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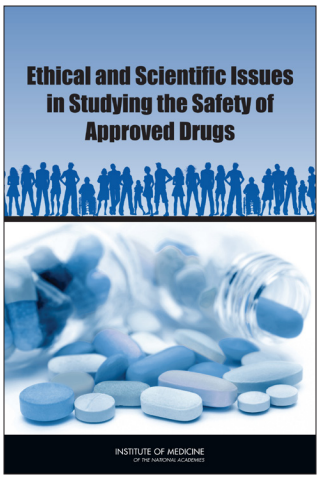
Ethical and Scientific Issues in Studying the Safety of Approved Drugs



Prescription drugs are crucial for preventing and treating diseases and improving the public's health, but they also can have unintended harmful effects. Often, their benefits and risks cannot be fully identified until after a drug is on the market and has been used by a large, diverse group of patients over time, mainly because clinical trials conducted before approval may be too small or too short to detect all possible risks.

Changes in federal law, especially passage of the Food and Drug Administration Amendments Act in 2007, along with advances in information technology, have provided an opportunity for the Food and Drug Administration (FDA) to improve its system for ensuring that drugs are safe and effective after they are approved for sale. Previously, the agency could either withdraw a drug from the market or negotiate with manufacturers to persuade them to accept changes to drug labels and warnings. The 2007 law provides the FDA with additional postmarketing regulatory tools to better protect the health of the public, including the authority to require manufacturers to continue studying drugs that are being marketed.

This new authority also presents the FDA with new challenges, including determining when it is appropriate to require a postmarketing study, which types of studies to require, how best to protect the rights and interests of patients who participate in research, and how to use information from both manufacturers' studies and other research in making regulatory decisions. To help answer these questions, the FDA asked the Institute of Medicine (IOM) to evaluate the scientific and ethical aspects of conducting safety studies for approved drugs.

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Implementing and Documenting a Life Cycle Approach

The IOM committee appointed to consider these questions issued a preliminary report in July 2010, which presented a conceptual framework for analyzing the postmarketing studies that the FDA might require. The committee presents its final findings and recommendations in its report, *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

As a key step, the committee recommends that the FDA more fully embrace a life cycle approach to drug safety oversight. The life cycle approach places substantial emphasis on drug safety after the FDA approves a medicine for sale, and requires that the FDA anticipate and plan well in advance how it will monitor a drug's safety over its market lifetime. The agency should use a consistent process for evaluating information about the benefits and risks of drugs, the committee recommends, and the process should consider both scientific and ethical issues, including scientific disagreements and public values. A central component of the decision-making framework the committee proposes is the need to seek out and consider the perspective of patients and other stakeholders.

To implement this life cycle approach, the committee recommends that the FDA require and maintain a comprehensive benefit and risk assessment and management plan (BRAMP) to track the medicine's benefits and harms during its entire life cycle. The BRAMP should be a living document that is publicly available and easy to understand. Working with relevant stakeholders, including drug manufacturers, the FDA should review and update the BRAMP document at both prespecified times and whenever it reevaluates the drug's benefit-risk profile.

The FDA also should revisit postmarketing safety decisions that are particularly controversial or difficult, or when it makes a major regulatory decision after approving a medicine. Reviews should include assessing the decision-making process itself, as well as gauging the public health effects of the final FDA decision.

When to Require Postmarketing Surveillance

Although no general algorithm can dictate when the FDA should require a postmarketing study or which type of study to require, the committee offers specific guidance on how to identify potential red flags, such as when safety concerns arise prior to FDA approval, as well as the scientific and ethical advantages of different study designs to help resolve health questions as they emerge.

Among suggested actions, the FDA should prospectively determine and publicly identify the risk factors associated with greater uncertainty about a drug's benefit-risk profile in the postmarketing setting. Where the FDA finds higher risk, the agency should seriously consider requiring timely postmarketing research and should make public the rationale either for requiring research or for not requiring research, if there is a compelling argument against it.

Such risk factors may include

- drugs approved through the use of several surrogate endpoints that provide conflicting evidence about likely health outcomes associated with the drug;
- a first-in-class approval that used surrogate endpoints employed for medicines from a different drug class; and
- a medicine associated with a worrisome safety profile that could affect a large number of people, that could trigger severe side effects, or that carries a strong biological rationale for a particular side effect.

Surrogate endpoints are biological measurements, such as lowered blood pressure, that predict a clinical condition or outcome. By contrast, clinical endpoints are actual health outcomes, such as heart attacks or stroke, that directly measure how a patient feels, functions, or survives.

To aid in this effort, the FDA should maintain and update annually a list of surrogate endpoints allowed for use in drug approval, as well as maintain information on their correlation with actual

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health outcomes. Postmarketing research also may be required when a drug is anticipated to have a different benefit-risk profile in a subgroup of the population or in the general public, outside of clinical trials.

Choosing Appropriate Study Designs

While randomized clinical trials may be the gold standard for studying drug efficacy prior to FDA approval, the committee finds that in practice a number of constraints that arise after approval—such as patients' refusal to participate once the medicine is readily available—can make the kinds of trials needed for certain safety evaluations impractical. Depending on the frequency, magnitude, seriousness, and timing of a suspected adverse event, in many situations observational studies may be preferred for postmarketing research to assess a drug's risks. Observational studies provide evidence about the possible effect of a treatment for patients who choose to take or not to take a drug—and are not randomly divided into treated groups and control groups, as is done in randomized clinical trials.

By law, the FDA may require a postmarketing clinical trial only under certain conditions, such as when observational studies cannot provide sufficient information to guide agency actions. As a public health agency, the FDA has an ethical obligation to protect people from unsafe medicines and to safeguard the rights and interests of research participants. The FDA must balance these two obligations in deciding which type of postmarketing study to require, and it will need to work with external boards to strengthen ethics oversight over the course of the research.

The committee concludes that the FDA may be justified in requiring studies that could expose patients to heightened risk—but only if a public health question of pressing importance is at stake, if no other study design could supply the needed evidence, and if the FDA relies on the research findings in a timely fashion in formulating its regulatory response. In addition, appropriate safeguards to protect patients' rights and interests must be in place to ensure that the additional risk is acceptable, and the study should employ a well-designed informed consent process tailored for the unique aspects of the postmarketing setting.

Conclusion

An estimated 48 percent of all Americans take at least one prescription drug during any given month, according to a 2010 study by the Centers for Disease Control and Prevention. With such widespread use, improving the FDA's system for assessing the safety of approved drugs could have a major impact on health nationwide.

The FDA's current approach to drug oversight in the postmarketing setting is not sufficiently systematic and does not ensure that it assesses the benefits and risks of drugs consistently over a drug's life cycle. Adopting a regulatory framework that is standardized across all drugs, yet flexible

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enough to adapt to regulatory decisions of differing complexity, could help make the agency's decision-making process more predictable, transparent, and proactive, allowing the FDA to better anticipate post-approval research needs and improving drug safety for all Americans.

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