

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

## Final Guidance for Industry

### What is recommended in this guidance?

The final guidance, *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease*, provides important recommendations on the development of treatments that address molecular alterations that cause or contribute to diseases and the type and quantity of evidence that can demonstrate efficacy across patients with different molecular alterations, particularly those that are present in a small subset of patients.



### Drug Development and Regulatory Considerations



#### Determining the Appropriateness of Pursuing a Molecular Subset for Inclusion in Clinical Trials

Sponsors should justify why the strength of evidence supports the hypothesis that patients with the molecular alteration of interest will be more likely to respond to the targeted therapy.

#### Generalizability of Findings

It is acceptable to use an enrichment strategy based on molecular criteria, 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 supported by computational, experimental, and/or clinical evidence. In most circumstances, FDA will approve the drug for patients who meet inclusion criteria irrespective of the extent to which each subgroup or molecular alterations is represented.

#### Labeling

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).

#### Refining the Target Population/Indication After Initial Approval

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. In addition, sponsors should collect data in the postmarket setting for the subsets of patients with limited or no enrollment in clinical trials to provide additional information regarding the risks and benefits of the drug.

To learn more about assessing targeted therapies in low-frequency molecular subsets of a disease, read the guidance: <https://www.fda.gov/media/117173/download>



## Background About the Guidance

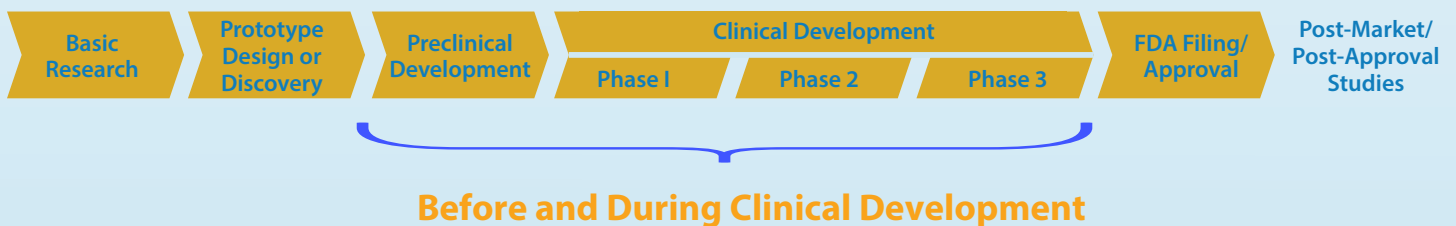
Targeted therapies are an effective treatment option for some patients. However, in a population of patients with the same clinical disease, the molecular causes may differ and can influence response to a particular treatment. In these situations, it is challenging to demonstrate efficacy in all possible molecular subsets, some of which are extremely rare.

## Why is this guidance important?

Many clinically defined diseases are caused by a range of different molecular alterations, some of which occur at low frequencies. Most medical treatments are designed for the “average patient” as a one-size-fits-all-approach. In contrast, targeted therapies may be designed to work in subsets of patients who have specific molecular alterations because they may be more effective or better tolerated in certain patient subsets. FDA issued this guidance to provide recommendations for evaluating the benefits and risks of targeted therapies in subsets of patients with specific molecular alterations within a clinically defined disease that do not occur frequently, making them difficult to evaluate.



## Drug Development Timeline – When to Apply the Guidance Recommendations?



Before and during clinical development, sponsors should provide strong scientific rationale for how patients with different molecular alterations should be grouped for clinical trials. For example, patients with different molecular alterations should be expected to have similar response to the targeted therapy based on clinical studies, nonclinical studies, in silico or mechanism-based evidence, evidence from other drugs in the same pharmacological class, and phenotypic characterization of molecular alterations. In general, clinical studies are considered the strongest type of evidence to support grouping of molecular alterations for clinical trial enrollment.

To learn more about targeted therapies, read the guidance: <https://www.fda.gov/media/117173/download>