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By Electronic Submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Comment on "Promoting Effective Drug Development Programs: Opportunities and Priorities for the Food and Drug Administration's Office of New Drugs"
[Docket No. FDA-2019-N-3453]

Dear Madam/Sir:

Pfizer Inc. (Pfizer) is submitting these comments in response to the Federal Register notice of August 12, 2019 (84 FR 39856-39858). We applaud the FDA for having convened the November 7th, 2019 hearing on promoting effective drug development programs, and Pfizer appreciated the opportunity to offer our perspectives. The written comments below elaborate upon the verbal statement delivered at the public hearing.

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety, and value in the discovery, development, and manufacture of health care products. From specialized efforts in biosimilars and rare disease to oncology and vaccines, we are committed to developing medical solutions that will matter most to the people we serve.

Pfizer appreciates the agency's ongoing efforts to enhance the drug development process within the broader context of the modernization of the Office of New Drugs (OND). We agree that a flatter OND organization driven by cross-disciplinary collaboration and an integrated review template will lead to a more efficient, consistent, and predictable review process. A dedicated OND policy function coupled with new opportunities for FDA division directors to engage the scientific and patient communities will help to further advance new innovative standards for drug development.

Pfizer would like to offer several recommendations that FDA, industry, academia, and patients can take jointly to enhance the drug development and review process:

- Development of new medicines for severely debilitating or life-threatening disorders (SDLTs) beyond oncology and hematology
- Post-market requirement (PMR) and commitment (PMC) process reforms
- Address variation in the application of existing FDA guidance
- Adoption of novel regulatory science tools and methods

*"**Question #1:** FDA is interested in input from stakeholders about where OND can provide additional guidance or prioritize additional scientific discussion in the near-term to improve clarity and encourage effective drug development. Given that OND's portfolio includes a diverse spectrum of drugs and diseases, such input should focus on specific policy needs for various clinical areas linked by a shared therapeutic context (e.g., drugs intended to treat serious, life-threatening rare diseases; non-serious, self-limited conditions; etc.), rather than focusing on any specific disease or condition."*

A. Severely Debilitating or Life-Threatening Disorders

Question #1 in the FR notice asks if there are "specific policy needs for various clinical areas linked by a shared therapeutic context" including serious and life-threatening diseases and Question #2 discusses new policy that could promote drug development in underserved diseases in need of therapeutic innovation. Pfizer would welcome additional stakeholder engagement and policy development in the area of Severely Debilitating or Life-Threatening disorders, or SDLTs.

FDA has made considerable progress leveraging expedited programs and regulatory process innovations in oncology and rare diseases, but we recognize that there are debilitating conditions and life-threatening diseases across a wide variety of therapeutic areas, including severe congestive heart failure, late-stage diabetic nephropathy, lupus nephritis, advanced Parkinson's disease, and progressive multiple sclerosis, to name a few.[1,2] Many of these diseases are characterized by short-term survival rates and rapidly progressive disease. However, our approach to drug development for many of these critical public health needs has not changed in decades. For example, the development of therapeutics for those SDLT conditions currently follows ICH M3(R2), which is the standard paradigm also used for non-SDLT conditions. Equal urgency is needed to spur R&D investment in these underserved therapeutic areas and to accelerate the pre-clinical and clinical development of new therapies.

For SDLT disorders in which life expectancy is short or quality of life is greatly diminished, a streamlined development approach should apply. In fact, FDA precedent for streamlining development of SDLT therapeutics already exists. In March 2019, CDER's Office of Hematology and Oncology Products issued final guidance on an ICH S9-like approach for nonclinical development of pharmaceuticals treating SDLT hematologic disorders (SDLTHD).[3] While the recent guidance represents a positive step, we encourage FDA to broaden the scope of the guidance to include SDLTs across other therapeutic areas.

The benefits of enabling efficient development of SDLT therapeutics include earlier patient access to new therapies for SDLT diseases, avoidance of unnecessary use of animals and other drug development resources, and reduction in the economic burden and societal costs associated with late-stage and end-of-life conditions.

Our recommendations focus on supporting the streamlined development of therapies for SDLT conditions across therapeutic areas while ensuring consistency in the regulatory approach and maintaining patient safety. As a first step, we suggest that FDA convene a

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[1] *Evaluation of Therapeutics for Advanced-Stage Heart Failure and Other Severely-Debilitating or Life-Threatening Diseases*, JS Prescott, PA Andrews, RW Baker, et al. Clinical Pharmacology & Therapeutics 102(2), 219-227 (August 2017), https://www.ncbi.nlm.nih.gov/pubmed/28474798

[2] *Evaluation of Therapeutics for Severely Debilitating or Life-Threatening Diseases or Conditions: Defining Scope to Enable Global Guidance Development*, Prescott, Liu, Fields, Bello, Bower, Darakjy, Hartke, Kadambi, Lapadula, Stoch, Derzi, Clinical Pharmacology & Therapeutics (October 2019), https://doi.org/10.1002/cpt.1673

[3] US Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry. Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals (March 2019). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM605393.pdf

public workshop focused on objective criteria to define SDLTs across therapeutic areas and as an outcome of that meeting, we would welcome expanded FDA guidance. Such guidance could address the following topics:

- Broaden Definitions to Include SDLT Across Therapeutic Areas: First, FDA guidance could help align consensus around relevant terminology. The current definition of SDLTs for hematologic disorders relates to conditions which are severely debilitating or life threatening despite available therapies, independent of disease incidence or prevalence. This definition could also apply to other SDLTs across therapeutic areas in which life expectancy is also short or quality of life is greatly diminished and where there is a high unmet need.

- Establish Objective Scope and Criteria for Consistent Application of SDLT Designation: Second, FDA guidance could clearly articulate objective criteria for what conditions outside of oncology and hematology would warrant streamlined and flexible development plans. This is of critical importance because it is likely that a given disease could be considered both an SDLT and non-SDLT depending on either the trajectory of the disease and/or the subset of patients affected. In some instances, a given disease may be SDLT for some patients at certain points during the disease trajectory, but not SDLT (*i.e.,* neither severely debilitating nor life threatening) for all patients at all times throughout the course of the disease. In other instances, SDLTs may represent severe manifestations that are not shared by all patients with the broader disease.

  Therefore, the proposed SDLT guidance should outline key elements of SDLT development programs to ensure the consistent application of the SDLT designation and safeguard patient safety. At a minimum, these elements should include objective and quantifiable medical, clinical, or scientific data which supports the following:

  - A defined patient population including objective criteria that distinguishes between SDLT and non-SDLT patients

  - Evidence that the selected patient population is either severely debilitated or has a shortened life expectancy due to the disease, and that adequate therapy is unavailable resulting in a high unmet medical need

  - Evidence that the safety and efficacy of the investigative drug can be appropriately monitored in the clinic

  Inclusion of potential SDLT examples across therapeutic areas in the proposed guidance, similar to examples provided in the current SDLTHD guidance, would promote better understanding of the FDA's thinking and more productive and efficient meetings with the agency.

- Clarify Nonclinical and Clinical Development Expectations: Finally, FDA guidance could clearly define the nonclinical development expectations for non-oncology SDLT disease therapeutics and outlining considerations for more efficient clinical development modeled after ICH S9. This would foster investment in this area and give patients earlier and continued access to urgently-needed, potentially efficacious therapeutics.

Ultimately, the availability of harmonized international guidance via ICH would be highly desirable, but we believe that having FDA guidance in the interim would help to pave the way for successful international harmonization, with FDA championing such efforts.

*"**Question #3**: Some therapeutic areas, particularly those that include serious and life-threatening diseases, have begun to implement novel trial designs, such as the use of master protocols to study multiple therapies and/or multiple diseases under a common infrastructure. FDA is interested in stakeholders' views regarding the advantages and disadvantages of extending these approaches to additional therapeutic areas, and what guidance development would be most useful."*

B. Post-Marketing Requirement and Commitment Process Reform

Question #3 in the FR asks about novel trial designs. Pfizer strongly supports innovation in clinical trial design, including adaptive trials, platform trials or master protocols, and decentralized 'virtual' trials. We also see a strong role for model-informed drug development to enhance the efficiency of R&D. In addition to the use of innovative clinical trial strategies in a pre-market setting, we recommend the acceptance of novel trial designs to satisfy post-marketing requirements (PMRs) and commitments (PMCs).

We appreciate that FDA has recently updated the 2011 Guidance on *Post-Marketing Studies and Clinical Trials* (October 2019), which we hope will lead to a more uniform approach for selecting PMR/PMCs or determining if the Sentinel System is sufficient to address a scientific research question. For instance, we have experienced variation in how review divisions approach the selection of PMC/PMRs, both with respect to the types of studies required and the timing of these discussions which can occur quite late in the review period. This can lead to insufficient opportunity for scientific dialogue around study objectives and feasibility. We believe this process would benefit from standardization and modernization.

1. Adequate Time for Scientific Discussion of PMR Objectives and Feasibility: The process for determining new PMRs or PMCs both during the drug review period and post-market should be predictable, articulate a clear scientific rationale regarding the scientific question(s) addressed, and allow for sufficient time for FDA-Sponsor dialogue and review of study objectives, feasibility, and design, including the potential opportunity to propose and successfully implement a novel trial design. We also hope that under the new OND integrated review process and consistent with the principles of 21st Century Review, divisions will engage sponsors earlier around the scientific objectives of phase IV studies after completion of the primary review.

2. Post-Market Dialogue around PMC/PMR Study Progress: Additionally, as the state of science and the practice of medicine evolve in the post-market setting, we would welcome opportunities for FDA and sponsors to periodically discuss progress in satisfying PMR/PMCs, including issues surrounding timelines, feasibility, and relevancy.

3. Novel Approaches to Satisfy PMC/PMRs: Well-designed, non-traditional trial designs and novel data sources should be considered as a potentially more efficient means of generating evidence to satisfy PMRs and PMCs, both at the initial time the PMR/PMC is proposed and when a PMR/PMC is reassessed for any revision. Sponsors should be supported by the Agency to use real world evidence (RWE) and the Sentinel Network to satisfy post-marketing requirements for PMCs/PMRs, or to use composite datasets integrated from different sources. As discussed in the updated PMR/PMC guidance, before requiring a PMR study, FDA and the sponsor should discuss and determine if passive surveillance and Sentinel will not be sufficient to meet the purposes described in section 505(o)(3)(B), and FDA should provide its rationale to the sponsor.

*"**Question #4:** FDA has published many guidances intended to explain the Agency's current thinking regarding drug development topics that are not specific to a particular disease or indication. If stakeholders believe that OND review divisions are implementing these guidances in different ways, which are not explained by case-specific features, this may reflect a need for guidance revision or additional policy development. FDA is interested in hearing specific recommendations for topics where further clarity of the Agency's current thinking may be warranted."*

C. Examples of Variation in the Application of Existing FDA Guidance

Question #4 asks stakeholders to help identify instances where OND review divisions are implementing FDA guidances in a variable manner, and we believe there are several areas where there are established FDA or ICH guidance that are being applied inconsistently. This may be partly due to older guidelines in need of updates or unique circumstances in a therapeutic area, so it would be beneficial to further study the root cause of potential variations in regulatory practice.

For instance, the ICH E1A guideline specifies "100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base," but we see wide variation in actual expectations across divisions. We have also seen inconsistency in how the divisions 'count' safety data in other indications that should be applicable for safety assessment purposes, which has the effect of expanding the clinical database needed to support new indications.

We are also seeing inconsistencies around 'waiving' collection/submission of non-serious adverse events for drugs that have a well characterized safety profile stemming from the *Safety Reporting Requirements for INDs and BA/BE Studies* 2012 guidance. This may be due to the case-by-case basis for review divisions accepting alternative reporting arrangements or waivers, and we expect this will ultimately be resolved through uniform adoption of ICH E19. While we agree with the agency's flexible approach, it may be helpful to have additional parameters in place in the interim.

In addition, we have seen uneven policy application of the requirement for replication of pivotal trials in those cases where there are Phase 2 data that are compelling and highly statistically significant and those cases in which a single Phase 3 study provides compelling evidence for the efficacy of two doses versus placebo. We are pleased to see that the recent release of FDA guidance on *Demonstrating Substantial Evidence for Human Drug and Biological Products* (December 2019) provides additional considerations on this and similar circumstances, and we look forward to providing comments to the docket.

Finally, with respect to the application review process, we encourage broader adoption of the optional application orientation meeting and more in-depth FDA-sponsor discussion during the mid-cycle meeting under the 21st Century Review Process.

***"Question #5:** Innovative approaches can bring additional uncertainty to drug development, since the advantages and disadvantages of the approaches may not yet be fully understood by either the Agency or sponsors because of their novelty. Sometimes, a well-understood development pathway may be chosen solely because of existing precedents in the therapeutic area. FDA would like to hear how OND can promote effective drug development programs when this tension exists."*

D. Regulatory Science Adoption and Change Management

Question #5 discusses the tension between the uncertainty related to innovative new approaches and the predictability of established precedent. Nowhere is that more apparent than in the field of regulatory science. Since the Critical Path Initiative was established in 2004, FDA and industry have invested considerable resources into new regulatory science initiatives, consortium, and pilot projects intended to modernize drug development and evaluation. However, over the past fifteen years, there has been variable success in translating these efforts into new regulatory practices that are consistently and routinely embraced across FDA review divisions with legacy tools and methods formally retired.

These scientific collaborations have been developing novel approaches to evidence generation, including innovative clinical trial designs and statistical methods, virtual clinical trials, biomarkers, and patient experience data. These approaches can offer a more efficient, patient-centric method for developing new drugs. Despite several strategies to build confidence around the acceptance of new scientific methods, such as the Drug Development Tool (DDT) Qualification process and the issuance of formal guidance for industry, it can still be unclear how these innovative strategies will be integrated into FDA regulatory frameworks and what weight they will be given in FDA decision-making across therapeutic areas.

FDA regulatory science initiatives and pilots would benefit from a structured change management and implementation process across the project lifecycle - from ideation to initiation of new initiatives to full-scale adoption (or non-adoption) of the regulatory science approach across review divisions. A more structured regulatory science implementation process should be based upon the principles of change management to build quality into regulatory science programs from the outset and ensure clarity in the process.

This should include:

1. Identification of what regulatory practice or tool will be changed,
2. Evaluation of the impact of the change on drug development, review, and regulation,
3. Planning and implementation of the change across all relevant offices and functions, and
4. Validation and monitoring of the change to ensure consistent and effective implementation.

Finally, a public communication plan for regulatory science change management would improve transparency to improve predictability. Taken in tandem, such a strategy for regulatory science change management could engender a safe space for experimentation and innovation based upon pre-specified processes and expectations jointly held by FDA and industry.

E. Conclusion

Thank you for the opportunity to offer Pfizer's perspective on opportunities to enhance consistency, predictability, and clarity in the Office of New Drug's scientific decision-making and policy development. By advancing standards for the development of novel therapies for severely debilitating or life-threatening disorders, enhancing the consistency of the PMR/PMC process, and implementing a framework for the adoption of new regulatory science tools and strategies, together we can help to streamline and modernize the drug development and review process.

If you have any questions about these comments, please contact me at andrew.emmett@pfizer.com.

Sincerely,

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