INSTITUTE FOR HEALTH POLICY FORUM

DRUG POLICY 101: The state of the pharmaceutical evidence base

Having sound evidence about a drug's safety and effectiveness is critical to understanding its benefits and value. In recent years, shifts in the pharmaceutical evidence base have created challenges for evaluating drugs after they come to market. This brief describes how pharmaceutical evidence is generated, how the drug approval process has evolved over the years, and the resulting implications for patients and the broader health care system.

The stages of pharmaceutical research

Research over the course of a drug's life cycle can be broken into 4 stages: discovery, preclinical, clinical, and post-market.[1]

Discovery. During drug discovery, researchers identify promising therapies that may treat a disease or improve a chronic condition. Drug discovery is predicated on basic research – usually conducted by academic scientists – that yields insights on how a disease progresses or a condition arises.

Preclinical research. Preclinical research is the first phase of research leading to the Food and Drug Administration drug approval process. Preclinical research involves animal and laboratory testing, primarily to understand toxicity thresholds.

Clinical research. Clinical research comprises 3 phases of human trials.

Phase I trials study safety and efficacy of a drug in a small population of healthy volunteers (typically 20-100 people).

Phase II trials study the drug's efficacy (how well it performs in a controlled environment) on larger groups of people – often hundreds – with the condition the drug is intended to treat.

Phase III trials study safety and efficacy over a longer period of time and include even larger groups of people with the condition – hundreds to thousands. Due to their greater size and duration, Phase III trials provide the best evidence of a drug's true clinical benefit.

Once clinical research is complete, the FDA reviews the evidence and makes an approval determination. Approval hinges on 2 broad considerations:

1. whether the drug's benefits outweigh its risks; and
2. whether the evidence a company submits on a drug's benefits and risks – ideally at least 2 well-designed clinical trials – is sufficient to make a determination.

Post-market research. The FDA often requires or requests companies to conduct research on drug safety and effectiveness after the drug comes to market.[2] Post-market research is important because it tracks real-world (not controlled) outcomes over long periods of time and can fill gaps in evidence that may have existed when drugs were approved on an expedited basis.

Evidence and study design

Ideally, clinical research should consist of double-blind, randomized control trials (known as RCTs). RCTs occur in highly controlled environments with a carefully selected group of participants who are randomly assigned to be in a control group (receiving a placebo or the current standard treatment for a condition) or a group that receives the drug. In a double-blind study, researchers and participants are not told what group has received the intervention. This study design allows researchers to control for variables that could otherwise mask the effects of the drug. RCTs look at drug safety and efficacy, have fixed durations (usually not long enough to study long-term effects), and can be costly.

In contrast, studies that look at a drug's effectiveness in real-world circumstances – such as observational studies – can include entire populations of patients taking a drug and use real-world data from electronic health records, health insurance claims, disease registries, patient surveys, questionnaires, and personal devices and applications. These studies can be short or long in duration, are mostly conducted after a drug comes to market, and are generally less costly than RCTs. Both types of research have limitations but taken together provide a better picture of drug outcomes and value.

Evidence generation: Trends and implications

Industry observers are growing concerned about the strength of the evidence base required to support FDA approval. For example, companies are increasingly developing highly specialized drugs for very small patient populations (known as orphan drugs) that come to market with less reliable evidence on safety and efficacy.[3]

In addition, the FDA is granting expedited approvals to a greater proportion of drugs. These are drugs that show promise in treating serious conditions for which there are

few or no good treatment options. They gain approval at earlier stages in the research process to reach patients quickly. In some cases, approvals are based on a single study lasting months, not years. Approval has often been based on interim results, such as changes biomarkers (such as blood sugar level), or surrogate endpoints that are "reasonably likely" to predict clinical outcomes. For example, cancer drugs have received accelerated approval for improving tumor shrinkage (a surrogate endpoint), even though longer-term clinical outcomes, such as improved survival rates, were not yet known. The FDA may also approve drugs for populations that were not studied in clinical trials.

In 2019, 73% of new drugs went through fast-track approval — a type of expedited approval for drugs that fill an unmet need — compared with 38% in 2009.[4] The safety and clinical benefits of these drugs can be largely unknown even after they come to market. According to one analysis, 94% of post-market studies for drugs that had received accelerated approval between 2009 and 2013 only contained surrogate endpoints, and many studies suffered the same design flaws —such as not randomizing subjects — as the pre-approval trials.[5]

As the FDA allows more drugs to come to market through expedited approval pathways, the agency is shifting product evaluation into post-market settings. Manufacturers, however, do not always complete post-market studies on a timely basis and sometimes do not complete those studies at all.[6] Even when studies are completed, they are not always publicly posted and can be biased. According to one analysis, at least a quarter of required post-market studies were not posted to the government's public clinical research repository, clinicaltrials.gov.[7] Two-thirds of posted studies were released beyond the FDA deadline, and most were inadequately described, rendering it difficult to assess their results, design, and rigor.

Publication bias — whereby negative studies about a drug do not get published in scientific journals — has also been an enduring issue. In some cases, pharmaceutical companies have posted studies on their websites, but the results overemphasized positive findings and/or deemphasized negative findings.[8] Broadly, evidence indicates that trials conducted or financed by pharmaceutical companies show more favorable outcomes than those conducted by organizations without financial ties to industry.[9]

Looking ahead: Strengthening the pharmaceutical evidence base

The state of the pharmaceutical evidence base has important implications. Of most concern is that providers and patients may not know about the true safety risks of a drug until after it is on the market. For example, the arthritis drug Vioxx was pulled from the market 5 years after it was released, after evidence mounted about its increased risk for heart attacks and strokes. Beyond safety risks, patients and doctors may not know whether a drug will be effective, potentially delaying receipt of effective treatment alternatives.[10]

Having a sound evidence base to support a drug's efficacy is also critical to understanding its value. It is not possible to understand the clinical and cost benefits of a drug without full access to reliable information on drug safety and clinical outcomes. In an era where multimillion-dollar therapies — such as gene therapies — are on the rise, knowing a drug's true value is necessary for setting fair list prices, and as the foundation for executing successful value-based contracts.

With these challenges in mind, several proposals could strengthen the pharmaceutical evidence base:

Tighten standards for expedited approvals
As more drugs with expedited approval come to market, clinicians and patients are left without sufficient information to make sound treatment decisions. Some ideas to tighten standards for expedited approvals include:[11] enhancing pre- and post-market product evaluation when surrogate endpoints and biomarkers are used as primary endpoints for a trial; heightening qualifications for expedited approval pathways; formalizing processes to scrutinize the quality and soundness of evidence submitted by companies; and providing the FDA with more resources to approve drugs.

Bolster use of real-world evidence. The FDA supports increased use of real-world evidence, or RWE, to complement clinical trial data, which improves understanding of a drug's safety and effectiveness after it comes to market. The FDA has also proposed using RWE for approving new indications on existing drugs. However, RWE should be used judiciously,as it may not be robust or reliable enough for approval determinations.

Increase oversight of post-market studies.
The FDA should consider raising the bar on required post-market studies, enforcing timely, public submission of studies. It can also request more voluntary studies from companies, known as post-market commitments. Robust post-market data is especially important for expedited drugs, because they confirm and build evidence about the drug's safety and effectiveness.

Pharmaceutical research will always have flaws, but there are significant opportunities to strengthen the evidence base. Policy and regulatory action, public vigilance, and the industry's commitment to produce high-quality research are all necessary to bring about change.

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