March 26, 2021

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

Re: Docket No. FDA-2021-N-0031: Best Practices for Development and Application of Disease Progression Models; Public Workshop.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the upcoming public workshop on *Best Practices for Development and Application of Disease Progression Models.*

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 supports of the upcoming workshop on *Best Practices for Development and Application of Disease Progression Models* in order to fulfill FDA commitments under the VI iteration of the Prescription Drug User Fee Agreement (PDUFA). BIO appreciates that FDA is seeking input from stakeholders on three key areas, including: The Development and Application of Different Types of Disease Progression Models, Modeling Natural History of Disease, Specifically Methodological Considerations and Challenges in Characterizing the Natural Relationship Between Pharmacodynamic Markers and Clinical Outcomes, and Clinical Trial Simulations Based on Disease Progression/Natural History Models to Support Drug Development and Regulatory Decisions.

As indicated in the Federal Register Notice for the upcoming FDA workshop on disease progression modeling, the purpose of this public workshop includes sharing experiences and case studies that highlight the opportunities and limitations in the development and application of disease progression models. Although the FDA is requesting public input on topic areas of focus, it is unclear if FDA will also solicit case study examples. To enhance the public workshop, we encourage FDA to include case study examples from the public domain that would be illustrative of disease progression models. Additionally, we encourage the FDA to invite sponsors to present case examples that may not yet be in the public domain, including those that highlight both positive outcomes, lessons learned from negative outcome use cases, as well as use cases from the Model Informed Drug Development (MIDD) pilot program. To support this discussion, BIO members are willing to offer case study examples for inclusion in the agenda topics. We also encourage FDA to develop hypothetical case examples based on Agency experience that illustrate key issues and serve to generate discussion on how those challenges may be overcome.

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BIO has outlined below additional topics that FDA may consider discussing at the public meeting in addition to responses to FDA's request for best practice considerations development and application of disease progression models.

I. Additional Topics for Consideration for Discussion at the Public Meeting.

In addition to the topics mentioned above, we encourage the Agency to consider including discussion at the public meeting focused on best practices for engaging with FDA to gather feedback on models and their application in regulatory contexts. It would be beneficial for FDA to discuss how to best work with FDA to base regulatory decisions on model-based prediction. It may also be helpful for FDA to discuss whether there are specific areas of unmet need and that FDA might consider to be priority areas for application of disease progression models. We also recommend a session of the workshop be devoted to discussing how sponsors can work with FDA to integrate models to support benefit-risk assessments and decision-making (e.g., labeling and approval). This session could address how to communicate and apply the assessment of model risk and residual uncertainty to these decisions and could be informed by experience with the MIDD pilot program. This will help provide greater alignment and clarity to sponsors regarding when models are suitable for internal decision making and when they provide enough support for regulatory decisions. It would also be helpful for the workshop to discuss how FDA envisions submission of disease progression models that include data across molecules, especially for milestone meetings for a given molecule. This discussion could also address additional data-sharing challenges posed for disease models based on consortium or commercial databases (e.g., some real-world data).

Academic studies that could serve as sources of data for disease progression modeling often do not include the type or quality of information the FDA may require for regulatory decision making. To this end, the public meeting would also benefit from discussion of regulatory expectations for the use of existing natural history study databases, particularly those that were established without regulatory applications in mind for disease modeling/progression and specific regulatory contexts-of-use (e.g., use as an external control). Such discussion could include reference to existing efforts on this topic including, but not limited to the TransCelerate Historical Trial Data Sharing Efforts.[1] This discussion may consider the utility of qualifying disease progression models in targeted areas and as to whether the Agency would consider qualification of disease progression biomarkers.

II. The Development and Application of Different Types of Disease Progression Models (e.g., Empirical, Semi-Mechanistic, and Fully Mechanistic or Systems Modeling).

Characterizing long-term progression of disease and the rate of the clinical progression are among the highest clinical research priorities. From a data-analytic perspective, these objectives are achieved by developing disease progression models, and those models can vary substantially in complexity.

[1] TransCelerate Historical Trial Data Sharing.

It would be useful for the workshop to include discussion on how disease modeling can be used to support drug development in a variety of ways, including:

- Enabling a more accurate estimate of drug effects by accounting for disease progression;
- Informing trial design (e.g., study duration, time of endpoint assessment, dose regimen, sample size, extrapolation from Ph2 to Ph3);
- Understanding between-subject variability present during disease progression and differentiating this from the drug effect variability;
- Describing patient subgroups (e.g., fast / slow progressors) and informing clinical trial patient selection / patient enrichment strategies;
- Understanding disease pathogenic mechanisms (e.g., interplay between biomarkers evolution and clinical state, rationale for drug combination); and
- Supporting pediatric trials to understand potential differences between adults and pediatrics in terms of disease characteristics/progression.

For disease progression applications, models should be fit-for-purpose balancing advantages and disadvantages of various approaches based on the technical robustness and application scenario. We recommend that FDA select case studies that can be used to illustrate the level and type of validation, as well as the most appropriate type of data to use with various modelling approaches required to apply a disease progression model in different drug development or regulatory review contexts of use. Several examples of disease models that could form the basis of such case studies are provided below:

- Empirical tumor growth inhibition-overall survival modeling: use tumor dynamic as a predictor of survival in parametric survival model;
- Pharmacometric disease progression model to describe natural disease progression in degenerative diseases (e.g., Alzheimer's disease) to be compared to on-treatment response for a robust assessment of the drug effect and selection of drug candidates;
- Disease progression models of retinal diseases such as diabetic macular edema and wet age-related macular degeneration;
- More complex models involving several biomarkers and several endpoints (e.g., item response theory-based models); and
- Artificial Intelligence/Machine Learning (AI/ML) model to predict disease progression based on many prognostic/predictive variables, and/or to incorporate high-dimensional data for disease progression prediction (e.g., imaging, omics).

In the context of discussions at the workshop focused on the development and application of different types of disease progression models it may also be helpful for the Agency to share insights during the public meeting on topics such as:

- The hierarchy of evidence for various types of disease progression models;
- Mechanisms to perform model averaging techniques with disease progression models;
- The level of evidence and type of data required to use modeling to support endpoints;
- Mechanisms to report modeling and simulation in support of disease progression to FDA (e.g., file types and required reports);
- The source of data that can be modeled (e.g., real-world data, individual patient level data, aggregate data) and the approaches for combining two or more data sources to model a composite endpoint;

- Imputation of missing clinical outcomes data in a rare disease setting;
- Requirements needed for modeling to demonstrate that the therapy changed the disease progression;
- Model based Meta-Analysis (MBMA) models established on published aggregate clinical trial data that could inform disease progression and quantify the impact on some population/design characteristics; and
- Requirements needed to obtain a label claim based on the modeling results.

III. Modeling Natural History of Disease, Specifically Methodological Considerations and Challenges in Characterizing the Natural Relationship Between Pharmacodynamic Markers and Clinical Outcomes.

Modeling natural progression of disease offers several potential benefits. It allows for a more accurate understanding of the natural history of disease decline and thereby allows optimization of trial designs to detect disease-modifying effects of drugs. An adequate disease progression model can help identification of risk factors, demographics, and other covariates that affect baseline disease status and the rate of disease progression. Therefore, these covariates may serve as stratification variables in clinical trials.

In the context of discussions at the workshop focused on modeling the natural history of disease it may also be helpful for the Agency to share insights during the public meeting on topics such as:

- Recommendations on the use of statistical versus causal inference methods to describe natural history studies to support a surrogate efficacy endpoint, especially for rare diseases where investigators may be unable to control for confounding variables due to low event rates;
- Recommendations regarding situations where clinical outcomes reported by patients may be challenging to validate because of lack of electronic charts or consistency in site of care for patients;
- General guidance on data sources (e.g., aggregate level data from published clinical trials) for disease progression characterization (e.g., natural history of disease, disease progression without treatment intervention, placebo effect, diet/exercise, disease progression under backbone therapy or standard of care);
- Use of real-world data (e.g., patient registries) to learn about the relationship between pharmacodynamic markers and clinical performance/progression;
- Recommendations for handling of missing the pharmacodynamic endpoint (e.g., when the pharmacodynamic marker is missing due to disease progression 1) When the missing pharmacodynamic marker is informative of the pharmacodynamic value (missing not at random); and 2) When the observed pharmacodynamic value is causing the missingness (missing at random). In both cases the amount of PD data available will depend on the response to treatment and makes prediction of outcome more difficult;
- Consideration for developing models for regulatory purposes using novel data sources (e.g., radiomic features derived from computerized tomography scans); and
- Recommendations on deconvoluting the effects of the natural drivers of disease progression from the effects of treatments on disease progression, including potential placebo effects.

IV. Clinical Trial Simulations Based on Disease Progression/Natural History Models to Support Drug Development and Regulatory Decisions.

One of the key applications of disease progression modeling in drug development is its ability to optimize clinical trial design. For instance, designing clinical trials that detect disease modifying effects could be made more informative by using outcomes from clinical trial simulations, which require a quantitative understanding of disease progression. This is usually achieved by simulating many trials to calculate power and sample sizes and to estimate the treatment effects of pharmacologic agents on disease progression. It is important to note that, with the availability of new data sets, these modeling strategies will need to be adjusted to reflect an increased understanding of the progression of the disease. Such effort could strongly contribute to sharpening our understanding of the optimization of clinical trials and to facilitating regulator acceptance of the overall results of the disease progression models. Furthermore, with the increase of publicly available data and the increase in the use of remote patient monitoring (e.g., sensors, wearable technologies) disease progression modeling techniques should be adapted to both interpret this new class of data and to compare how these measures relate to the current standard markers of disease progression.

In certain cases, for example, in pediatric trials or with orphan diseases, it may be difficult or impossible to recruit sufficient patients for a placebo-controlled study. Disease progression models that have been built using data from previous clinical trials, or that are built on the sound understanding of systems biology could provide a credible benchmark against which to judge the efficacy of a novel treatment.

We recommend that FDA include a session at the workshop discussing regulatory considerations for when clinical trial simulations are based on disease progression models could:

- Reduce or eliminate the need for data from placebo or standard of care controls;
- Be used as virtual control arm for analysis of open label extension;
- Make long-term predictions of clinical outcomes using multistate models disease progression models calibrated on relatively short-term interim or early phase data;
- Inform selection of trial endpoints; and
- Support finding an optimal dose (via virtual simulation) given a target effect size.

It may also be helpful for the Agency to share insights during the public workshop on topics such as:

- Recommendations on the use of a historical real-world comparator cohort with issues with available data, like incomplete information on dose or substantial loss to follow-up.
- Practical recommendations on matching methodologies while using a real-world comparator cohort (e.g., optimal caliper widths for propensity-score matching);
- Identifying and addressing biases when using real-world data to quantify time to event analyses;
- Use of MBMA models established on published aggregate clinical trial data that could inform disease progression and quantify the impact on some population/design characteristics; and

- Recommendations on an acceptable datasets and analytical approaches for regulators to accept clinical trials without a placebo arm.

BIO appreciates this opportunity to submit comments regarding FDA's upcoming workshop, *Best Practices for Development and Application of Disease Progression*. We would be pleased to provide further input or clarification of our comments, as needed.

/S/
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