
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DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

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

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1 **Postmarketing Approaches to Obtain Data on Populations**
2 **Underrepresented in Clinical Trials for Drugs and Biological**
3 **Products**
4 **Guidance for Industry¹**
5

6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
12

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15
16 **I. INTRODUCTION**
17

18 FDA regulations require sponsors to present information from premarket clinical trials on the
19 safety and effectiveness of drugs² in terms of sex, age, and racial subgroups.^{3,4} These clinical
20 trials should include patient populations that are historically underrepresented in clinical research
21 (e.g., populations based on race, ethnicity, sex, or age.)⁵ However, if, despite the sponsor's best
22 efforts, these populations are not adequately represented in premarket clinical trials, it may be
23 appropriate to collect such data in the postmarketing setting. The purpose of this guidance is to
24 describe FDA requirements and provide recommendations for obtaining safety and effectiveness
25 information on drugs, when appropriate, in the postmarketing setting in historically
26 underrepresented patient populations in clinical trials.
27

28 Specifically, this guidance will discuss the following:
29

- 30 • Mechanisms by which FDA can require or request information on safety and
31 effectiveness be collected in the postmarketing setting
32 • 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, sex, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity.

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- 33 • Postmarketing approaches to obtain information on the benefit-risk profile in
34 underrepresented clinical trial populations
35

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

41
42 **II. BACKGROUND**
43

44 Having information on the safety and efficacy of a drug across a diverse patient population is
45 important to support the generalizability of the results to the broad patient population expected to
46 take a drug if it is FDA-approved. Disease occurrence and outcome may vary based on
47 associated demographic factors such as race, ethnicity, sex, or age, among others. Toxicity due
48 to the drug may also differentially occur in relation to these factors. Such differences may occur
49 due to intrinsic factors (e.g., genetics, metabolism, elimination, physiologic changes), extrinsic
50 factors (e.g., diet, environmental exposure, socioeconomic status, culture), or interactions among
51 these factors.⁶
52

53 Reviews of clinical trial data indicate that there is persistent under-representation of patient
54 populations, based on race, ethnicity, sex, or age^{7,8,9,10,11}. FDA has published various guidance
55 documents to improve diversity in clinical trials including *Collection of Race and Ethnicity Data*
56 *in Clinical Trials* (October 2016); *Enhancing the Diversity of Clinical Trial Populations –*
57 *Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020); and *Inclusion of*
58 *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.

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59 multiple public workshops^{12,13,14} to further engage with the broader community on the
60 importance of diverse representation in clinical trials. FDA encourages efforts to include
61 underrepresented populations in clinical trials, including populations based on race, ethnicity,
62 sex, age, geographic location, sex, socioeconomic status, disability, pregnancy status,
63 lactation status, and co-morbidity.
64

65 The Agency strongly recommends sponsors obtain information from a diverse, representative
66 patient population early in drug development before initial approval but recognizes that in certain
67 circumstances this information may be limited and must be balanced within the benefit-risk
68 framework, including whether there is unmet medical need and the importance of the product
69 within the overall therapeutic armamentarium.¹⁵ Obtaining information early in development
70 can be advantageous in that information about differential pharmacokinetics (PK),
71 pharmacodynamics (PD), efficacy, or safety may help inform subsequent clinical trials and,
72 ultimately, result in more efficient, informative, and successful drug development. However, if
73 despite the sponsor’s best efforts, such information could not be obtained prior to initial approval
74 of a drug, this information can be obtained in the postmarketing setting.
75

III. MECHANISMS FOR OBTAINING POSTMARKETING DATA ON 77 UNDERREPRESENTED POPULATIONS

78
79 There are various mechanisms for obtaining postmarketing data on underrepresented
80 populations. FDA may require an applicant to conduct postapproval studies or clinical trials¹⁶ as
81 a postmarketing requirement (PMR) where the statutory criteria are met,¹⁷ or FDA may enter
82 into a written agreement with the applicant to collect these data as a postmarketing commitment
83 (PMC).¹⁸ Section 505(o)(3)(E) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
84 requires an applicant to provide certain information to FDA about its PMR, including a timetable
85 for study or clinical trial completion and periodic reports on the status of the study or clinical

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 interventions 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.

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

97
98 If the drug is to be granted accelerated approval, FDA has required confirmation of clinical
99 benefit in a confirmatory trial.²³ The confirmatory trial should represent the diversity of patients
100 expected to use the drug in the United States.

101 102 **A. PMRs**

103 If adverse event reporting and ARIA are determined to be insufficient under Section
104 505(o)(3) of the FD&C Act, FDA can require applicants to conduct postmarketing studies
105 or, as applicable, clinical trials for a drug product either at the time of or after approval.²⁴
106 FDA can require PMRs to assess a known serious risk, signals of a serious risk, or to
107 identify an unexpected serious risk when data indicate the potential for a serious risk.²⁵ This
108 includes postmarketing studies or, as applicable, clinical trials to further assess or identify a
109 serious risk related to failure of expected pharmacological action, including reduced
110 effectiveness under the conditions of use prescribed in labeling, but which may not include
111 reduced effectiveness that is in accordance with such labeling.²⁶

112
113 For example, FDA may require an applicant to evaluate the incidence rates of certain serious
114 adverse events among U.S. racial and ethnic minorities or older patients when there are data
115 to suggest that those adverse events may occur at a higher rate in these populations but an
116 insufficient number of participants from these populations participated in the pivotal trial to
117 adequately evaluate the signal. This may include evaluation of a potential serious risk
118 related to reduced effectiveness in a subpopulation of patients (e.g., defined by race,
119 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.

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

123 124 **B. PMCs**

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

134 135 136 **IV. STUDY DESIGN AND STATISTICAL CONSIDERATIONS**

137
138 The sections below describe design and statistical considerations for various postmarketing
139 approaches to provide additional information regarding traditionally under-represented
140 populations.

141 142 **A. Considerations for Single-Arm Trials**

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

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163 analysis population to allow for enrollment of a larger number of patients from the
164 underrepresented population.
165

B. Considerations for Randomized Trials

- 167
- 168 • Randomized trials that are planned at the time of the NDA or BLA submission may
169 be revised to enrich the trial for the subpopulation(s) of interest to obtain
170 postmarketing data. Trials that are ongoing at the time of the NDA or BLA
171 submission may also be modified in some cases, but it is important to consider and
172 discuss with the Agency the rationale for the potential changes and any impact on
173 statistical analyses.²⁷
 - 174 • Sponsors could also stratify based on the subpopulation(s) of interest if there are
175 potential prognostic implications associated with the subpopulation. For example, a
176 trial can stratify based on race, ethnicity, sex, age, or a hypothesized difference in
177 efficacy in the population of interest versus the general population, so that analyses
178 can focus on benefits and risks in the underrepresented population.
 - 179 • The trial should collect adequate PK and PD information (if applicable) to inform or
180 understand any differences in the subpopulation(s) of interest.

C. Real-World Data (RWD) Sources

- 181
- 182 • Real world data,²⁸ including electronic health records^{29,30} and registries,³¹ can be
183 used to provide postmarketing data when appropriate. Sponsors should carefully
184 assess the adequacy of the RWD to appropriately answer the questions relevant to
185 the subpopulation(s) of interest (e.g., ensuring the RWD source is fit for purpose).
 - 186 • There are multiple complex issues when considering the use of RWD to obtain
187 postmarketing information on traditionally underrepresented populations. The
188 Agency recommends that sponsors discuss the proposed use of RWD with the FDA
189 review division to obtain feedback and guidance early in their development.
- 190

D. Pooled Studies

- 191
- 192 • Meta-analyses of randomized trials can be conducted to obtain postmarketing data
193 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 Records 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.

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- 194 enrollment of the subpopulation of interest, and comparable drug exposure across the
195 selected studies and therapeutic indications.³²
- 196 • Pooling data across trials, if methodologically appropriate, may allow for a
197 meaningful evaluation of the drug in patients from different clinically relevant
198 subpopulations if the clinical studies include an adequate number of patients and
199 sufficient data (PK, PD, efficacy, and safety) from each subpopulation is collected.
200 Sponsors should discuss with the relevant review division what may be considered
201 adequate representation to answer the questions of interest for a specific
202 development program.

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

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

A. Develop recruitment strategies tailored to the intended population

215 The guidance for industry, *Enhancing the Diversity of Clinical Trial Populations –
216 Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020) includes
217 recommendations for inclusive trial practices, trial design and methodological
218 approaches, and other study design and conduct considerations for improving enrollment
219 that sponsors should consider regarding underrepresented populations. The same
220 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.

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227 of a more diverse study population. These consideration would be applicable to trials
228 conducted in the post-marketing setting.
229

B. Foreign Clinical Data

231
232 Under 21 CFR 314.106, FDA may approve a marketing application based solely on
233 foreign clinical data if, among other factors, the data are applicable to the U.S. population
234 and U.S. medical practice. If a sponsor submits a marketing application comprised of
235 patients enrolled predominantly outside of the United States, data and rationale should be
236 submitted to support applicability to the U.S. population and medical practice. FDA may
237 request or require studies or trials to further characterize the efficacy or safety of the
238 product in subpopulations relevant to the U.S. population.