July 3, 2023

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


To Whom It May Concern:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments to the Food and Drug Administration (FDA or the Agency) on the draft guidance, Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making. PhRMA and its member companies are committed to ensuring that patient experience data (PED), clinical outcome assessments (COA) data, and other relevant information from patients and caregivers help in medical product development and regulatory decision-making. PhRMA has long supported FDA’s patient-


5 See comments filed by PhRMA on July 3, 2023. 88 FR 27521, Methodological Challenges Related to Patient Experience Data; Request for Information and Comments (May 2023); Available at
focused drug development (PFDD) efforts. PhRMA looks forward to working with FDA as the Agency continues to enhance the incorporation of the patient’s voice in drug development and decision-making, and looks forward to the finalization of the PFDD guidances under PDUFA VI and the issuance of future draft guidance on the use and submission of patient preference information with respect to treatment of the disease or condition. These efforts will further enhance stakeholder understanding of how PED informs meaningful clinical benefit or benefit-risk decisions in various therapeutic areas.

PhRMA is a voluntary, nonprofit association that represents the country’s leading biopharmaceutical research and biotechnology companies that are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested more than $1.1 trillion in the search for new treatments and cures, including $102.3 billion in 2021 alone.

GENERAL COMMENTS

PhRMA appreciates the Agency’s issuance of this fourth PFDD draft guidance, the final in the PDUFA VI PFDD series. PhRMA appreciates the Agency sharing its current thinking on the methods, standards, and technologies for collecting and analyzing COA data for regulatory decision-making, including selecting the COA-based endpoint and determining clinically meaningful change in that endpoint. PhRMA recognizes that this draft guidance builds on previous guidances, including considerations for COA-based endpoints, emphasizing the importance of understanding how COA-based endpoints correspond to changes relevant to patients, and providing recommendations to aid in the interpretation of treatment effects on COA-based endpoints.

PhRMA believes the Agency should leverage existing literature to focus on the need for advancement of existing evidence-based approaches, rather than introduce new methodologies and terminologies as the draft guidance does. We believe that any new concepts should have a clear foundation within existing literature. For example, PhRMA recommends that the Agency


8 PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027. https://www.fda.gov/media/151712/download

update the draft guidance to align with current endpoint-related literature and consensus documents (e.g., ISPOR Good Practice Guidelines,\textsuperscript{10} and other methods that are in the published literature, have been peer reviewed, and therefore subject to academic discussions of their merits and limitations) along with previous PFDD guidances.

PhRMA recommends that FDA update the PFDD glossary\textsuperscript{11} to ensure consistency in use of terms across FDA’s PFDD-related guidances and resources, and additionally that FDA cross-reference the glossary, as appropriate, in the current draft guidance. PhRMA also suggests that updates to the PFDD glossary reference the BEST (Biomarkers, Endpoints, and other Tools) Resource.\textsuperscript{12, 13} PhRMA also stresses the importance of being clear in the use and application of new terminologies. PhRMA believes the draft guidance introduces a number of new terms and approaches (such as Meaningful Score Difference (MSD) and Meaningful Score Regions (MSR)), but does not include clarifications or associations with other terms commonly used by stakeholders and subject matter experts. PhRMA believes it will be very helpful if the Agency includes a table of terminologies and associated definitions, and their interrelatedness.

PhRMA requests that FDA includes more examples, use cases, and/or considerations to illustrate how the high-level principles in this draft guidance should be applied. For example, the draft guidance does not provide a specific example for creating an endpoint for a fixed time in relation to recall period, as well as other study specific issues (e.g., treatment durability, trajectory of change in symptoms) that would give further clarity to the fixed time point. Another issue where an example may be helpful is in the use of multi-domain scales and how to handle situations when subscales might present qualitatively different results (i.e., one subscale suggests improvement while other subscales show no change or decline). PhRMA would also find it helpful if the Agency provided examples demonstrating how to select an assessment to analyze changes in baselines if multiple baseline assessments are used.

PhRMA recommends that FDA better align the draft guidance with the previous PFDD and PED-related guidances. For example, the Core Patient-Reported Outcomes in Cancer Clinical Trials draft guidance\textsuperscript{14} is focused on specific PRO measures but does not recommend sponsors seek evidence supporting the fitness of those PROs across cancer populations. Additionally, when

\textsuperscript{10} The Professional Society for Health Economics and Outcomes research (ISPOR). Available at \url{https://www.ispor.org/}

\textsuperscript{11} FDA, Patient-Focused Drug Development Glossary. Available at \url{https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary}.

\textsuperscript{12} Patient-Focused Drug Development Glossary. Available at \url{https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary}

\textsuperscript{13} BEST (Biomarkers, Endpoints, and other Tools) Resource. \url{https://www.ncbi.nlm.nih.gov/books/NBK338448/}

\textsuperscript{14} FDA Draft Guidance for Industry: Core Patient-Reported Outcomes in Cancer Clinical Trials. June 2021. \url{https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials}
discussing anchors and their ability to aid in the assessment and interpretation of the target COA endpoints, we recommend that the Agency refers to the Patient-Focused Drug Development: Selecting, Developing, or modifying Fit-for-Purpose Clinical Outcome Assessments guidance (PFDD draft guidance 3) for the selection criteria for a clear and appropriate recall period. PhRMA notes that the draft guidance does provide some examples to clarify specific time points but additional examples would be helpful.

In addition to the general comments above, PhRMA provides the following specific comments.

SPECIFIC COMMENTS

A. Labeling To Communicate COA Data

As stated in our response to the RFI on Methodological Challenges to Patient Experience Data, PhRMA supports FDA's ongoing efforts to advance the appropriate inclusion of PED, including patient preference data and patient-reported outcomes (PROs), in labeling to ensure access to relevant information to help inform point of care decisions. PhRMA encourages FDA to adopt policies that support broader inclusion of important information, such as fit-for-purpose PROs, in FDA-approved labeling. This could be achieved by, among other steps, leveraging existing frameworks that facilitate the use of published PRO instrumentation. FDA should consider adopting approaches to better incorporate PRO data in labeling or other initiatives such as Project Patient Voice. This would facilitate informed decision-making on treatment and broader access to medicines.

In general, PhRMA believes there is a lack of clarity on what PED is suitable for inclusion in FDA-approved labeling. For example, PhRMA suggests future guidance on how patient preference study results and exit interview data can be incorporated into FDA-approved labeling. More specifically, PhRMA also requests FDA identify the key factors sponsors should consider in determining whether to include qualitative PED in FDA-approved labeling.


16 Recall period – The period of time patients are asked to consider in responding to a PR item or question. Recall can be momentary (real time) or retrospective of varying lengths.


18 Project Patient Voice: an online platform for patients and caregivers along with their healthcare providers to look at patient-reported symptom data collected from cancer clinical trials. https://www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice
B. Meaningful Score Difference (MSD) and Meaningful Score Regions (MSR)

PhRMA believes the draft guidance introduced novel methodologies and terminologies without a strong evidence base to support their value. PhRMA notes that alignment on meaningful change methodology has been emerging amongst experts through groups such as International Society for Quality of Life Research (ISOQOL),\(^\text{19}\) the International Society for Pharmacoeconomics and Outcomes Research (ISPOR),\(^\text{20}\) and the C-Path PRO Consortium\(^\text{21}\) and encourages the Agency to reference and adopt these approaches, where applicable. PhRMA believes that any new concepts introduced in the draft guidance should have a clear foundation within existing literature to avoid unnecessary confusion (i.e., the difference between “within-patient meaningful change” and “between-groups meaningful change”, or when to use “meaningful score differences” (MSD) or “meaningful score regions” (MSR) to support interpretation of meaningful change).

PhRMA appreciates FDA’s effort to define best approaches for collecting evidence to support interpretability of COA based endpoints. As the Agency develops guidance in this space, it will be critical that FDA outline approaches that are appropriate and consistent. The section on MSR, for example, suggests methods not yet in general use and novel to industry with limited evidence to demonstrate that these methods are appropriate. Furthermore, following these recommendations will lead to the need for specific estimates for each target population, context of treatment and possibly ranges for a COA endpoint, which may add further confusion to understanding COA results rather than clarify the results. PhRMA recommends including the anchor-based approach, among other acceptable approaches and evidence, as well as considerations for defining responders, as this makes use of patient ratings of change/severity administered at different periods of time or upon exit from a clinical trial.\(^\text{22}\)

PhRMA urges FDA to define terms to avoid confusion among stakeholders. Specifically, PhRMA requests greater clarity from FDA when using and applying differences to within person, within group or between group, and also how the individual responder threshold versus these score differences in score regions should be addressed. Multiple terms and/or the interchangeability between “meaningful score differences” and “meaningful score regions” used to describe meaningful or clinically important difference in score and thresholds may be confusing.

\(^{19}\) International Society for Quality of Life Research (ISOQOL). Available at https://www.isoqol.org/

\(^{20}\) The Professional Society for Health Economics and Outcomes research (ISPOR). Available at https://www.ispor.org/

\(^{21}\) The C-Path Patient-Reported Outcome (PRO) Consortium. Available at https://c-path.org/programs/proc/

especially when trying to calculate and interpret differences for within person, within group, and between group.\textsuperscript{23}

In addition, PhRMA suggests FDA provide clarity on MSD and MSR applications (i.e., within-patient, within-group) and consider changing the terms MSD and MSR to align with terms in the FDA Guidance 4 Discussion Document\textsuperscript{24} such as replacing “MSD” with “Meaningful Within-Patient Change (MWPC)” and MSR with meaningful group-level difference (MGLD). PhRMA notes that MWPC best characterizes the concept of within-patient change, while MGLD could be used to interpret the treatment effect between two arms or between two time points within the same arm. In addition, PhRMA suggests that FDA considers reintroducing the “responder” terminology to better align with that used in the 2009 PRO Guidance.\textsuperscript{25}

While FDA acknowledges that there is inherent variability in estimates of MSD regardless of the method, the Agency nevertheless recommends fulfilment of an extensive set of assumptions to derive an MSD and further recommends multiple MSD values for a given COA tool depending on baseline scores, as well as clinical and demographic characteristics of the population or treatment setting. Setting specific criteria to justify the MSD or MSR for each target population will impact the overall value of the COA endpoints to support regulatory decision-making and ultimately limit the value of COA data to key stakeholders including patients and physicians. Users of COA data will need to familiarize themselves with novel MSD or MSR values for each context of use, rather than use the general standard value or range. PhRMA requests the Agency take a more flexible approach and not establish specific MSD and MSR criteria as this may lead to inconsistent application and reporting of COA results to patients. Such specific estimates may be beyond the actual precision of the underlying methods given the inherent variability in the supportive data from anchors and qualitative research, along with general patient population variability for a particular condition versus the variability seen within the clinical trial patient population with the same condition.

In the event that FDA continues to use the terms MSD and MSR, PhRMA requests the Agency clarify how MSD and MSR ranges will be applied.\textsuperscript{26} Additional explanations are needed for why the within-patient MSD should be used to evaluate between-treatment differences at the population level. In the draft guidance, MSD is defined as being a within-patient difference, yet its use is suggested to evaluate the “expected treatment effect for the average patient,”

\textsuperscript{23} Lines 773-795.


\textsuperscript{26} Lines 699-757.
implying a between-treatment evaluation at the population level.\textsuperscript{27} Additionally, PhRMA would like clarity on whether an item within a multi-item PRO measure could be used as an anchor to define an MSR for the score of that same multi-item measure. If so, further guidance on evidence and methodology for this process would be greatly appreciated.\textsuperscript{28}

In addition, the draft guidance recommends the use of a multi-component endpoint to incorporate multiple manifestations of a condition in one endpoint. PhRMA would appreciate greater clarity surrounding the approaches to scoring for multi-component endpoints. This includes clarifying how sponsors may determine how to weigh the different components and what else is needed to establish the validity of the scoring.\textsuperscript{29} PhRMA believes it would be helpful for FDA to include examples of multi-component endpoints and in particular, within-patient multi-component endpoints.\textsuperscript{30, 31}

Moreover, we request that the FDA clarify its expectations regarding score thresholds and the need for pre-specification and/or additional analyses. The draft guidance notes that sponsors should pre-specify only a single score threshold and provide evidence for this threshold, while also suggesting additional analyses to explore treatment effects over a range of thresholds.\textsuperscript{32} We believe that if there is evidence for a single score threshold, then there should not be a need for exploratory analyses looking at different thresholds (i.e., when exploring robustness of results by exploring additional thresholds). However, if the most appropriate score threshold is not clear, then designing endpoints to analyze a range of score thresholds may be most appropriate.

The draft guidance indicates that data from a registration trial should be used to support score threshold definitions. In situations where this may not be feasible, PhRMA requests guidance on alternative approaches to the use of registration trial data to support score threshold definitions. This might include use of a predefined selected portion of the data to determine a threshold for a new COA endpoint. PhRMA encourages the Agency to also include the possibility of using a partial set of blinded data from the registration trial to be accounted for when

\textsuperscript{27} Lines 785-789.

\textsuperscript{28} Lines 1005-1009.

\textsuperscript{29} Line 377.


\textsuperscript{31} Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development. https://healthpolicy.duke.edu/events/rare-disease-endpoint-advancement-pilot-program-workshop-novel-endpoints-rare-disease-drug

\textsuperscript{32} Lines 254 and 261.
deriving meaningful change thresholds. This is especially relevant for rare disease trials where it is by definition challenging to obtain a large sample size.

C. Dichotomization

PhRMA recommends FDA provide more guidance regarding the dichotomization of continuous and ordinal data, and the associated interpretability issues (including the loss of statistical power with dichotomization of continuous data) which may arise. PhRMA notes that the draft guidance also describes potential issues with comparing changes from baseline by treatment for ordinal scale variables. Recognizing that the specific model selected will be dependent on a variety of factors, PhRMA asks that FDA provide considerations to assess the appropriateness of modeling approaches such as ordinal logistic regression models, cumulative logit models and others to analyze change from by baseline for ordinal scales. PhRMA believes it is important to recognize that ordinal logistic regression models have their own assumptions. For example, the cumulative logit model assumes proportional odds, which may be violated in many circumstances. Analyses should generally be based on means, not odd ratios, for outcomes that have an underlying continuous distribution.

D. Estimand and Scope

PhRMA recommends that FDA align the estimand framework in the guidance with ICH E9(R1) estimands addendum. We would also encourage the Agency to consider the handling of intercurrent events in describing the endpoint regarding the estimand framework, in particular how to include intervening events into the endpoint and analysis.

Furthermore, PhRMA believes that this draft guidance should address therapeutic areas with special considerations (e.g., rare drug development). PhRMA recommends that FDA include a

33 Ibid.
39 Lines 138-140.
discussion on the importance of patient input into intercurrent events. PhRMA also requests additional details on the issues associated with post-baseline events, approaches to handle them (e.g., principal stratification), and how these relate to the estimands framework.

E. Use of Digital Health Technologies for Collecting and Analyzing COA data

PhRMA appreciates the Agency’s consideration regarding the use of digital health technologies (DHTs) for collecting and analyzing COA data in the draft guidance and for including the example on mobile sensor assessments. Event-triggered assessments may be a good use case for DHTs that passively monitor activity (e.g., sensors). As such, PhRMA recommends that the Agency add an example on the use of DHTs to passively capture triggering events, such as acoustic recognition of a coughing fit used to prompt a patient report of respiratory symptoms. Additionally, PhRMA believes that the Agency should include a discussion or reference to other FDA guidances to address how DHT-derived passively monitored activities fit into the spectrum of COAs. PhRMA appreciates that FDA acknowledges several strategies for constructing COA-based endpoints and assessing meaningful change, alongside the use of technologies such as mobile sensor assessments.\(^\text{40}\)

F. Other Study Design Considerations and Minimizing Participant Burden

While double blinded treatment assignment is typically preferred, it is often infeasible for oncology or rare diseases trials. PhRMA also notes there have also been studies showing patients knowing treatment assignments did not meaningfully impact their responses.\(^\text{41}\) PhRMA recommends that FDA address this in the “Other Study Design Considerations” section.

G. Regulatory Interactions and Decision-Making

PhRMA suggests the Agency provide recommendations on the purposeful inclusion of PED and outline the appropriate mechanisms for requesting FDA feedback on PED. PhRMA acknowledges that there is no dedicated meeting type for sponsors to discuss PED with the Agency. Guidance documents regularly recommend that sponsors contact FDA early and often but do not specify the appropriate meeting type for holding these discussions. PhRMA believes this information would assist sponsors in planning patient preference studies and informing decision-making on whether and how to incorporate results into a development program.

In cases where sponsors have been able to discuss PED with FDA, PhRMA highlights that there have been challenges in the timeliness of the meetings and in getting feedback in time to implement FDA’s recommendations within clinical programs. This is particularly the case when

\(^{40}\) Lines 141 – 147.

receiving feedback via written response only (WRO) as it will often require additional clarification.

PhRMA and its member companies also request greater clarity on how the Agency uses PED in regulatory decision-making and how the Agency evaluates the quality of PED. The publication of case studies would help sponsors understand how the Agency considers PED and help provide greater transparency in FDA’s use of PED in its regulatory decision-making.

H. COA Review Process

PhRMA appreciates FDA’s commitment to continue to strengthen the Agency’s capacity to facilitate development and use of patient-focused methods to inform drug development and regulatory decisions. PhRMA looks forward to FDA’s implementation of a broad-based effort to conduct outreach and training that emphasizes PFDD methods and tools-related guidance and practice across the Agency. PhRMA believes that broader acceptance and integration will support consistency in regulatory decision-making across review divisions and medical development programs.

PhRMA member companies have also observed an inconsistency in the timing of when COA reviewers become involved in the review process, as well as the documentation and level of information that is shared with the COA reviewer. Of note, sponsors have reported FDA requesting information on COAs that has already been included in a submission package. As FDA strengthens its capacity in this area, PhRMA requests that COA reviewers be consistently involved earlier in the review process and recommends the Agency outline the internal process for including COA experts in the review process.

Anecdotally, PhRMA member companies have reported receiving inconsistent feedback from different review divisions on the selection, modification, and development of fit-for-purpose clinical outcome assessments (COAs). PhRMA notes that consistent feedback from review division on COAs is both appreciated and important for ensuring efficient and effective medical product development.

CONCLUSION

PhRMA and its member companies support efforts to include stakeholders, including patients, caregivers, researchers, medical product developers and others, in the process of collecting and submitting patient experience data to the Agency. PhRMA looks forward to working with FDA as the Agency continues to enhance the incorporation of the patient’s voice in drug development and regulatory decision-making.

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Respectfully submitted,

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