

22 CASE
STUDIES
WHERE PHASE
2 AND PHASE 3
TRIALS HAD
DIVERGENT
RESULTS

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22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results

I. Overview

Pre-market clinical testing usually progresses in phases, with increasingly rigorous methods at each phase. Product candidates that appear insufficiently safe or effective at one phase may not proceed to the next phase. Roughly 9 in 10 drugs/biologics that are tested in humans are never submitted to FDA for approval.[1] Typically, a candidate drug is submitted to the FDA for marketing approval after phase 3 testing. In recent years, there has been growing interest in exploring alternatives to requiring phase 3 testing before product approval, such as relying on different types of data and unvalidated surrogate endpoints.

To better understand the nature of the evidence obtained from many phase 2 trials and the contributions of phase 3 trials, we identified, based on publicly available information, 22 case studies of drugs, vaccines and medical devices since 1999 in which promising phase 2 clinical trial results were not confirmed in phase 3 clinical testing.* Phase 3 studies did not confirm phase 2 findings of effectiveness in 14 cases, safety in 1 case, and both safety and effectiveness in 7 cases. These unexpected results could occur even when the phase 2 study was relatively large and even when the phase 2 trials assessed clinical outcomes. In two cases, the phase 3 studies showed that the experimental product increased the frequency of the problem it was intended to prevent.

This paper is not intended to assess why each of these unexpected results occurred or why further product development was not pursued. Rather, these cases, chosen from a large pool of similar examples, illustrate the ways in which controlled trials of appropriate size and duration contribute to the scientific understanding of medical products.

II. Clinical Trials: Understanding Medical Product Testing

In the classical drug development paradigm, pre-market clinical trials for drugs are conducted in three phases. The trials at each phase have a different purpose and help scientists answer different questions.

- *Phase 1 Trials.* In phase 1, researchers test the potential product in humans for the first time, to identify rudimentary product characteristics, such as how the body metabolizes a drug and how long it stays in the body, and to provide evidence that the product is not too toxic for further human testing. The treatment group is small (typically 20 – 80 healthy volunteers), but allows researchers to begin to evaluate the treatment's safety, adjust dosing schemes, and start to identify side effects. This information guides the design of phase 2 studies.
- *Phase 2 Trials.* Phase 2 studies are intended to explore the effectiveness of the product for a particular indication over a range of doses, and to assess short-term side effects. These studies typically involve a few hundred patients who have the target condition, but do not generally have other diseases that might obscure the effect of the drug on the target condition. Phase 2 trials may be randomized and/or controlled, but often measure laboratory values or other biomarkers rather than clinical outcomes (i.e., effects on how a patient feels, functions, or survives). When a phase

* For the purposes of this analysis, the terms “trial” and “study” are used interchangeably.

2 study does assess clinical outcomes, it is usually for relatively short periods of time and in a relatively small number of people. Sponsors assess phase 2 results to determine if the preliminary results are sufficiently promising to justify a phase 3 study.

- *Phase 3 Trials.* Compared to phase 2 trials, the goal of phase 3 trials is to test the experimental product in larger groups of people (typically 300 – 3000), in people who are more similar to those likely to use the product once marketed, and for longer periods of time. Phase 3 studies generally assess clinical outcomes, and are designed to determine whether the demonstrated benefits of the product outweigh its risks.

As discussed in Section III, below, the appropriate size and duration of clinical trials varies significantly from condition to condition, and product to product.[†]

For most approved drug products, clinical evaluation may be continued even after a product is on the market. These studies are termed phase 4 trials, and can be helpful to uncover information on new uses that can be shared with health care providers to refine prescribing advice or can indicate that new warnings should be added to the product's label.

III. Flexibility in Clinical Trial Design

In practice, clinical testing progression and design has become increasingly flexible as the science of clinical trials has evolved. Phase 1 might be combined with phase 2 if the drug is expected to have toxicity unacceptable for healthy volunteers. If the product's mechanism of action and safety profile are well characterized, phase 2 testing may be shortened or skipped altogether. When there is sufficient evidence that a change in a biomarker reliably predicts a clinical benefit, the biomarker can serve as a surrogate measure for that clinical benefit in a trial, and the effect of the product on the surrogate measure can be a basis for product approval. Surrogate measures are often biomarkers that help diagnose or monitor a disease, such as blood pressure to predict stroke risk or the amount of human immunodeficiency virus in the blood to predict the development of acquired immunodeficiency syndrome.

The nature of definitive trials also varies. Larger and longer trials may be needed if, for example, the condition to be treated is chronic or if the event the drug is intended to prevent occurs infrequently. Smaller or shorter trials may be needed where, for example, the drug produces a dramatic improvement in patients, or is intended for short-term conditions like many infections. Other factors, such as whether the condition is widespread or rare, whether it is life-threatening, and whether there are other effective treatments for the condition are also important in determining what kind of clinical testing is appropriate.

Where a drug or biologic is intended to treat a serious condition for which there are limited available alternative therapies, FDA has implemented four separate expedited development and review programs.[2] For example, when there is evidence that a biomarker is “reasonably likely to predict”

[†] Medical device testing often does not follow this “phase 1 - 3” paradigm or use the same “phase 1 – 3” vocabulary. In some cases, practical limitations related to the device or disease condition may limit the feasibility of a large randomized, controlled trial design. But the need, in certain circumstances, for one or more large well controlled studies to determine whether a device actually improves clinical outcomes can be equally applicable. Such trials serve a purpose similar to phase 3 drug and biologic trials. For editorial convenience, we use the phrase “phase 3” throughout the document to refer to both phase 3 drug and biologics trials, as well as “pivotal” and similar trials for devices.

clinical benefit, that biomarker can be a basis for approval under FDA's accelerated approval authority. In these situations, sponsors have been required to conduct post-market confirmatory studies to further define the clinical benefit of the drug.

While clinical testing progression and design has become increasingly flexible, and advances in biomedical science and statistics have enabled introduction of non-traditional study designs and data sources into phase 3 testing, a randomized, controlled, clinical trial (RCT) of a size and duration that reflect the product and target condition remains the gold standard for determining whether there is an acceptable benefit/risk profile for drugs and biologics. For more discussion on clinical trial design, including the unique features of RCTs that make such trials more likely to be definitive, see Appendix A.

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