ADAPTIVE PARTIAL DRUG APPROVAL

Charles F. Manski

Department of Economics and Institute for Policy Research
Northwestern University

Public discourse on drug approval has seen considerable debate over the length of the approval process.

Pharmaceutical firms are eager for returns on investments and some patient advocates want fast access.

Health researchers and some patient advocates are concerned that approval decisions are rushed and made with inadequate knowledge of treatment response.

Attention has focused on the length of the process because the permitted use of a new drug has a sharp discontinuity at the date of the FDA approval decision.

Before approval, a small fraction of the patient population receives the new drug in trials.

Afterwards, use of the drug is essentially unconstrained if approval is granted and zero if approval is not granted.

Requiring a yes/no approval decision constrains the set of policy options that warrant consideration.

I suggest broadening the set of options by empowering the FDA to institute an *adaptive partial approval* process.

The extent of the permitted use of a new drug would vary smoothly as evidence accumulates.

The FDA would permit more use of a new drug as the evidence on health outcomes of interest becomes stronger.

Type I and II Errors in FDA Drug Approval

Evaluation of new drugs occurs with partial knowledge of treatment response. Approval decisions are susceptible to two types of errors.

Type I errors occur when ineffective or unsafe drugs are approved because they appear worthy when evaluated using the limited available information.

Type II errors occur when worthy drugs are disapproved because they appear deficient when evaluated using available information.

Type I errors eventually may be corrected through post-market surveillance.

Type II errors may be permanent because, when a drug is not approved, use ceases and no further data are produced.

Sources of Error

One source of error is the statistical imprecision of findings from RCTs.

The dominant sources of errors are *identification problems*.

These are difficulties in learning about treatment response that would persist even if statistical imprecision were eliminated by doing huge trials.

External validity is an identification problem.

Extrapolation from Surrogate Outcomes

An identification problem that particularly motivates the idea of adaptive partial drug approval stems from the fact that trials currently have short durations.

When trials are not long enough to observe health outcomes of real interest, approval is based on surrogate outcomes.

For example, treatments for heart disease may be evaluated using data on patient cholesterol levels and blood pressure rather than data on heart attacks and life span.

Researchers have noted the difficulty of extrapolating from surrogate outcomes to health outcomes of interest.

Fleming and Demets (*AIM*, 1996) declared

> "Surrogate end points are rarely, if ever, adequate substitutes for the definitive clinical outcome in phase 3 trials."

The obvious solution is to perform trials of sufficient length to measure the health outcomes of interest.

However, this has been thought politically infeasible.

Psaty et al. (*JAMA*, 1999) wrote

> "One systematic approach is a requirement that, prior to their approval, new drug therapies for cardiovascular risk factors should be evaluated in large, long-term clinical trials to assess their effects on major disease end points. The use of surrogate outcomes is avoided, and the major health outcomes are known prior to marketing."

However, they went on to write

> "Such an approach would slow the time to drug approval and may meet with resistance from pharmaceutical manufacturers."

Adaptive Diversification

To see why adaptive partial drug approval can improve on the present process, suppose there is a status quo treatment whose properties are known from experience.

Suppose a new drug shows promise in Phase 1 and 2 trials.

Phase 3 trials usually enroll at most a few thousand subjects, whereas the relevant patient population may contain hundreds of thousands or millions of persons.

Thus, society currently makes the new drug available to only a small fraction of the patient population while Phase 3 trials are underway.

A society concerned with both Type I and Type II errors should seek to balance their potential welfare effects.

This can be achieved by *treatment diversification*. The fraction of patients receiving the new drug should be chosen to balance its upside potential against its downside risk.

Over time, society can learn by observing the outcomes experienced by patients who receive the new drug.

As information accumulates, society can modify accordingly the fraction of patients receiving the new drug. This is *adaptive diversification*.

Manski, C. (2009), "Diversified Treatment under Ambiguity," *International Economic Review*, 50, 1013-1041.

Manski, C. (2013), *Public Policy in an Uncertain World*, Harvard University Press.

Implementation

To optimally diversify and learn, society should randomly allocate the entire patient population between the status quo treatment and the new drug.

Adaptive partial approval is a second-best approach.

The FDA would be empowered to grant limited-term sales licenses while Phase 3 trials are underway.

A license would permit a firm seeking approval of a new drug to sell no more than a specified quantity over a specified time period.

The firm would report updated outcome data to the FDA periodically, and the licensing decision updated accordingly.

The maximum quantity of drug that a firm is permitted to sell would be set with the assistance of an FDA expert advisory board, similar to those now used in drug approval.

The task of the advisory board would be to assess the upside potential and downside risk of the new drug, given the information available at the time.

Phase 3 trials would be longer than at present.

This would enable measurement of health outcomes of interest, reducing the role of surrogate outcomes.

When the outcomes of health interest have been observed, the FDA would make a yes/no approval decision.

As at present, the FDA would retain the right to rescind approval should new evidence warrant.

Related Ideas

Adaptive trials sequentially draw subjects into traditional RCTs and use a statistical criterion to make the allocation of new subjects across treatments a function of the outcomes observed to date for subjects drawn earlier. The objective (Tamura *et al., JASA*, 1994), is to

> "use the observed response data to adapt the allocation probabilities, so that more patients will hopefully receive the better treatment."

A proposals broadly similar to adaptive partial approval has been made in

Eichler, H. et al. (2012), "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval," *Clinical Pharmacology & Therapeutics*, 91, 426-437.

Open Questions

How would limited-term sales licenses be implemented?

How would adaptive partial drug approval affect the innovation process that generates new drugs?