Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease

Guidance for Industry

U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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Contains Nonbinding Recommendations

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This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION AND BACKGROUND

Insights into the molecular basis of disease have led to the development of targeted therapies.[2] Often, the pharmacological effect of a targeted therapy is related to a particular molecular alteration.[3] Many clinically defined diseases are caused by a range of different molecular alterations, some of which may occur at low frequencies, that impact common proteins or pathways involved in the pathogenesis of diseases. In a population of patients with the same clinical disease, the heterogeneity in the molecular etiology may influence responsiveness to a particular targeted therapy. However, certain targeted therapies may be effective in multiple groups of patients who have different underlying molecular alterations because the functional effect of the molecular alterations may be similar. Therefore, the FDA is providing guidance on the type and quantity of evidence that can demonstrate efficacy across molecular subsets within a disease, particularly when one or more molecular subsets occur at a low frequency.

The purpose of this guidance is to describe: (1) the FDA's current recommendations on how to group patients with different molecular alterations for eligibility in clinical trials; and (2) general

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

[2] For the purpose of this guidance, a *targeted therapy* is defined as a drug intended for populations that are subsets of clinically-defined diseases and that are identified by using diagnostic testing. For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] For the purpose of this guidance, *molecular alteration* refers to a broad array of molecular changes in DNA, RNA, or proteins, including point mutations, gene fusions, mutational load, epigenetic changes, and over- or under-expression. *Molecular subset* refers to a subgroup of the clinically defined disease caused by a specific molecular alteration or group of molecular alterations that are observed in the clinical disease.

approaches to evaluating the benefits and risks of targeted therapies within a clinically defined disease where some molecular alterations may occur at low frequencies.[4]

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. DEVELOPMENT AND REGULATORY CONSIDERATIONS

A. Identification of Patients for Inclusion in Clinical Trials

- The appropriateness of pursuing an indication in a molecular subset of a disease depends on the strength of evidence supporting the hypothesis that patients with the molecular alteration of interest will be more likely to respond to the targeted therapy owing to some property of the drug (e.g., based on a putative mechanism of action or previous clinical experience with the drug) than patients without the molecular alteration.[5]

- If a sponsor is pursuing an enrichment strategy based on molecular criteria for the purposes of clinical trial design and eligibility, the FDA will accept grouping patients with different molecular alterations if it is reasonable to expect that the grouped patients will have similar pharmacological responses based on a strong scientific rationale. The rationale for grouping patients can be based on computational (e.g., in silico), experimental (e.g., in vitro or animal experiments), or clinical evidence. The grouping of molecular alterations may be defined in many ways, including a list of individual alterations (within a single gene or multiple genes) or a functionally defined group of alterations (e.g., deleterious or sensitizing). Sponsors should discuss any proposed grouping strategy and plans for identifying the proposed group in the clinical setting with the FDA.

- Types of evidence that could support a grouping strategy are listed below, although other sources of evidence may also be appropriate. In general, clinical studies are considered

[4] For the purpose of this guidance, *low-frequency* molecular alterations are those that occur at frequencies low enough that enrolling a sufficient number of patients to conduct a clinical trial limited to the specific molecular alteration of interest is not feasible or practical.

[5] For further discussion on clinical trial enrichment strategies, refer to the draft guidance for industry entitled *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs or Biologics guidance Web pages at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

the strongest type of evidence; however, other types of evidence may also support a grouping strategy (in combination with or independent of clinical studies). When consistent effects are observed across more than one line of evidence, the strength of the evidence increases.

- **Clinical studies**: Preliminary studies demonstrate that patients with the proposed group of specific molecular alterations exhibit similar responses to the investigational drug based on a clinical efficacy endpoint or pharmacodynamic (PD) biomarker.

- **Nonclinical studies**: Similar drug effects are observed across a model system with the proposed group of molecular alterations in nonclinical studies (e.g., similar activity demonstrated across molecular alterations at clinically relevant concentrations or dosages).

- **In silico or mechanism-based evidence**: The investigational drug is expected to have a similar effect across patients with the proposed group of molecular alterations based on computational studies or mechanistic rationale (e.g., all protein-truncating mutations or over-expression of the drug target in tumor tissue).

- **Evidence from other drugs in the same pharmacological class**: Drugs with the same mechanism of action as the drug under investigation show similar effects across the proposed group of molecular alterations in a nonclinical model or clinical trials. Note that confidence in the extrapolation of findings from one drug to another in the same class depends on their similarity in structure, binding sites, and other drug properties.

- **Phenotypic characterization of molecular alterations**: The proposed group of molecular alterations results in a similar baseline of disease-related nonclinical or clinical phenotypes (e.g., mutations that result in increased activity of the drug target).

- In some situations, it may be desirable to include patients who have molecular alterations that are less likely to be responsive (e.g., unmet medical need) or for which the likelihood of response is not known based on the available evidence. In this setting, the sponsor has the option of either splitting study alpha assessment of the primary efficacy endpoint between a subgroup of patients with specific molecular alterations of interest and a broader enrolled population or using an adaptive design with interim assessments of efficacy. Alternatively, the sponsor may limit the assessment of the primary efficacy endpoint to the subgroup of patients with the specific molecular alteration(s) of interest while enrolling additional subgroups to generate preliminary clinical data.

- Sponsors should use analytically validated assays for the identification of molecular alterations used for enrollment of patients into clinical trials.[6] The FDA recognizes that the clinical trial assay method may limit who is eligible for clinical trials. Ideally, clinical trial assays should be designed to detect all possible molecular alterations that comprise the group that is expected to respond.

B. Generalizability of Findings

- Targeted therapies may be effective in multiple molecular subsets that make up a clinical disease. However, the FDA anticipates that for certain subsets only a small number of patients (or even none despite eligibility criteria that are inclusive of such patients) will be enrolled into the trial. The low numbers or the absence of such patients would in most settings preclude meaningful empirical inferences about treatment benefits or risks in patients with those particular molecular alterations. However, when sponsors follow the principles for grouping patients set out in section II.A., Identification of Patients for Inclusion in Clinical Trials, extrapolation of efficacy findings across multiple subsets may be possible despite the low frequency or absence of patients in some subsets.

- Given the above considerations, if the clinical trials are successful and other conditions for approval are met, the FDA will, in most circumstances, approve the drug for all patients who meet the inclusion criteria for the trial based on the prespecified criteria, irrespective of the extent to which patients with various molecular alterations were represented in the clinical trial. Substantial evidence of effectiveness for the drug in the indicated population would be based on the strength of evidence (see section II.A., Identification of Patients for Inclusion in Clinical Trials) demonstrating that patients in the molecular grouping defined by the inclusion criteria will respond similarly to the patients who participated in the study.

- As with all new drug approvals, the FDA will consider the totality of evidence in weighing the benefits and risks of the drug. If after trial enrollment, the FDA or sponsor newly identifies a substantial scientific issue essential to determining the safety or effectiveness of the drug in some molecular subset included in the trial, the indicated patient population may be narrower than the clinical trial enrollment criteria.

C. Benefit and Risk Determination and Labeling

- Labeling will reflect the overall benefits and risks of the drug in the target population. When the drug is approved for all patients who meet the inclusion criteria for the

[6] For additional information, see the draft guidance for industry and FDA staff entitled *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs or Biologics guidance Web pages at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

registration trials as discussed in section II.B., Generalizability of Findings, the indication as described in the INDICATIONS AND USAGE section of labeling should be sufficiently broad to include treatment of patients with low-frequency molecular alterations who would have been eligible for the trial irrespective of the extent to which they were represented in clinical trials. The studies informing the basis for grouping patients (e.g., cell or animal models, PD data) should be clearly specified (e.g., in the CLINICAL PHARMACOLOGY or CLINICAL STUDIES section of labeling).

- Recognizing the analyses may be exploratory, evidence supporting the efficacy of the drug for each molecular subset should be transparently displayed (e.g., tabulation of the number of patients with specific molecular alterations that were enrolled in the clinical trial and the outcomes of the patients) in the CLINICAL STUDIES section of labeling.

- When accurate testing for molecular alterations (whether as a class or as specific alterations) is essential for the safe and effective use of the drug, an FDA-cleared or -approved assay should be commercially available at the time of drug approval to identify patients in the clinical setting. The FDA may grant exceptions when the drug is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists, and the FDA determines that the benefits from the use of the drug outweigh the risks from the lack of an approved or cleared in vitro companion diagnostic device.[7]

D. Refining the Target Population/Indication After Initial Approval

- Incremental expansion of the population eligible for a drug may be part of a lifecycle strategy, and sponsors are encouraged to conduct additional studies in molecular subsets that may respond to the drug but were not eligible for inclusion in the original trials. The amount and nature of clinical efficacy data needed to expand a drug's indication depends on the similarity of pharmacologic responses and the mechanistic rationale for the drug's effect in the population for which efficacy was initially established and in the population to which the indication is being expanded. Similarly, if substantive data emerge from studies (whether observational or randomized trials) indicating lack of efficacy in certain molecular subgroups for which the drug was initially indicated, the FDA will consider narrowing the intended population as appropriate.

- In some cases, generating data in the postmarket setting may be necessary to provide additional information regarding the risks and benefits of the drug in subsets of patients with limited or no enrollment in clinical trials. Real-world evidence (e.g., from observational studies or registry data), traditional controlled trials, or data from other sources (including trials already ongoing) may be appropriate. As with all drug development programs, if the FDA approves the drug under the accelerated approval

[7] For additional information, see the guidance for industry and FDA staff entitled *In Vitro Companion Diagnostic Devices*.

program[8] or identifies safety concerns during the review process, the FDA may require postmarketing studies.

[8] See the guidance for industry entitled *Expedited Programs for Serious Conditions—Drugs and Biologics*.