The Food and Drug Administration: Our Role in Clinical Research

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Key Words: clinical research, critical path

Thank you, Alan, and thank you to the organizers for inviting me to speak. This topic is near and dear to my heart. I talk about the Food and Drug Administration (FDA) and clinical research in any opportunity I am given. I want to start with 2 messages. First, the FDA is aware of the same issues that the American Federation for Medical Research sees. We see the same failings of the current paradigm to deliver medical products that we as Americans expect, that we demand, that we all believe, and, appropriately, that we should have. We know the FDA's role in changing and confronting these issues. We have some steps that we can take as regulators to help solve these issues. Second, the change that is required is not small. We are in a place where the current paradigm will not provide the medical therapies that we want and expect and demand and appropriately deserve unless we change fundamentally things. I am going to speak today about parts of the current situation: parts of the FDA response to make that fundamental change.

THE CHALLENGES THAT CLINICAL RESEARCHERS FACE

What are some of the challenges facing us? I am going to only highlight these challenges.

Consumers are demanding a lot. They want access to more information. They want that information sooner in the process than they ever have. They want drugs earlier than they ever have, and at the same time, they want those drugs to be safer. Earlier and safer are conflicting goals; they are difficult to align, as far as meeting those goals at the same time. Consumers also want an assurance that the benefits outweigh the risks. Obviously, we are all aiming toward that assurance. At the same time, medical product development has not kept pace with the scientific discoveries that the National Institutes of Health (NIH) and other groups have been delivering. Development is delaying access to innovations.

In addition, rising investments in biomedical research from the private and from the government side have promised a plethora of new medical products. Despite the promises, for the last several years, investments and developments have been relatively flat after 2005. We have not seen a rising tide of new approved drugs for new therapeutic areas. Why is that?

CURRENT OBJECTIVES OF THE FDA

The FDA believes that we need to rethink the way we are moving from the discovery phase to the marketing phase and to the approval phase: the so-called critical path. We also believe that targeted support of individual product development has a role within a narrower paradigm as far as what the FDA can accomplish. Hopefully, other organizations can do more.

With regard to targeted support for product development, the FDA does have a role. We support specific trials to try orphan drug products and critical trials to identify postmarketing challenges. We are supporting many clinical trials of orphan diseases, and we also have ongoing trials to determine how to treat specific diseases, such as Huntington disease, glioma, and familial Mediterranean fever. We provide many incentives for the development of novel products for orphan diseases, which are diseases that affect less than 100,000 patients. Together, these orphan diseases account for approximately 25 million patients in the United States and are not a trivial health burden.

With regard to the postmarketing challenges, the FDA is studying anesthetics to decide whether they are posing a long-term neurologic risk to children; this study involves a complicated controversy and a scientifically challenging area. We are also working on a 20-year, 30,000-patient trial in a drug eluting stent environment now; we are trying to answer a safety question that we need to address. We work on off-patent pediatric drug development, but we will not address that today.

The FDA is funding about 90 trials, currently around $14 million, and this year will be allocated a small fraction relative to some other budgets, but again, with focused effort and focused discussion with regulators, we believe we can help these trials be more successful because the investigators will know what they need to accomplish to get approval and ultimately marketing. We partner with many other groups to accomplish these studies.

THE CRITICAL PATH INITIATIVE

Since 2004, the FDA has been working to reinvigorate medical product under the so-called critical path initiative. We began with the premise that the old approaches were not working and that change would require not one of us but a collaborative sharing environment. No one institution can change the system alone. The Clinical and Translational Science Awards are a good example of the sharing environment.

The FDA has a clear role in this space to develop new products for approval. We have a regulatory role that is very clear: we are the gatekeepers, if you will, for that final approval. We see the failures, we see the successes, we see the efficiencies, and we see the inefficiencies. Consequently, we want to help, and we can help make this process more efficient.

Imagine that we have a bridge between the discovery of a molecule in an NIH laboratory or of a potential therapy in a physician's office and the marketing and approval of that product so everyone in the United States can access that product. The bridge represents a critical period: a period that has become inefficient: in a variety of places and clinical trials conduct.
We, as regulators, need to focus our attention on this period because we live and have influence in this place of the enterprise. We need to make sure this place in the process is as efficient as possible. The regulator’s role is not to be promotional or to choose winners and losers. The regulator’s role is to provide an even playing field, clarity about the rules, and direction on how to proceed through the development phase as quickly, efficiently, and thoughtfully as possible. Our role requires infrastructure and tools, guidance, and collaboration when possible to make sure the data groups share to establish new disease models. We also serve to develop data standards so researchers can share data and communicate. The FDA wants to build support for better science: to make more thoughtful decisions about safety and efficacy earlier in the development process and then to share the knowledge as soon as you can.

**PARTNERSHIPS WITH THE FDA**

 Consortia will help to solve scientific challenges, and the FDA is encouraging such collaboration. For example, the FDA formed a consortia with the National Cancer Institute to establish electronic storage—the Janus data warehouse. We have worked to create enabling standards, and we are working to improve scientific decision making by creating a central place where investigators can store their clinical-trials data. Our goal is to create a common electronic document and a common standard, so investigators can store their data, aggregate it, analyze it with improved tools, and thus make better decisions.

The FDA is also working with public partners. In one partnership, the FDA is working with the academic and industry organizations that together form the Coalition Against Major Diseases; the group recognizes that we were not doing what we should as far as developing therapeutics for chronic diseases. This particular group is currently focusing on disease models, trying to pull together all the data on diseases such as Parkinson and Alzheimer diseases. We are asking questions, such as “What really happens as a patient progresses through Alzheimer disease?” “How can you use that disease model to decide whether a drug works more efficiently, reducing the trials’ sizes and the time of the trials for chronic diseases?” As we consider these models, we are seeking to effectively use the time and the money that the drug companies need to invest so we can make better decisions faster, which equals more efficient drug development.

The FDA is collaborating with many groups, in particular around the Sentinel System, a system that Congress mandated for the FDA to accomplish in 2007 as a part of the FDA Amendments Act. The Act states that, by 2012, Congress expects 100 million individuals’ medical records to be stored in a national electronic database that the FDA can search. Because of the scale of the project, the database needs to be interoperable: that is, the data will not exist in FDA storage but will exist on servers in locations such as the Department of Defense, the Centers for Medicare and Medicaid Services, and private partners. The FDA can access various kinds of data, combine the data into one analysis, and therefore more efficiently and quickly search for signals of safety and efficacy.

Linked databases such as this one do not exist elsewhere in the United States. We are building the system as we proceed, meeting regularly to discuss the Sentinel System. We are facing many large challenges, but this database will take clinical research into the next millennia, if you will, of development and detection of adverse events. The database will allow data mining in ways that we could never accomplish with our spontaneous adverse events data.

The FDA is also aware that conducting clinical trials is not as efficient as the process needs to be. We see the results of the clinical data, for example, the case report forms, the reports of the inspections that are part of the trials. We see the efficiencies, or rather the inefficiencies, in all of those systems and the cost that those inefficiencies are having in medical product development. We are working with partners to eliminate inefficiencies and improve the process. For example, we are working on the Clinical Trials Transformation Initiative, which is not about small changes at the margins of how people conduct clinical trials. Ideally, the initiative will change researcher’s processes to obtain institutional review board oversight, to collect data in their case report forms, and to monitor processes in a clinical trial as part of a larger trial.

Typically, a company will sample 100% of the participating sites for a given clinical trial. Every 2 to 3 months during the trial, a company representative will visit the site and expect the nursing staff, the physicians, and the clinical investigators to open their records so the representative can see that they have been conducting the trial appropriately. This system is not efficient and not risk based. The representative is not asking which site needs more attention or adjustments, and the process is inefficient in cost, time, and resources. This initiative will change this process.

The FDA is also working to generate evidence about how to conduct clinical trials. We have been conducting controlled clinical trials since the early 1960s, and we have conducted trials in the same way without review or thought. We believe we can make the process more efficient. We will identify those processes and practices, and as regulators at the agency that will ultimately oversee the conduct of those trials, we will make changes to increase efficiency. For example, in serious adverse-event reporting, per regulation, sponsors must inform all investigators in a large trial, perhaps 4000 to 5000 investigators, of all potential serious adverse events associated with the drugs; in some trials, investigators may list tens of thousands of potential serious adverse events. The investigators are overwhelmed by the paperwork to be part of a trial, and as a result, they stop participating after that first trial, and we lose them to the clinical trial’s endeavor. The FDA recognizes that this is one small part of the problem, but we need to improve this: how investigators report serious adverse events.

**CONCLUSIONS**

The FDA sees and understands the challenges of clinical trials. We understand that the current paradigm will not suffice in producing the medicines that we all deserve and expect because of the incredible work that the NIH and other scientists must accomplish. To succeed, we must find a way to fundamentally reenergize, make the current processes more efficient, and ask hard questions. I described the critical path initiative as fundamentally reexamining your values, asking whether you can defend processes from the past. If you cannot defend a process, be prepared to change it.

My boss, Janet Woodcock, and the whole of the Center for Drug Evaluation and Research are committed to improving the drug development process, and we are working with a variety of outside partners. We look to collaborate. We do not have the resources and the time. We have the interest and the motivation, and together, we could make a difference in clinical research. This is a critical time in the development of medical products, and we need to do a more efficient job.