Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA regulations require sponsors to present information from premarket clinical trials on the safety and effectiveness of drugs[2] in terms of gender, age, and racial subgroups.[3,4] These clinical trials should include patient populations that are historically underrepresented in clinical research (e.g., populations based on race, ethnicity, sex, or age.)[5] However, if, despite the sponsor's best efforts, these populations are not adequately represented in premarket clinical trials, it may be appropriate to collect such data in the postmarketing setting. The purpose of this guidance is to describe FDA requirements and provide recommendations for obtaining safety and effectiveness information on drugs, when appropriate, in the postmarketing setting in historically underrepresented patient populations in clinical trials.

Specifically, this guidance will discuss the following:

- Mechanisms by which FDA can require or request information on safety and effectiveness be collected in the postmarketing setting
- Design and statistical considerations for subpopulation analyses

[1] This guidance has been prepared by the Oncology Center of Excellence in cooperation with the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] This guidance applies to drugs, including biological products. For the purposes of this guidance, drug or drug product is used to refer to human drugs and human biological products that are regulated as drugs.

[3] See 21 CFR 314.50(d)(5)(v)-(vi); 21 CFR 312.33(a)(2).

[4] See also section 505(z) of the FD&C Act, which would require sponsors to submit a diversity action plan for a phase 3 study or other pivotal study of a drug. This requirement will apply with respect to clinical investigations for which enrollment commences 180 days after the publication of a final guidance on diversity action plans. FDA will also hold public workshops on this matter.

[5] This list is not all inclusive. Efforts should be made, whether in the premarket or postmarketing setting, to include other underrepresented populations including but not limited to, geographic location, gender identity, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity.

- Postmarketing approaches to obtain information on the benefit-risk profile in underrepresented clinical trial populations

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required

II. BACKGROUND

Having information on the safety and efficacy of a drug across a diverse patient population is important to support the generalizability of the results to the broad patient population expected to take a drug if it is FDA-approved. Disease occurrence and outcome may vary based on associated demographic factors such as race, ethnicity, sex, or age, among others. Toxicity due to the drug may also differentially occur in relation to these factors. Such differences may occur due to intrinsic factors (e.g., genetics, metabolism, elimination, physiologic changes), extrinsic factors (e.g., diet, environmental exposure, socioeconomic status, culture), or interactions among these factors.[6]

Reviews of clinical trial data indicate that there is persistent under-representation of patient populations, based on race, ethnicity, sex, or age[7,8,9,10,11]. FDA has published various guidance documents to improve diversity in clinical trials including *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016)*; Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020); and *Inclusion of Older Adults in Cancer Clinical Trials* (March 2022). Additionally, FDA has sponsored

[6] ICH Harmonized Tripartite Guideline: Ethnic Factors in the Acceptability of Foreign Clinical Data. E5(R1), at https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf

[7] Bhatnagar V, Gormley N, Kazadjian D, Goldberg K, McKee A, Blumenthal G, Farrell AT, Pazdur R. FDA Analysis of Racial Demographics in Multiple Myeloma Trials. Blood. 2017;130:4352.

[8] Singh H, Kanapuru B, Smith C, Fashoyin-Aje LA, Myers A, Kim G, Pazdur R. FDA Analysis of Enrollment of Older Adults in Clinical Trials for Cancer Drug Registration: A 10-Year Experience by the U.S. Food and Drug Administration. J Clin Oncol. 2017;35:15 suppl, 10009.

[9] Kanapuru B, et al. FDA Analysis of MM. In press

[10] Gifford AL, Cunningham WE, Heslin KC, Andersen RM, Nakazono T, Lieu DK, Shapiro MF, Bozzette SA; HIV Cost and Services Utilization Study Consortium. Participation in research and access to experimental treatments by HIV-infected patients. N Engl J Med. 2002;346(18):1373-82.

[11] Strong B, Pudar J, Thrift AG, Howard VJ, Hussain M, Carcel C, de Los Campos G, Reeves MJ. Sex Disparities in Enrollment in Recent Randomized Clinical Trials of Acute Stroke: A Meta-analysis. JAMA Neurol. 2021;78(6):666–677.

multiple public workshops[12,13,14] to further engage with the broader community on the importance of diverse representation in clinical trials. FDA encourages efforts to include underrepresented populations in clinical trials, including populations based on race, ethnicity, sex, age, geographic location, gender identity, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity.

The Agency strongly recommends sponsors obtain information from a diverse, representative patient population early in drug development before initial approval but recognizes that in certain circumstances this information may be limited and must be balanced within the benefit-risk framework, including whether there is unmet medical need and the importance of the product within the overall therapeutic armamentarium.[15] Obtaining information early in development can be advantageous in that information about differential pharmacokinetics (PK), pharmacodynamics (PD), efficacy, or safety may help inform subsequent clinical trials and, ultimately, result in more efficient, informative, and successful drug development. However, if despite the sponsor's best efforts, such information could not be obtained prior to initial approval of a drug, this information can be obtained in the postmarketing setting.

III. MECHANISMS FOR OBTAINING POSTMARKETING DATA ON UNDERREPRESENTED POPULATIONS

There are various mechanisms for obtaining postmarketing data on underrepresented populations. FDA may require an applicant to conduct postapproval studies or clinical trials[16] as a postmarketing requirement (PMR) where the statutory criteria are met,[17] or FDA may enter into a written agreement with the applicant to collect these data as a postmarketing commitment (PMC).[18] Section 505(o)(3)(E) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires an applicant to provide certain information to FDA about its PMR, including a timetable for study or clinical trial completion and periodic reports on the status of the study or clinical

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[12] Levit L, Singh H, Klepin H, Hurria A, 2018, Expanding the Evidence Base in Geriatric Oncology: Action Items from an FDA-ASCO Workshop. J Natl Cancer Inst. 2018. 110(11):1163-1170.

[13] FDA Workshop Roadmap to 2030 for New Drug Evaluation in Older Adults. 2021 Mar 23: https://www.fda.gov/drugs/news-events-human-drugs/roadmap-2030-new-drug-evaluation-older-adults-03232021-03232021.

[14] FDA-AACR Workshop to Examine Under-representation of African Americans in Multiple Myeloma Clinical Trials. 2021 Feb 13: https://www.fda.gov/drugs/fda-aacr-workshop-examine-under-representation-african-americans-multiple-myeloma-clinical-trials.

[15] See also section 505(z) of the FD&C Act, which would require sponsors to submit a diversity action plan for an applicable phase 3 study or other pivotal study of a drug.

[16] For the purposes of implementing section 505(o)(3) of the FD&C Act, FDA defines clinical trials as "any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other intereventions to one or more human subjects" and defines clinical studies as "all other investigations, such as investigations with human that are not clinical trials (e.g., observational epidemiologic studies) animal studies, and laboratory experiments."

[17] See*, e.g.,* section 505(o)(3) and 506 of the FD&C Act; see also draft guidance for industry *Postmarketing Studies and Clinical Trials-Implementation of 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[18] *See* section 506B of the FD&C Act; 21 CFR 314.81, 601.70.

trial.[19] Additionally, Section 506B of the FD&C Act provides FDA with the authority to monitor the progress of certain postmarketing studies by requiring the applicant to submit a report annually that provides information on the status of such studies.[20] Before requiring a postmarketing study or clinical trial under Section 505(o)(3), FDA must find that adverse event reporting under Section 505(k)(1) of the FD&C Act and the active risk identification and analysis (ARIA) system under section 505(k)(3) of the FD&C Act will not be sufficient (1) to assess a known serious risk related to the use of the drug; (2) to assess signals of serious risk related to use of the drug; or (3) to identify an unexpected serious risk when available data indicates the potential for a serious risk.[21] Further, before requiring a postmarketing clinical trial, FDA must find that a postmarketing study or studies will not be sufficient to meet those purposes.[22]

If the drug is to be granted accelerated approval, FDA has required confirmation of clinical benefit in a confirmatory trial.[23] The confirmatory trial should represent the diversity of patients expected to use the drug in the United States.

A. PMRs

If adverse event reporting and ARIA are determined to be insufficient under Section 505(o)(3) of the FD&C Act, FDA can require applicants to conduct postmarketing studies or, as applicable, clinical trials for a drug product either at the time of or after approval.[24] FDA can require PMRs to assess a known serious risk, signals of a serious risk, or to identify an unexpected serious risk when data indicate the potential for a serious risk.[25] This includes postmarketing studies or, as applicable, clinical trials to further assess or identify a serious risk related to failure of expected pharmacological action, including reduced effectiveness under the conditions of use prescribed in labeling, but which may not include reduced effectiveness that is in accordance with such labeling.[26]

For example, FDA may require an applicant to evaluate the incidence rates of certain serious adverse events among U.S. racial and ethnic minorities or older patients when there are data to suggest that those adverse events may occur at a higher rate in these populations but an insufficient number of participants from these populations participated in the pivotal trial to adequately evaluate the signal. This may include evaluation of a potential serious risk related to reduced effectiveness in a subpopulation of patients (e.g., defined by race, ethnicity, sex or age) compared to the overall populations. For example, FDA may require a

[19] Section 505(o)(3)(E) of the FD&C Act.

[20] Section 506B of the FD&C Act; see also guidance for industry *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* (February 2006).

[21] Section 505(o)(3)(B) and (D)(i) of the FD&C Act.

[22] Section 505(o)(3)(B) and (D)(ii) of the FD&C Act; see also draft guidance for industry *Postmarketing Studies and Clinical Trials-Implementation of 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). When final, this guidance will represent FDA's current thinking on this topic.

[23] Section 506(c)(3)(A) of the FD&C Act and 21 CFR 314.510 and 601.41. See also guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

[24] Section 505(o)(3)(D) of the FD&C Act.

[25] Section 505(o)(3)(B) and (D) of the FD&C Act.

[26] See section 505(o)(3) and 505-1(b) of the FD&C Act.

PMR if there is data to suggest a signal of a serious risk related to reduced effectiveness in an underrepresented population or a subgroup of patients with a particular genetic mutation that occurs more commonly in patients of a particular race.

B. PMCs

FDA may enter into a written agreement with the applicant to conduct postmarketing studies and clinical trials under a PMC. In some cases, underrepresentation of certain sub-population in clinical trials can lead to a lack of data on the sub-population. FDA may enter into a written agreement with the applicant to collect data from clinical trials, postmarketing studies, or additional data sources to further characterize clinical benefit or safety in those sub-populations under a PMC. For example, if there is a lack of data in a certain subpopulation of patients (e.g., defined by race, ethnicity, sex, age), FDA may enter into a written agreement with the applicant to collect data under a PMC to obtain additional safety and efficacy data in that subpopulation.

IV. STUDY DESIGN AND STATISTICAL CONSIDERATIONS

The sections below describe design and statistical considerations for various postmarketing approaches to provide additional information regarding traditionally under-represented populations.

A. Considerations for Single-Arm Trials

- Single-arm trials can be designed with a sample size calculation intended to rule out a historical rate of safety or efficacy to help provide assurance that the medical product is safe and effective in the relevant subpopulation(s).
- Single-arm trials can use a Bayesian posterior probability model to exclude the historical rate at pre-specified levels, e.g., 90 percent or higher.
- Single-arm trial designs can also allow for 'borrowing' of patients from the pre-approval study(ies) when appropriate to obtain a larger sample size of the subpopulation of interest.
- Single arm trials should collect PK and PD (if applicable) information to inform or understand any differences in the subpopulation of interest detected in the registrational studies.
- Single arm trials can enroll and analyze subpopulations underrepresented in the main analysis population in a separate cohort as a parallel arm of the trial. When clinically appropriate, the separate cohort may be opened/closed simultaneously with the main cohort or in an asynchronous manner. In some cases, the separate cohort can be actively accruing at the time of the new drug application (NDA) or biologics license application (BLA) submission. For example, if the separate cohort is evaluating a group at high risk for toxicity, the cohort may open after the primary analysis portion of the trial to obtain more safety information prior to enrollment of the higher risk population. Alternatively, the separate cohort may remain open after the primary

analysis population to allow for enrollment of a larger number of patients from the underrepresented population.

B. Considerations for Randomized Trials

- Randomized trials that are planned at the time of the NDA or BLA submission may be revised to enrich the trial for the subpopulation(s) of interest to obtain postmarketing data. Trials that are ongoing at the time of the NDA or BLA submission may also be modified in some cases, but it is important to consider and discuss with the Agency the rationale for the potential changes and any impact on statistical analyses.[27]
- Sponsors could also stratify based on the subpopulation(s) of interest if there are potential prognostic implications associated with the subpopulation. For example, a trial can stratify based on race, ethnicity, sex, age, or a hypothesized difference in efficacy in the population of interest versus the general population, so that analyses can focus on benefits and risks in the underrepresented population.
- The trial should collect adequate PK and PD information (if applicable) to inform or understand any differences in the subpopulation(s) of interest.

C. Real-World Data (RWD) Sources

- Real world data,[28] including electronic health records[29,30] and registries,[31] can be used to provide postmarketing data when appropriate. Sponsors should carefully assess the adequacy of the RWD to appropriately answer the questions relevant to the subpopulation(s) of interest (e.g., ensuring the RWD source is fit for purpose).
- There are multiple complex issues when considering the use of RWD to obtain postmarketing information on traditionally underrepresented populations. The Agency recommends that sponsors discuss the proposed use of RWD with the FDA review division to obtain feedback and guidance early in their development.

D. Pooled Studies

- Meta-analyses of randomized trials can be conducted to obtain postmarketing data provided similarly designed trials evaluating the drug are available with sufficient

[27] See guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* (December 2019)
[28] Refer to FDA's *Framework for FDA's Real-World Evidence Program* (December 2018)
[29] See draft guidance for industry *Real-World Data: Assessing Electronic Health Reords and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (September 2021). When final, this guidance will represent FDA's current thinking on this topic.
[30] See guidance for industry *Use of Electronic Health Record Data in Clinical Investigations* (July 2018)
[31] See draft guidance for industry *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (November 2021). When final, this guidance will represent FDA's current thinking on this topic.

enrollment of the subpopulation of interest, and comparable drug exposure across the selected studies and therapeutic indications.[32]

- Pooling data across trials, if methodologically appropriate, may allow for a meaningful evaluation of the drug in patients from different clinically relevant subpopulations if the clinical studies include an adequate number of patients and sufficient data (PK, PD, efficacy, and safety) from each subpopulation is collected. Sponsors should discuss with the relevant review division what may be considered adequate representation to answer the questions of interest for a specific development program.

V. POSTMARKETING APPROACHES TO OBTAIN DATA ON UNDERREPRESENTED POPULATIONS AND OTHER CONSIDERATIONS

The sponsor's approach to provide information on underrepresented populations should be discussed with the FDA review division early in a product development program. FDA recommends submission of a diversity plan as outlined in the guidance for industry, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials.*[33,34] As noted above, the sponsor and FDA should work together to determine appropriate benchmarks for an inclusive and representative data package that is specific to each development plan. If during the course of the clinical development program, the strategies implemented to recruit and retain a representative population appear unlikely to accomplish the intended objective despite best efforts, the sponsor and FDA should discuss next steps. If it is determined that additional information should be collected in the postmarketing period, such data can provide clinically useful information and can potentially be added to drug labeling, when appropriate.

A. Develop recruitment strategies tailored to the intended population

The guidance for industry, *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020) includes recommendations for inclusive trial practices, trial design and methodological approaches, and other study design and conduct considerations for improving enrollment that sponsors should consider regarding underrepresented populations. The same guidance discusses the importance of clinical trial site selection to allow for recruitment

[32] See draft guidance for industry *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (November 2018). When final, this guidance will represent FDA's current thinking on this topic.

[33] See draft guidance for industry *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials (April 2022).* When final, this guidance will represent FDA's current thinking on this topic.

[34] See also section 505(z) of the FD&C Act, which would require sponsors to submit a diversity action plan for a phase 3 study or other pivotal study of a drug. This requirement will apply with respect to clinical investigations for which enrollment commences 180 days after the publication of a final guidance on diversity action plans. FDA will also hold public workshops on this matter.

of a more diverse study population. These consideration would be applicable to trials conducted in the post-marketing setting.

B. Foreign Clinical Data

Under 21 CFR 314.106, FDA may approve a marketing application based solely on foreign clinical data if, among other factors, the data are applicable to the U.S. population and U.S. medical practice. If a sponsor submits a marketing application comprised of patients enrolled predominantly outside of the United States, data and rationale should be submitted to support applicability to the U.S. population and medical practice. FDA may request or require studies or trials to further characterize the efficacy or safety of the product in subpopulations relevant to the U.S. population.