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# Client Alert


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## FDA Issues Guidance on Enrichment Strategies for Drug and Biologic Clinical Trials

In December 2012, the Food and Drug Administration (FDA) published a draft guidance entitled, *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*, to address approaches on selecting a study population in clinical trials for new drugs and biologics.[1] The issuance fulfills one of the performance goals to which FDA committed as part of the reauthorization of the Prescription Drug User Fee Act (PDUFA) IV.[2] The guidance delineates several tactics for "enrichment," which it defines as "the prospective use of any patient characteristic to select a study population in which detection of a drug effect … is more likely than it would be in an unselected population." While the draft is not legally binding, it provides FDA's current thinking. Comments on the draft guidance may be submitted to FDA until February 15, 2013.[3]

As background, FDA has explained that the main goal of enrichment is study efficiency, i.e., increasing the chance of study success, frequently with a smaller sample size. Enrichment can also provide individualization by directing treatment where it will do the most good (i.e., personalized medicine) while sparing those that might not benefit from a potential treatment. The draft guidance explains that such study designs can have many benefits, including an improved risk-benefit evaluation if a population with an increased likelihood of response can be identified, and efficiency in drug development when smaller studies are sufficient to demonstrate effectiveness.


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1 77 Fed. Reg. 74,670 (Dec. 17, 2012). The draft guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf.

2 See "Section A: PDUFA Reauthorization Performance Goals and Procedures Fiscal years 2008 Through 2012" available at: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

3 In a 2012 FDA/DIA speech, Dr. Robert Temple explained:

> We don't do clinical trials in a random sample of the population. We try to make sure people have the disease we're studying (entry criteria), have stable disease with stable measurements (lead in periods), do not respond too well to placebo (placebo lead in periods), have disease of some defined severity, and do not have conditions that would obscure benefit. These efforts are all kinds of ENRICHMENT, and almost every clinical trial uses them. There are, in addition, other steps, not as regularly used, that can be taken to increase the likelihood that a drug effect can be detected (if, of course, there is one).


This bulletin highlights some of the major points described in the draft guidance. It is not intended to address all of the technical issues.

**Three Principal Enrichment Strategies**

- Decreasing Heterogeneity – Practical Enrichment

To increase a trial's ability to demonstrate a treatment effect, FDA suggests certain strategies to decrease heterogeneity, or the variability of effects not related to the drug.

Some of the recommendations include, but are not limited to:

(1) Define entry criteria carefully.

- exclude patients unlikely to tolerate the study drug

(2) Find likely compliers prospectively before randomization.

- encourage patient compliance with the study by familiarizing patients with the trial's requirements
- exclude those who might drop out for non-medical reasons

(3) Eliminate placebo responders in a lead-in period.

- treat patients with a placebo prior to randomizing them, in order to eliminate patients from the trial who improve spontaneously or have large placebo responses
- this approach attempts to eliminate those patients that might have improved for reasons other than the study drug

(4) Eliminate people taking drugs with the same effect as the study drug.

However, the agency cautions against certain strategies, such as removing patients from the study with "concomitant illness likely to lead to early death or … drop-out," because doing so may not provide enough information about the range of people who may receive the treatment in practice, such as the elderly or people with multiple illnesses. Further, the guidance noted there is uncertainty as to whether these illnesses do not affect survival or other clinical endpoints (a sign of one of the target outcomes of the trial).


- Prognostic Enrichment -- Identifying High-Risk Patients

Another way sponsors may be able to more readily detect a treatment effect is through prognostic enrichment strategies, where sponsors choose patients more likely to have the medical condition under study (study endpoint) or have a large change in the endpoint being measured during the study. FDA particularly encourages these strategies for cardiovascular disease or cancer trials aiming to reduce the rate of death or serious events, as well as trials intending to delay progression of diseases such as Alzheimer's or Parkinson's. These strategies may allow for a trial to have a smaller sample size, because they increase the trial's "absolute effect size."

- Predictive Enrichment -- Choosing Patients More Likely to Respond to Treatment

In order to increase a trial's absolute and relative effect size, the agency recommends utilizing predictive enrichment strategies, where a sponsor selects patients with a greater likelihood of responding to the study drug. The agency advises using these strategies particularly early in studies to demonstrate effectiveness, because they can provide "proof of concept" (feasibility of conducting a study) and facilitate selection of appropriate doses for subsequent studies. FDA also suggests that a predictive enrichment strategy is appropriate to show effectiveness when the number of patients responding to the drug is a "small fraction of all patients, say 20%," and even facilitates "development and approval" for significantly toxic drugs, because it avoids toxicity exposure in patients not benefiting from treatment.

FDA describes a number of factors to take into account when selecting subjects, including patient characteristics (e.g., pathophysiology, genomic) or empiric factors (e.g., patient history of response to similar drugs, past response to the test drug in a randomized withdrawal study).

Each selection approach has its advantages and disadvantages.

FDA recommends when certain strategies might be preferable. For example, an empiric approach might be useful for treatments with low response rates, early outcome trials, trials specifically designed to compare fixed doses' effects on responses, trials for populations with potentially different responses to treatment, and trials for populations that are not identifiable pathophysiologically or genetically before treatment.

FDA supports study designs that choose patients who fail to respond to an existing drug or who are intolerant of a drug. The agency finds these studies useful to compare drugs' effectiveness, as long as patients are randomized to both the new drug and the drug that did not provide therapeutic benefit previously; patients sometimes respond to drugs to which they had previously failed to respond.


**Study Design Considerations**

In addition to emphasizing the need to specify enrichment strategies in study protocols, the draft guidance highlights the significance of accurate selection criteria, or markers. FDA suggests introducing adaptive designs (changes in design guided by examination of the accumulated data) during later trial stages to exclude non-respondents if a sponsor is unsure about the marker.

Although the agency does not expect all studies to follow its recommendation, it suggests collecting data on "marker-negative population," or patients who do not meet the selected criteria. FDA reasons that a more responsive population does not necessarily imply that the marker-negative population will not also benefit from the treatment. However, if a sponsor is uncertain about marker-negative patients' responsiveness, the guidance suggests including a "reasonable" sample of marker-negative patients, though "reasonable" is left undefined. Further, when a marker is found not to be prevalent, the guidance advises separating patients who have the marker from those who do not.

Concerning labeling, whether enrichment information will be included in the Clinical Studies or Indications sections of the Package Insert depends on the strategies used. FDA maintains that the labeling may "not overstate its likelihood of a response."