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5 Questions: Goodman on recommendations to help FDA detect drug risks earlier

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Steven Goodman

There's growing concern about how the U.S. Food and Drug Administration evaluates the effects of drugs after it has approved them. The unexpected harms that people have suffered in recent years from taking the antidiabetes drug Avandia, the pain-reliever Vioxx and the cholesterol-reducing drug Crestor have underscored the need for improvements. A report released today by a committee from the Institute of Medicine recommends steps that the agency can take to better identify risks of drugs after FDA approval. Committee co-chair Steven Goodman, MD, PhD, professor of medicine and of health research and policy at the Stanford University School of Medicine, explains the proposed measures and why they are needed. Goodman is also the medical school's associate dean for clinical and translational research.

Q. The FDA sometimes approves a drug and then later, with new evidence, changes its position. Why is it difficult for the agency to get it right the first time?

Goodman: These sorts of changes are inevitable. The evidence that the FDA has at the time of approval is based on a small number of patients who can be followed for a relatively short time. The evidence that the FDA receives after the drug is approved can involve millions of patients, with all their diversity, who are taking a drug in natural living conditions. The follow-up can be for as long as the drug is on the market. So the evidence that the FDA has for this second decision is far greater than what it has when deciding on the initial approval. Our recommendation is that we view the initial approval as just one early step in a process that requires continuous, long-term monitoring, which we call the "life-cycle approach."

Q. What's wrong with the FDA's current ways of tracking drug safety post-approval?

Goodman: The FDA has many approaches to monitoring the effects of drugs once they are approved, but none are as comprehensive or as systematic as the attention the drug gets before it is approved. One is based on voluntary reports from doctors about drug adverse events seen in their patients. The FDA also does drug surveillance using specialized databases. But these two methods lack critical information about each patient that would enable the FDA to determine whether a particular symptom should be associated with a particular drug.

This is an imperfect system, and it's changing. A law passed in 2007 gave the FDA the power to require a manufacturer — after a drug's initial approval — to conduct new studies that would be designed to assess drug safety. These post-approval studies focus on a specific drug

and a well-defined patient population, rather than casting a wide net. But the FDA needed guidance on how best to use this new power. That's what our report seeks to provide.

Q. The report calls for the FDA to create a new type of plan for monitoring each drug after it's been introduced to the market. How would such an administrative change lead to greater safety?

Goodman: The report recommends that the FDA adopt a systematic way to anticipate what type of investigation each drug will need post-approval and then closely follow up on the results of that investigation. We hope that in being as systematic in requiring such studies after the drug is approved as it is before approval, the FDA will be better able to prevent the kind of crises that have occurred over the last decade. With the proper studies started early in the drug's life cycle, the necessary safety evidence can be obtained much earlier. To use a common metaphor, right now many studies are commissioned mainly when there's a fire; we think it's better to initiate them when there's just smoke.

We highlighted a variety of warning signs that are present at the time of a drug's approval. A trigger, for instance, could be if a drug's approval was based on clinical trials that provide conflicting evidence regarding risks, such as an anti-hypertensive drug that lowers blood pressure, but increases weight. Another flag could be for drugs that are "first in class" and that were approved based on predictors of health outcomes (called surrogate endpoints) rather than the outcomes themselves.

Various technological and methodological advances could improve the FDA's drug surveillance that systems. There is exciting work being done on this at Stanford that we couldn't cover in the report, and is just

coming out. Nigam Shah, PhD, assistant professor of medicine has shown how to find signals of drug harm using natural language processing of electronic medical records, and graduate student Nicholas Tatonetti, with genetics and bioengineering professor Russ Altman, MD, PhD, has demonstrated how to use available data from adverse events reported to the FDA to find dangers of drug interactions. We need methods that are faster, better and cheaper, and their work appears to be all three.

Q. Congress is in the process of reauthorizing the user fees that help fund FDA. Does the proposed legislation revise how the agency should approach post-market surveillance of drugs?

Goodman: Not really, although it is changing as we speak. It focuses mainly on ways to expedite drug approval using new methods or surrogate endpoints. But our recommendations are highly relevant to this, because I think that the more robust the after-approval monitoring process, the more flexible one can be in the pre-approval stage.

Q. The report says that conducting a study of a drug after its approval can raise ethical concerns. Why is this the case?

Goodman: The ethics of post-approval safety research have lately emerged as an issue because of several high-profile cases in which the FDA had to decide how to respond to troubling evidence about widely used drugs. The agency faced a dilemma: Require further studies — though it suspected a serious risk — or pull the drugs from the market despite doubts about their harms.

Let's look at Avandia for an example. It is an anti-diabetic drug that was supposed to provide better treatment, and thus minimize complications such as cardiovascular disease. However, evidence started coming out that it actually had the opposite effect: it appears to have increased cardiovascular risk. Many people both inside and outside the FDA argued that the agency could not require a study in which patients were randomized to a drug that might raise the heart attack risk without established, offsetting benefit. Others felt that the evidence was too weak to make a decision to withdraw the drug from the market. The ethical complications should be obvious if you think about whether you would want a relative to enroll in such a trial.

One way to avoid this conundrum is to do what I already mentioned: Start the study earlier. There was a hint in the early data about Avandia that it adversely affected lipid profiles. If the FDA had required a clinical trial at the time Avandia was approved that focused on the safety question, the evidence about its harm would have been there before it became a major ethical- scientific problem. That's the first line of defense.

Still, there are always going to be cases that will require launching a clinical trial some time after approval to investigate signals related to drug safety, and that is ethically problematic. It's unusual to enroll people in a trial not because of a treatment's potential benefit, but to see what harm it does. This raises red flags, as it did in the Avandia case. The verdict of our committee was that such studies could be conducted if they met certain criteria: The evidence is fuzzy; there's a compelling public health issue; the risk to participants is modest; and there is clear, ongoing informed consent by those who enroll in the trial. It is up to the FDA and IRBs to apply those principles.

Another ethical issue arises in the context of surveillance activities for drug harms. Whether this constitutes "public health" monitoring that

doesn't require consent or "research" that does is a complicated problem, with problems of confidentiality arising as well. We recommended that the FDA form an independent body to advise them, as needed, on the ethics of post-approval research and surveillance activities that it conducts or requires.

Provided by Stanford University Medical Center

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