacturing process with fewer interruptions in production, fewer product failures (before or after distribution), greater assurance that products manufactured will provide the expected clinical performance, and timely response to evolving demands of critical drugs, biological products, and medical devices.

The Honorable Diana Harshbarger

It has been over twenty years since the FDA promulgated a Rule to limit aluminum contamination and toxicity in parenteral nutrition ("PN") products which are used to sustain most preterm infants.[2] Preterm infants are especially at risk for aluminum toxicity, such as developmental delays, neurological disorders and bone toxicity, because their kidneys, which are the primary aluminum elimination mechanism, are underdeveloped. The FDA established that total daily exposure of greater than 4-to-5 mcg/kg aluminum will result in toxicity, and tissue accumulation starts even at lower doses. The medical and scientific consensus points to minimizing aluminum exposure for the safety of patients utilizing PN products. Aluminum toxicity danger to neonatal patients can come from products even if they are labeled solely for adult use. There are more than 380,000 preterm infants born each year in the United States with distinct health inequity profiles, which amount to an economic burden estimated at $25 billion per year. This ongoing serious public health issue is very **preventable**.

1) **Why does the FDA seem to be moving in the opposite direction of safeguarding the nation's most vulnerable neonatal patients from aluminum toxicity from PN products? More specifically: Instead of requiring drug manufacturers to reduce aluminum in their PN products to as low a level as technically feasible, why does the Agency's December 2022 draft guidance seem to give allowance to PN products with aluminum levels higher than other comparable approved PN products (regardless of whether they are labeled for adult or pediatric patients), thus possibly endangering vulnerable**

neonatal patients?

- **How is this consistent as a matter of policy with the FDA's proposed FY '24 budget request for increased Agency authority and funds to effectuate and enforce lower levels of toxic metals (aluminum included) in foods for pediatric population?**

The December 2022 draft guidance for industry, *Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations* (Draft Guidance),[4] [5] recommends that the daily total aluminum exposure from parenteral nutrition (PN) products should "not exceed 5 mcg/kg/day" to protect the safety of all patients. The recommendation is applied to "all patients" because patients with renal impairment, including all preterm neonates, comprise a major portion of all patients requiring PN support, and as specified in the warning language in FDA's existing regulatory requirement at 21 CFR 201.323(e) that predates the December 2022 draft guidance, patients with renal impairment who receive prolonged parenteral administration are at particular risk of aluminum toxicity.

Your question cites the following statement in the required labeling warning language for aluminum toxicity (21 CFR 201.323(e)), in relation to the Total Aluminum Exposure (TAE) of 4-5 mcg/kg/day:

"Tissue loading may occur at even lower rates of administration."

This statement indicates that loading (accumulation) of aluminum in tissues may occur at exposures lower than 4-5 mcg/kg/day. However, we are not aware of clinical data indicating that central nervous system or bone toxicity has occurred at aluminum exposures lower than 4-5 mcg/kg/day. Further, if the TAE was required to be lower than 4-5 mcg/kg/day, then this may severely diminish the availability of approved parenteral nutrition products because it may not be feasible for manufacturers to achieve lower aluminum levels in their products without a significant investment of resources. Such requirements could drive manufacturers out of a market for which there is already only a small number of suppliers. Thus, the Agency's recommendation of a daily TAE limit of 5 mcg/kg/day is the result of a benefit/risk approach based on the available scientific data and current manufacturing and supply considerations, and is also consistent with the existing regulatory warning label requirement. This approach is optimized to meet the medical needs of the targeted patient population.

<u>The Honorable Morgan Griffith</u>

1) During an exchange during the PAHPA hearing on May 11th the Congressman Morgan Griffith requested a response in writing regarding enforcement of the CARES Act volume

[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/small-volume-parenteral-drug-products-and-pharmacy-bulk-packages-parenteral-nutrition-aluminum

[5] When final, this guidance will reflect the Agency's current thinking.

reporting provisions.

Thank you for your thoughtful questions during the Energy and Commerce Health Subcommittee hearing "Health Subcommittee Hearing: "Preparing For And Responding To Future Public Health Security Threats". During our exchange you asked for more information regarding Section 3112 of the CARES Act, "Additional manufacturer reporting requirements in response to drug shortages." You were specifically interested in the number of firms reporting and any enforcement actions the Agency has taken against noncompliant firms.

For background, the Agency has taken several steps to implement the amount reporting requirements under FD&C Act section 510(j)(3), as added by CARES Act section 3112(e), including releasing a draft guidance (and technical conformance guide)[6][7], expanding our electronic portal to accept drug amount reporting information from registrants, and hosting a day-long webinar with multiple question and answer sessions dedicated to providing manufacturers and the public with information regarding the drug amount reporting requirements[8].

The Agency has also made clear that while the process is ongoing to finalize the reporting guidance as part of the Agency's implementation efforts, it is manufacturers' legal obligation under the statute to report annually on the amount of each listed drug manufactured, prepared, propagated, compounded, or processed for commercial distribution. The Agency has communicated to drug establishments that FDA expects industry to fulfill their statutory obligation to report the appropriate data and as of May 21, 2023, the Agency has received reported data associated with 3,493 establishments, or approximately 50 percent of registered drug establishments. We anticipate increased compliance after the issuance of a final guidance on drug amount reporting. FDA is currently reviewing numerous comments to the draft guidance as part of the ongoing process in finalizing the drug amount reporting guidance.

The Agency has continued to remind firms of their obligation to provide this amount reporting data. As noted earlier, since FDA's initial communication to industry in October 2021 announcing the draft guidance and use of a web-based portal for reporting, we have held two webinars in January and September 2022 to educate firms on how to upload data, notified firms of a March 2022 Portal update, and in January 2023 reminded firms of their obligation to report. We also anticipate that issuance of the final guidance will lead to further reporting. The Agency intends to consider taking action against firms that have not fulfilled their statutory obligation to report this information after the final guidance is issued.

It is important to note that the Agency is actively working with firms to bring them into compliance with this reporting provision. The Agency, as part of our general drug shortage mitigation efforts, maintains communication with firms to help ensure they are providing the Agency the most up-to-date information and are working with the Agency to resolve shortages when they occur. The Agency takes our responsibility to ensure that we receive this amount reporting information seriously but the Agency has not yet taken enforcement actions against firms. The Agency actively works to avoid steps that could potentially cause or exacerbate shortages. Should firms continue to not report the required information under section 510(j)(3) of the FD&C Act (as added by section 3112 of the CARES Act), we may consider taking action in the future.

We also note that the drug amounts that manufacturers must report annually under the requirements of

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[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-amount-listed-drugs-and-biological-products-under-section-510j3-federal-food-drug-and

[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-amount-listed-drugs-and-biological-products-technical-conformance-guide

[8] See "Webinars" section on FDA's Website: https://www.fda.gov/drugs/drug-shortages/coronavirus-aid-relief-and-economic-security-act-cares-act-drug-shortage-mitigation-efforts#Reporting

FD&C Act section 510(j)(3) (as added by the CARES Act) will provide insight into supply chains that could identify products at greater risk of shortage. However, the manufacturing amount data required to be submitted does not require manufacturers to identify their suppliers (e.g., where the sourced the API) and how reliant they are on such suppliers (e.g., how much API they used from each supplier to manufacture the amount of finished dosage form product they reported). This lack of a linkage between the amount of active pharmaceutical ingredient (API) manufactured and its allocation to specific finished dosage form (FDF) manufacturers, limit the utility of the data. The requested authority in the FY 2024 Budget to require a link of these data reflect our effort to be responsive to requests from Congress regarding how our authorities could be enhanced to help address ongoing drug shortages. This proposal would greatly enhance the work we do to help address shortages.