January 7, 2020

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

Re: Docket No. FDA–2019-N-3453: Promoting Effective Drug Development Programs: Opportunities and Priorities for the Food and Drug Administration's Office of New Drugs

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments following the FDA public meeting on Promoting Effective Drug Development Programs: Opportunities and Priorities for the Food and Drug Administration's Office of New Drugs.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO appreciates the Agency's efforts to seek input from stakeholders on actionable policy suggestions that could be implemented in the near-term by the staff of the Center for Drug Evaluation and Research's (CDER's) Office of New Drugs (OND) to promote effective drug development programs without compromising regulatory standards for the assessment of safety and effectiveness. It is through discussions such as these that various stakeholders can work together to identify challenges and barriers as well as potential solutions for making drug development and review more efficient, with the shared goal of bringing safe, effective, and high-quality medicines to patients in a timely manner.

BIO has included in this letter several specific recommendations for CDER on how to promote effective drug development programs. We note that the FDA has indicated that topics such as real world evidence (RWE) and patient focused drug development (PFDD) are out of scope for the purposes of the public meeting and docket response, however, both of these topics have an integral role in improving efficiencies in drug development and regulatory decision making. Additionally, OND sits at the apex of review divisions, providing guidance on policy which may include RWE and PFDD and as a result, these topics should be kept in mind.

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I. Opportunities to Support Consistent and Efficient Sponsor-FDA Communication

Appropriate communication between the FDA and industry Sponsors is integral to ensuring that data on safety and efficacy is sufficient for regulatory approval. BIO recognizes the many ways in which the FDA has worked to support communication between the Agency and Sponsors, for example through the issuance of guidance documents, organization of public meetings, and providing opportunities for product-specific discussions.

However, the inability to obtain clear, comprehensive, and timely feedback and responses to questions remains a significant source of uncertainty and delay in many programs, as Sponsors seek a response from the Agency. While the Prescription Drug User Fee Agreements (PDUFA) and the New Molecular Entity (NME) Review Program have provided much-needed structure for meetings with the Agency, often times following a milestone meeting, Sponsors may have clarifying questions for the FDA. These questions often do not necessitate another formal PDUFA meeting, but because there is no other consistent and broadly utilized means for receiving this follow-up information the Sponsor may submit another meeting request. BIO requests the FDA consider a mechanism for Sponsors to consistently, predictably, and efficiently obtain answers to clarifying questions that Sponsors may have following milestone meetings.

BIO recognizes that recently, the FDA has received an unprecedented number of meeting requests, and we believe that establishing a mechanism for Sponsors to receive efficient follow-up and obtain answers to clarifying questions following milestone meetings will likely reduce the number of meeting requests that the FDA receives. We believe that OND and the OND Office of Policy could be instrumental in developing best practices to enable Sponsors to obtain feedback in a timely manner.

BIO also requests that the FDA consider working with Sponsors to establish communication plans early on in drug development and review, which can later be updated and edited, in order to identify the most appropriate times for FDA-Industry engagement. For example, an appropriate time for engagement may not always follow the traditional drug development time (e.g., have a meeting after End-of-Phase 2, as more innovative approaches to clinical trial designs are employed).

BIO further requests that FDA consider a mechanism for Sponsors to request a review and discussion of scientific advice provided by a review division when there are discrepancies between the Sponsor and review staff, outside the formal dispute resolution. BIO encourages the Agency to develop a dialogue mechanism between the Sponsor, the Agency's review divisions, and management in order to foster scientific discussion throughout the application review process.

II. Opportunities to Support Consistency Across OND Review Divisions (Federal Register Question #4)

BIO notes that several comments made by various stakeholders at the November 7, 2019 public meeting requested consistency and flexibility from the Agency when it comes to review of drug development programs. BIO fully supports the FDA's new drug regulatory program modernization, reorganization, and establishment of a Knowledge Management

System to drive consistency across review divisions as part of the FDA's drug and device review programs[1] and looks forward to their implementation and evaluation of impact.

While consistency and flexibility may appear mutually exclusive, when we discuss "flexible consistency" we are seeking flexibility in the ability to use different approaches to meet the scientific regulatory standards and application of different approaches to meeting these standards across similar situations in a more consistent manner. BIO has provided below a few case examples to illustrate where flexibility in approach has been granted by the Agency but the flexibility is not applied consistently.

- Case Example 1: Clinical Studies Required for Demonstration of Safety and Efficacy
  Not all review divisions consistently apply flexibility when considering the kind and quantity of data and information a Sponsor is required to provide for a particular drug to meet the statutory standards (21 CFR 314.105). For example, for a rare disease, a particular review division may require Sponsors to conduct one adequate and well-controlled clinical study to demonstrate safety and efficacy whereas for a similar therapy used to treat a different rare disease another review division may require two adequate well-controlled clinical studies to demonstrate safety and efficacy, even for a rare disease where two studies may not be feasible.

- Case Example 2: Acceptance of Innovative Clinical Trial Designs
  Acceptance of innovative drug development approaches across all therapeutic areas such as Bayesian clinical trial design, complex adaptive clinical trial design, use of pharmacometric modeling, alternative methods for nonclinical testing vary across review divisions. For example, while guidances have been developed for use of master protocols and for use of seamless "expansion cohort" designs, these are specific to oncology. Yet these types of trial designs and other innovative designs could greatly improve the efficiency of drug development in other serious disease areas with high unmet need, particularly those characterized by low patient numbers. Please also see Section V. of this letter (Opportunities for Use of Innovative Clinical Trial Designs Across Therapeutic Areas including Highly Prevalent Chronic Diseases and Rare Diseases) for additional detail regarding the use of innovative clinical trial designs for highly prevalent chronic diseases. Additionally, in the context of pediatric drug development, while one review division may allow for the use of extrapolation approaches from adults to pediatrics, another review division may not despite similarity between the adult and pediatric disease progression, benefit-risk profile, and response to treatment.

- Case Example: Labeling Differences related to Safety Signals
  There is a lack of consistency across review divisions when a particular safety signal is identified and placed in the label with the same active ingredient. For example, when a safety signal emerges for an active ingredient that is being reviewed in multiple divisions due to differing therapeutic areas, review divisions have asked Sponsors to portray the same safety signal differently in the label.

[1] Remarks from FDA Commissioner Scott Gottlieb, M.D. on Fiscal Year 2019 budget request for FDA

To better support the consistent use of flexible, innovative approaches, when appropriate, the FDA should explore opportunities for cross-division discussions with Sponsors during review. This may include expanding upon the ongoing efforts to modernize the New Drugs Regulatory Program through the integrated assessment which is designed to more effectively conduct issue-focused assessments, enhance communication both within the review team and with the applicant, and create a stronger interdisciplinary collaboration throughout the review process. In cases where a drug may target multiple indications or a technology may be broadly applicable to a number or products in development, the ability to have cross-division or cross-product discussions during review would help support a consistent approach for that product and/or technology.

The FDA should consider making publicly available "lessons learned" or "best practices" from pilot programs and other initiatives established by the Agency. For each pilot program that the FDA determines to expand across the Agency, to assist the implementation and consistent use across review divisions, the Agency should also make public a plan for change management related to the pilot. Approaches for change management may include mechanisms to increase knowledge and adoption both within and outside the Agency, including through webinars, FAQs, or Level 2 guidance, until formal guidance on the topic has been released.

In particular, BIO requests that the FDA consider implementing such an approach for recent pilots and initiatives, including:

- Innovative clinical trial designs
- Model Informed Drug Development
- Real World Evidence per 21st Century Cures (Section 3022)
- Patient-focused Drug Development
- Summary Level Review Per 21st Century Cures (Section 3031)
- Project Orbis, initiated in September 2019
- Real-time Oncology Review, initiated April 2019

Additionally, CDER may also consider mechanisms to increase awareness both within and outside the Agency when new guidance or novel approaches are identified, for example, hosting webinars when final guidance documents are released. This could help ensure that both external stakeholders and FDA staff are aware of new thinking around major new guidances and approaches to help drive consistency in use and application of approaches covered.

BIO believes that these suggestions will help promote consistency among FDA staff in understanding previous use in similar situations and will promote consistency in application of approaches across review divisions.

III. Opportunities for the Office of New Drugs (OND) to Provide Additional Guidance (Federal Register Question #1)

BIO appreciates that drafting and updating FDA guidances can require significant resources and needs to happen at appropriate times when guidance will be actionable, practical, and appropriate for the current environment. These documents are integral to both the Sponsor and Agency's understanding of the FDA's current thinking on important topics during the development, review, and lifecycle management of biopharmaceutical products.

As such, BIO believes that in general, in order to ensure up to date information is available to all stakeholders, FDA should work to finalize draft guidance, withdraw old or outdated guidance, and reissue draft guidance eliminating portions no longer applicable for overall clarity or revise portions based on updated understanding of the topic in a timely manner, and in a way that is reflective of the areas that are of the highest need for guidance. As science and understanding evolves it is critical that FDA guidance evolves as well to ensure requirements are being handled efficiently and with the best science. BIO has included below a consideration for greater engagement between CDER and stakeholders in determining areas that are in the highest need for guidance document development and/or updating as well as a few specific suggestions of guidance that is needed.

Identification of High Priority Guidance Areas

To help the Agency determine areas that are in the highest need for guidance or updating of guidance, BIO requests that CDER consider opportunities that enhance transparency and consistency across FDA's Centers and allow for greater stakeholder-FDA engagement in developing priorities for guidance document development and guidance revision. To this end, CDER may consider, for example, a mechanism to seek input from stakeholders via a public docket on areas where guidance should be developed or updated, similar to the Center for Devices and Radiological Health (CDRH) annual approach for seeking stakeholder input on guidance document development. This approach would allow FDA to gain insight from a broader group of stakeholders, including Sponsors, on what areas may be causing challenges and that updated or new guidance could help alleviate. Additionally, it may allow FDA to identify areas where guidance may reduce the number of meeting requests on specific topics.

Suggested Guidance to be Newly Developed

Digital Technologies

BIO believes that additional clarity and coordination across FDA review divisions and Centers on digital technologies is needed. BIO acknowledges that this is a newer area of drug development that is rapidly evolving. However, a clear understanding of the general principles for the use of these technologies during development, a harmonized approach across the Agency, and across review divisions, to the extent possible, and additional coordination between Centers regarding consistency of approach is needed as more of these technologies are brought forward. Further, while we understand that regulatory review of digital technologies often falls under the jurisdiction of CDRH, there remains confusion as to the regulatory requirements and Center that will lead review of certain digital products, especially those associated with a drug product for commercial use and the differences in regulatory requirements, if a digital tool is intended to be used only in a clinical trial.

More specifically, BIO believes that currently specific guidance addressing the use of decentralized/virtual trials, digital endpoints, combination products that contain a digital component, digital technologies used to support patient adherence, and pharmacovigilance are needed. These guidances should be Agency-wide and be co-developed by CDER, CBER, and CDRH in order to ensure consistency in approach, as appropriate.

Preclinical Considerations

We believe that clarity and additional guidance is needed regarding the use of alternative preclinical tools and non-animal, human-based methods for toxicology and pharmacology requirements. These methods are known as New Approach Methodologies or NAMs.[2] We appreciate FDA's Predictive Toxicology Roadmap[3] where the Agency encourages Sponsors to approach them with and use new toxicology methodologies and technologies. However, there currently is no guidance on the use of NAMs in preclinical studies, nor specific criteria and evidence requirements for regulatory acceptance in a dossier. Additionally, as alternatives are typically accepted on an ad-hoc basis there is a lack of transparency about what constitutes an acceptable NAM. Clear communication of the evidence required for a NAM to be accepted in a regulatory submission would help to drive the use of these alternative models when scientifically appropriate and drive consistency across review divisions.

Analgesics

FDA recently withdrew the 2014 *Draft Guidance Analgesic Indications: Developing Drugs and Biological Products*. While we appreciate the withdrawing of guidance, new guidance on analgesics is needed in order to better support the development of novel and safer therapies as we continue to try to mitigate the current opioid crisis.

Other areas

BIO believes that there is a need to promote development in non-rare diseases, chronic diseases, and the development of disease modifying therapies to treat these diseases. FDA should be encouraged to consider pragmatic approaches in measuring outcomes for approval for chronic diseases that develop slowly. Please also see Section V of this letter on Opportunities for Use of Innovative Clinical Trial Designs Across Therapeutic Areas including Highly Prevalent Chronic Diseases and Rare Diseases where we have included specific recommendations to the FDA on the development of possible guidance pertaining to innovative clinical trial designs.

<u>Existing Guidance to be Updated</u>

There are a number of guidance documents pertaining to pediatric drug development that we believe should be updated to be more current and take into account current science and understanding.

We ask FDA to finalize guidance on complying with the Best Pharmaceutical for Children Act (BPCA; 1999) to replace FDA's FAQ website. We also believe that FDA should consider updating the 1997 guidance *General Considerations for the Clinical Evaluation of Drugs in*

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[2] The term "new approach methodologies" (NAMs) has been adopted by the ICCVAM as a broadly descriptive reference to any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment. These new approaches include integrated approaches to testing and assessment (IATAs), defined approaches for data interpretation, and performance-based evaluation of test methods.

[3] FDA Predictive Toxicology Roadmap https://www.fda.gov/media/109634/download

Infants and Children. Updates should include terminology (e.g., "school-aged children", "special problems") and the addition of references to other pediatric guidances released since 1977.

BIO believes that the topic of evidence for demonstrating effectiveness is an important area for policy development and additional discussion among stakeholders. BIO also recognizes that the FDA recently released an updated Draft Guidance on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.* BIO looks forward to providing comments to the FDA on the Draft Guidance via the public docket.

Areas for Additional Scientific Discussion

While FDA guidance is extremely important to assist Sponsors who are developing therapies for FDA review, presently there are several areas that are important and are rapidly evolving or in early stages. We understand that it may be difficult for the FDA to develop guidance in these areas given the evolving landscape. In these cases, BIO strongly believes that the opportunity for additional scientific discussions between FDA and stakeholders would help to facilitate understanding and collaboration. These discussions could take many forms based on the topic, for example public meetings, milestone meetings, collaborations with other agencies, or the development of consortia or public-private partnerships.

Such areas include but are not limited to:

- Methods used by statisticians to support benefit-risk decisions such as Bayesian methods, use of external controls, and use of retrospective natural history data to support the control arm especially in the context of rare diseases where natural history data is limited.
- The use of artificial intelligence (AI) in regulatory decision making including, appropriate parameters and consideration for the use of AI for regulatory decision-making, include pharmacovigilance.
- Novel manufacturing technologies that may be used across several different product types (e.g., technologies that are applicable for discussions with the FDA CBER Advanced Technologies Team (CATT) or CDER Emerging Technology Team (ETT)).

BIO appreciates FDA's participation in public private partnerships, where industry, academia and government, can collaborate in pre-competitive pre-clinical space. For instance, Pediatric Cancer Preclinical Testing Partnership, Accelerating Medicines Partnership, Partnership for Accelerating Cancer Therapies (PACT), Biomarkers Consortium, C-Path, and Transcelerate. These can often also be opportunities for additional discussion and learning between FDA and stakeholders. We encourage continuation of such activities.

Finally, the FDA-NIH Joint Leadership Council[4] was formed approximately 20 years ago. It appears the Council may no longer be active, as the roster was last updated in 2016. BIO asks FDA to consider reactivating this important collaboration between NIH and FDA. Per FDA's website, "The Joint Leadership Council works together to help ensure that regulatory considerations form an integral component of biomedical research planning, and that the latest science is integrated into the regulatory review process. Such collaboration and

[4] FDA-NIH Joint Leadership Council Charter

integration advance the development of new products for the treatment, diagnosis, and prevention of common and rare diseases and enhances the safety, quality, and efficiency of the clinical research and medical product approval enterprise". This function is as important now, as it was then.

IV. Opportunities for OND to Undertake to Facilitate Drug Development for Diseases not Currently Amenable to Targeted Therapies (Federal Register Question #2)

BIO appreciates the difficulties of developing innovative products for areas where the current state of knowledge does not provide opportunities for precise genetic or molecular targeting; below we offer suggestions regarding highly prevalent chronic diseases and improvements to the post market commitment and requirement (PMC/PMR) processes that may help facilitate development in these areas.

Highly Prevalent Chronic Diseases

Highly prevalent chronic diseases (HPCDs) such as chronic heart disease, depression, pain and addiction, type 2 diabetes, and obesity among others, have a significant impact on public health and a large cost to the healthcare system. Since 2018, BIO has published a series of industry reports on the state of innovation in HPCDs, which highlight the significant unmet needs for new therapies across therapeutic areas.[5] Our reports show that despite the significant public health burden HPCDs represent, emerging company investment for drug development in many of these common diseases has been declining over the last decade and is low relative to total healthcare costs of these diseases. The persistence of this trend could have implications for the future output of innovative medicines in these disease areas. The cause for concern is magnified by the impact these chronic disease areas are having on the overall healthcare system in the US. Thus, it is important that barriers to therapeutic innovation are identified and removed.

The development of products to treat HPCDs has unique challenges due to the length and size of clinical trials. While some of the clinical trial challenges are not unique to HPCDs, additional guidance could address the barriers associated with development of these products, including:

- Promoting the acceptance of innovative clinical trial designs (see Section V for more detail) and use of digital technologies for data collection in order to make the trial more efficient and maximize recruitment and retention;
- Leveraging the use of existing data by increasing acceptance of real-world evidence (RWE) for regulatory submissions across the Agency (see BIO's white paper on the use of RWE for label expansion)[6];
- Promoting acceptance of novel endpoints; and
- Creating improvements to the PMC/PMR review process. We offer specific recommendations on this topic below.

[5] BIO Industry Analysis Reports https://www.bio.org/bio-industry-analysis-reports
[6] Incorporating Real-World Evidence Within the Label of an FDA-Approved Drug (June 2019) https://www.biotech-now.org/health/2019/06/new-bio-white-paper-incorporating-real-world-evidence-within-the-label-of-an-fda-approved-drug

Improvements to the Post Market Commitments and Requirements (PMC/PMR) Review Process

BIO believes that ensuring that post-market requirements (PMRs) and post market commitments (PMCs) are feasible, efficient, and effective and that information gained from them is effective in supporting benefit/risk assessments requires a continuous evaluation of the feasibility and relevance of the research question that begins pre-approval and extends throughout a product's lifecycle. As such, we encourage FDA to further enhance the process for determining PMRs under Section 505(o)(3) of the Food, Drug, and Cosmetic Act (FDCA) for the purpose of gathering additional safety data on a marketed product[7], including mechanisms for Sponsors and the Agency to re-discuss and/or re-evaluate the feasibility and/or need for a particular existing PMR/PMC as new information becomes available.

FDA's current review process for determining PMRs (and PMCs in some instances) can be inefficient in providing reliable development and execution of post-market studies and trials that would generate meaningful information regarding a product's safety profile. This process creates significant investment in resources, particularly in the cases when clinical trials are required, that may not meet the intended purpose, or in some cases are no longer feasible or necessary to conduct. Critically, poorly conceived PMRs draw resources from research and development efforts that could provide more value and benefit to patients, physicians, and the healthcare ecosystem. Improving this process can help reduce the cost burden associated with drug development and approval across therapeutic areas including HPCDs as well as rare conditions.

Recently, FDA has taken important steps to begin addressing some of the challenges around the PMC/PMR review process. Most recently, FDA published its Draft Guidance titled *Postmarketing Studies and Clinical Trials-Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*. BIO welcomes this Guidance as it is takes important action in ways to improve the PMC/PMR review process. More specifically, BIO is supportive of FDA's plans to inform applicants of the planned target date for communication of feedback from the review division regarding PMRs and PMCs in the filing communication letter, as well as FDA's plans to communicate a list of potential PMRs and PMCs, along with a brief rationale for why FDA thinks these studies and clinical trials are appropriate.

We also welcome the Draft Guidance's recognition on the importance of Sponsors discussing the design and conduct of the PMRs and PMCs with the FDA review team. We encourage FDA to consider additional structured timelines, for both Sponsors and FDA, around this communication process. Specifically, following the draft of the PMC/PMR proposal, the Sponsor and FDA could hold a meeting that is no later than two weeks from its communication to discuss study feasibility and design of the proposed study. Following this discussion, the Sponsor would provide the Agency with schedule milestones, and discussion,

[7] Section 505(o)(3)(A) of the FDCA allows FDA to require post marketing studies or trials for any of the three purposes in light of new safety information: (1) To assess a known serious risk related to the use of a drug; (2) To assess signals of serious risk related to the use of a drug; and (3) To identify an unexpected serious risk when available data indicates the potential for a serious risk.

that is no later than two weeks from first meeting, to address and resolve any differences between the FDA and the Sponsor.

BIO encourages FDA to address flexibility to alter agreed upon milestones and or timelines due to changes such as speed of enrolment of a study. For instance, if a study is slow to enroll and the original protocol anticipates a faster enrollment, the original completion date will need to be revised, and protocol amended. As currently discussed in the Guidance, Sponsors would not be able to correct milestones to reflect current realities.

BIO welcomes additional details regarding the procedures for FDA and Sponsors when the Agency deems its active post-market risk identification and analysis system, Active Risk Identification and Analysis (ARIA), as insufficient, but a Sponsor would like to propose and discuss an alternative. This applies both during review of a marketing application and during the postmarketing setting, although timely determination regarding ARIA sufficiency is needed during marketing application to allow for development and discussion of an alternative postmarketing study proposal. Determinations made and communicated to the sponsor *before* the mid-cycle communication should allow for adequate time to propose a postmarketing study and potentially reach agreement prior to the action date. With the goal of efficiency in mind, ARIA and other real-world data sources, are valuable tools for answering important questions about safety and efficacy without unnecessary expenditure of time and limited resources and as such, BIO encourages FDA to increase the reliance on these mechanisms for postmarket assessments.

V. Opportunities for Use of Innovative Clinical Trial Designs Across Therapeutic Areas including Highly Prevalent Chronic Diseases and Rare Diseases (Federal Register Question #3)

FDA has taken important steps to modernize drug development, improve efficiency, and promote innovation including efforts focused on advancing the use of complex innovative designs (CID) (e.g., Bayesian, adaptive, basket, and platform trials). These efforts include FDA's CID Pilot Meeting Program, which BIO continues to be supportive of as it offers the opportunity for public learning and subsequent advancement of CID across the Agency.

Furthermore, clinical development of medicines has multifaceted challenges which fit-for-purpose CIDs can help address across therapeutic areas, including rare diseases and HPCDs. For example, CID can help expedite advancement of new therapies for patients by improving patient recruitment; helping minimize unnecessary patient risk by using non-concurrent controls arms or synthetic control arms; and assuring adequate efficacy and safety assessment, thus minimizing clinical trial completion times and accelerating delivery of medicines.

Advancement of science and technology introduces tremendous opportunity that fit-for-purpose CIDs can synergize, such as efficient identification of optimal treatment doses/schedules; efficient identification of optimal combination treatments (best risk/benefit profile); efficient incorporation of and stratification on new biomarkers/diagnostics; ethical early termination of ineffective or intolerable treatment; and efficient use of external data to reduce study size and improve reliable decision making.

<u>Additional Clarity Regarding CID</u>

To further advance the use and acceptance of CID across the FDA, the Agency could provide further clarity, including guidance on a number of topics.

We acknowledge and appreciate the recently published draft guidance *Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products.* As FDA continues to gain more experience through the CID pilot, industry looks forward to this guidance also being revised in a timely manner.

We also acknowledge and appreciate that FDA has recently released the Final Guidance *Adaptive Designs for Clinical Trials of Drugs and Biologics* which finalizes FDA's current thinking on a number of important topics for adaptive designs. However, there are still a number of areas where additional clarity would be helpful. For instance, clarity regarding study conduct and data integrity would be helpful as data integrity during adaptive trials could be compromised if there are not appropriate data monitoring mechanisms in place. Additionally, Sponsors may need visibility of the data and guidance would be beneficial in understanding how the Sponsor and the FDA could work together to control for bias due to potentially unblinded data. In addition, in the context of a master protocol, given the large-scale, long-term nature and planning of a master protocol clinical trial, monitoring and executing the simultaneous sub-studies could impact the quality of monitoring.

Additionally, clarity regarding adequate evidence for decision making which describes how a Sponsor can make adequate early decisions on sparse data would be beneficial, particularly in the context of a complex adaptive, master protocol, or hybrid protocol with external control. In addition, regarding final interpretation of results, there is potentially an increased false positive rate ("type 1 error") and induced bias if prior and current patient populations are not similar (i.e., exchangeable) when using Bayesian methods or other methods that borrow historical data, as such, FDA insight into this example would be welcomed.

Information regarding adequate interventional and control arms is needed. Complex randomization could impact the types of clinical trial participants that are enrolled early in the trials compared to later in the process. In addition, given the long-term nature of a trial using a master protocol it is possible that a study might include outdated endpoints or comparators.

Finally, additional detail regarding adequate safety monitoring and comparisons including complex adaptive designs in which it could be challenging to assure how to achieve long-term safety when/if needed. In addition, when using historical controls, it might be challenging to determine when a Sponsor has adequate data from an experimental arm to establish safety profile.

CID for HPCDs

While BIO believes that several types of innovative clinical trial designs can be used to make the study of HPCDs more efficient, we have included below several examples of designs that could address challenges for HPCD trials.

- Case Example 1: Platform Trials

Studies which are designed to assess multiple interventions in the context of a single disease in a perpetual manner, with interventions entering or leaving the study on the basis of pre-defined rules. These designs are often referred to as platform trials[8] with the goal of demonstrating efficacy/safety of an intervention. This approach has been used to evaluate multiple therapies for Ebola virus (PREVAIL II) and for evaluation of multiple therapies in Lung Cancer within multiple biomarker-defined subgroups (LUNG-MAP). The benefits of this trial design include:

- Efficiency of assessing multiple interventions in one study
  - Use of common control data to evaluate efficacy of multiple therapies
  - Reducing number of patients exposed to control interventions
  - Allowing interventions to enter the study at differing times
- The ability to focus on interventions that demonstrate promising efficacy/safety, while "dropping" those that don't
- Exploring and assessing common principles to guide the innovative statistical approaches to study design and analysis including but not limited to:
  - Adaptive design aspects of trial design, response-adaptive randomization;
  - Statistical framework (e.g., Bayesian approaches) with focus on demonstration of efficacy in context of pivotal trial;
  - Extent of control data usable for interventions entering later into study (e.g., assessing temporal changes in control data, down-weighting control data from earlier in study); and
  - In the context of a perpetual trial: (1) what control data can be used for comparisons against a novel intervention and (2) if and when can the control be changed (i.e., one of the new interventions demonstrates efficacy and becomes the control)

- Case Example 2: Bayesian Augmented Control Design
  Bayesian augmented control design with a small placebo or active control for pediatrics investigation plans for common diseases (e.g., rheumatologic conditions, asthma). The goal of this approach is to conclude the efficacy of a molecule by borrowing historical information based on covariate-adjusted Bayesian hierarchical model, power prior or commensurate power prior method. The benefits of this trial design include:
  - Reducing sample size without lowering the power of the study
  - Concurrent placebo control allows robust assessment of efficacy through proper determination of statistical assumptions

- Case Example 3: Basket Studies
  Basket studies which are designed to answer questions about a specific intervention (agent +/- SOC) in multiple diseases or disease subtypes and/or multiple patient populations where there is some commonality among the diseases, subtypes or populations. These designs are commonly referred to as Basket designs.[9] The goal of

[8] Woodcock, J., LaVange, L.M., 2017. Master Protocols o Study Multiple Therapies, Multiple Diseases, or Both. The New England Journal of Medicine. 377: 62-70.
[9] Woodcock, J., LaVange, L.M., 2017. Master Protocols o Study Multiple Therapies, Multiple Diseases, or Both. The New England Journal of Medicine. 377: 62-70.

this trial design is to demonstrate efficacy/safety of intervention within and/or across diseases/subtypes/populations. This design could be used to test an intervention across different cancers with shared molecule etiology; across different infectious diseases driven by same pathogen; in a disease across different patient populations (e.g., patients with varying stage of disease where SOC differs, subgroups of age etc.); across rare diseases where a single study may be infeasible.

Benefits of this trial design include:

- Maximizing efficient use of study information and magnify the significance of individual test based on exchangeability of treatment effect and validate the adequacy of different significance levels, composite vs. individual
- The ability to focus on promising diseases or patient populations and evaluate new therapies in the context of "precision medicine"
- Considering generalization to a trial with different primary endpoints across the baskets
- Exploring and assessing common principles to guide the innovative statistical approaches to study design and analysis including but not limited to:
  - Adaptive design aspects of trial design (e.g., dropping/adding baskets);
  - Statistical framework (e.g., Bayesian approaches, independent tests vs. methods for sharing/pooling data across buckets); and
  - Considerations for study designs (e.g., minimum sample size per bucket (major benefit for rare disease studies), ability to extrapolate to buckets not studied or not powered (e.g., approve for all cancers with X-mutation))

VI. Opportunities to Advance Innovative Approaches that Might Not Yet be Fully Understood (Federal Register Question #5)

BIO appreciates FDA's acknowledgement of cases where a well-understood development pathway may be chosen due to the existing precedents even in cases where innovative approaches may ultimately be a better choice. All drug development should be based in science and opportunities should exist for Sponsor-FDA discussions regarding the ability to utilize new and innovative approaches to gain understanding and familiarity of these novel ideas. In order to aid areas where novel approaches are not fully understood or implemented consistently across the Agency, we suggest FDA consider:

- Development of opportunities for FDA-Sponsor interactions for focused discussions on innovative approaches in the context of product development.
- Identification of appropriate and effective mechanisms, such as additional training for review staff, to increase knowledge sharing across Centers and divisions.
- Mechanisms for dissemination of learning with stakeholders, even if not final FDA guidance. This could take the form of workshops, webinars, FAQ documents, peer reviewed publications, REdI workshops, SBIA conferences/webinars, or briefings.
- Encouraging FDA Staff to be open to innovative approaches to support the use of new tools. BIO would be willing to partner with FDA to hold seminars on specific new technologies for review staff.
- Ensuring FDA staff, especially division leadership, has latest training on new concepts/science, building expertise within FDA, and allowing additional expert input when needed. For example, FDA could develop and implement training plans on

these new concepts and partner with stakeholders to ensure appropriate experts are available.
- Ensuring portfolio development meetings with Sponsors are common practice across review divisions.

More specifically, in order to better disseminate learnings across Centers and divisions as well as with other stakeholders in the case of drug development tools that depend on case-specific features, FDA could develop case studies to explain what factors have underpinned the Agency's acceptance of certain approaches, such as the use of modeling, adaptive trial designs, and others. These case studies and discussion could explain why it was acceptable in some circumstances and not in others. This would allow for a more holistic understanding of the Agency's still-evolving thinking on many of these tools, enable broader public discussion to advance their use, and potentially serve as a precursor to guidance to provide clarity to Sponsors. Additionally, developing and rolling out a targeted decision support framework or other tool to support decision making that targets case-specific features for advanced innovative approaches may enhance consistent decision making. Furthermore, FDA could create additional transparency through issuance of FAQs and/or Level 2 guidance posted on FDA's website.

Finally, while we acknowledge and appreciate FDA's engagement with Stakeholders on important scientific topics, in some specific areas where there is significant alignment in the field, we ask FDA to consider additional expert input to align on innovative approaches, particularly around novel endpoints, including novel digital endpoints. When there is a body of evidence by experts in the field (for example diabetes hypoglycemia, continuous glucose monitors, and diabetes endpoints) and where there is alignment on an innovative approach or novel endpoint, FDA should work to adopt the information in a timely manner or provide additional opportunities for discussion of any issues or concerns, rather than require the information to be further vetted through a separate FDA qualification process. Particularly with novel endpoints, this separate qualification process can unnecessarily delay access to information and approaches that benefits patients.

BIO appreciates this opportunity to submit comments regarding the public meeting on Promoting Effective Drug Development Programs: Opportunities and Priorities for the Food and Drug Administration's Office of New Drugs. We have also included BIO's slide deck as prepared for the meeting in an appendix for reference. We would be pleased to provide further input or clarification of our comments, or additional expertise, as needed.

Sincerely,

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