Talking pharmacogenomics

The FDA hopes to encourage the development of genomic-based clinical trials through open dialogue with industry.

BY DAVID FILMORE

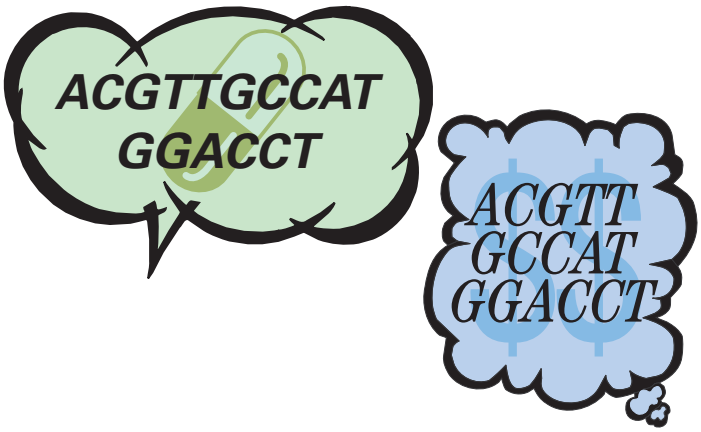
"Questions loom about the future of personalized medicine," reported Randall Willis and Mark Lesney in July (*1*). Many of these questions emanate from the regulatory arena. It seems that the conventional rules of drug review and approval do not provide a very clean fit for the novel information that genomic techniques would bring to the process. As a result, there has been much confusion and pause as companies move toward the clinical trial phases of drug projects that have a strong genomic basis. Fear of what the FDA might do with the volumes of genomic data, and worry that the FDA might not accept the data in the first place, have been common industry concerns.

The FDA hopes to quell these concerns through an open dialogue on the issue of incorporating pharmacogenomics into clinical trials, which it initiated about a year and a half ago. Although there are still more questions than answers, progress is evident.

Conversation starter

The ice was broken, so to speak, in early 2002 when the FDA published a paper entitled "Pharmacogenomic-guided drug development: Regulatory perspective" (*2*). "Up to the point we published the article, the FDA was relatively quiet in commenting on the science of pharmacogenomics," says Lawrence Lesko, director of the FDA's Office of Clinical Pharmacology and Biopharmaceutics and coauthor of the paper with Center for Drug Evaluation and Research (CDER) director Janet Woodcock. "We wrote the article to publicly say that the agency feels there is a huge potential for this science to impact therapeutics, and we want to express our enthusiasm for it and at the same time recognize the challenges and the difficulties that we face."

The response from industry to the paper, according to Lesko, was tremendous. And the "message received" signal was certainly evident in a talk given by Allen Roses, senior vice president of genetics research at GlaxoSmithKline (*www.gsk.com*), at the August 2002 Drug Discovery Technology conference in Boston. Roses discussed the resistance he experienced from his company to designing an obesity drug clinical trial that screened for participants based on specific SNPs. "The FDA will never allow it," he said, was a common response. "There were too many people who 'knew' what the FDA would never allow," Roses said, "until the FDA published differently."



Questions, questions

The paper was also successful in establishing a springboard for discussing very real concerns. For example, it enunciated the confusion that existed about how the FDA will deal with the approval of drug/diagnostic test combinations—an intrinsic aspect of pharmacogenomics medicine. This is complicated by the fact that these two product types are currently reviewed in two separate processes by two different divisions, CDER and the Center for Devices and Radiological Health (and some aspects of a pharmacogenomics approval process would also involve responsibilities of the Center for Biologics Evaluation and Research). In addition, the paper raised concerns that have been expressed by the pharmaceutical industry about the regulatory implications of genetic profile screening of patients, the FDA's acceptance of stratifying patients entering a trial a priori on the basis of pharmacogenomics, labeling requirements that would result from pharmacogenomics-"enriched" trials, several statistical and data analysis issues, and worries about a lack of FDA expertise on the subject, among many others.

"We weren't kidding ourselves," says Lesko. "We did not answer all the questions in the article." The purpose, he says, was simply to put the issues on the table and start a process. This process was continued at an FDA–industry workshop conducted in May 2002 (more are planned) and in courses on pharmacogenomics organized by CDER. In addition, a pharmacogenomics working group was formed (chaired by Lesko) that is currently developing a guidance document for industry that will hopefully remove some of the "cloak of uncertainty".

According to Lesko, clarification of many of the issues will come only with a full-fledged case study, that is, an NDA (New Drug Application) that explicitly uses genomics to predict safety or efficacy. But there are some aspects of the pharmacogenomics issue that are not new to the FDA. For example, Lesko says, "The agency is well experienced with enrichment trials. We have used them for trials in which people don't get entered unless they respond to a drug." This could provide a model for

the process of screening out patients on the basis of a genetic marker.

In addition, the case of Herceptin is mentioned as a partial precedent in the drug/diagnostic pairing issue—the drug was approved only for patients whose tumors overexpress the HER2 protein, and it would likely not have been approved without a diagnostic test that was also FDA-sanctioned (*2*). Even though the overexpression in this case is determined with a nongenetic test, Lesko thinks there are many similarities to a pharmacogenomics clinical trial on which to build. Reflecting on the future, however, he says, "I think we can do it much better."

Safe harbor

At this preliminary stage, perhaps the biggest apprehension of companies is whether submitting genomics data in an NDA will help or hinder the prospects of timely drug approval. "The early adopters perceive themselves as setting the standard, and they may be concerned that FDA recognizes that and may be more conservative than they need to be," says Lesko. A common question is, "Will the FDA look at this data and ask me to do additional clinical studies to document drug safety or do more proof-of-principle studies than I would normally do?" There is also a fear that the FDA could overinterpret genomics data, which "may lead to unfavorable regulatory impact and jeopardize a drug's development program," warned Brian Spear, director of pharmacogenomics at Abbott Laboratories (*http://abbott.com*), at an FDA Science Board Advisory Committee meeting in April.

These sentiments are the motivation behind the FDA proposal to develop a regulatory "safe harbor" for pharmacogenomics information. This would allow companies to submit exploratory genomic data to the FDA without it being a formal part of the application. "The reason we suggested this is that we felt it would open lines of communication with industry and remove the concern that the FDA would react prematurely to [pharmacogenomics data] if it was part of the NDA," says Lesko.

At the April meeting, CDER presented a draft proposal for incorporating this data into the regulatory process, which, according to a report by Jim Kling (*3*), suggested guidelines for separating submitted genomics data into two categories: data with a regulatory impact—generally, results intended to influence safety and efficacy decisions in the clinical development process—and data with no regulatory impact—purely research results that might be reviewed but would not be considered in the application. The proposal was well received. "I think most of us believe that if this is data that safety decisions are being made around, then you have to present the data. . . . I'm quite pleased with the proposal," says Harold David, Amgen (*www.amgen.com*) vice president of preclinical safety assessment (*3*).

The rapid evolution of pharmacogenomics applications in therapeutics is beginning.

Safety first

Although not the "barn-burner" examples that people are looking for, pharmacogenomics is claiming a growing presence in clinical trials. An informal survey of IND (Investigational New Drug) protocols and NDAs by Lesko and colleagues earlier this year counted more than 80 cases in which pharmacogenomics tests were contributing to clinical development (early in 2002, they counted about 15). These tests almost exclusively involved drug metabolism genotypes, predominantly of the cytochrome 2D6 enzyme—which is reported to have some effect on about 30% of drugs currently on the market. Determining polymorphisms of this enzyme can be directly applied to assessing the ideal drug doses for individuals, which is significant because incorrect drug dosing is widely believed to be a major source of adverse drug reactions.

"That is the sort of stuff we have known about for 20 years, but it is being used more in drug development now than ever," says Lesko. "One could imagine in the near future physicians will have access to not only good information in product labels of how genetics influences drug dosing, but also be aware of and can access the test that would allow them to individualize the dose to the patient's metabolism status." It seems that this application of pharmacogenomics will be the first out of the starting block, and it highlights what Lesko thinks will drive companies to apply genomics to drug development even amid regulatory uncertainty—the need to avoid serious adverse drug reactions, which, according to the FDA, is the fourth leading cause of death, ahead of AIDS and automobile accidents (*4*).

Not an obstacle

The vision of the future—the individualized prediction of who will respond to what drug and who will react adversely—is, of course, more grandiose, and according to Lesko, we haven't yet seen much evidence in the public domain that it is happening. (However, he thinks GlaxoSmithKline's recent single nucleotide polymorphism (SNP) mapping of HIV patients on the drug Abacavir to determine markers associated with a hypersensitivity reaction (*5*) is a good model.) But Lesko believes that "the rapid evolution of pharmacogenomics applications in therapeutics" is beginning this year and will continue. For now, from the FDA perspective, he says, it is imperative to maintain positive and informed communication. "We are recognizing that it is important for the agency to have people that have expertise in this area so that meetings with companies are beneficial, feedback is credible, and we can become a help, not an obstacle."

References

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