US FDA contemplates collection of pharmacogenomic data

On April 9, FDA's science advisory committee met to discuss a draft proposal for incorporating pharmacogenomic data into the regulatory process. At the meeting, Janet Woodcock, director of FDA's Center for Drug Evaluation & Research (CDER; Rockville, MD), presented a draft proposal that met with general approval from industry representatives.

Pharmacogenomic data attempts to define relationships between a patient's genomic profile and a response to a given drug. Some firms hope to use such information to develop drugs that are tailored to a patient's genetic profile, but most companies currently focus on toxicology studies that examine a patient's ability to metabolize the drug being tested. For example, of the top 27 drugs cited in reports of adverse reactions, at least 59% are metabolized by an enzyme that has a poor-metabolizing variant. While it is not conclusive that these protein variants are responsible for the adverse reactions, "[these data suggest that] polymorphism matters when it comes to drug safety," says Lawrence Lesko, a reviewer with CDER.

But the FDA recognizes that pharmacogenomics is still in its infancy, and very little clinical significance can be read into most studies. "It's unclear how this information fits into the regulatory process other than to raise a potential red flag," admits FDA commissioner Mark McClellan, and that is what worries industry. "The amount of data that would be submitted [for pharmacogenomic studies] is in the tens of thousands of data points, which is the potential subject for a great deal of *post hoc* analysis and data mining," says Brian Spear, director of pharmacogenomics at Abbott Laboratories (Abbott Park, IL, USA). "If you look hard enough, you can probably find some association with something that would give you pause."

At the April 9 meeting, Woodcock made clear that there are no plans to require pharmacogenomics testing, but when it is done, the agency intends to require submission of some data but not others. The proposal suggests that submitted data be separated into two categories: data with a regulatory impact, and data with no regulatory impact. Specifically, the agency would require access to data used in safety/efficacy evaluation, such as prescreening patients for a phase I clinical trial, or data that goes into dosing calculations. Even animal model pharmacogenomics might be included if, for example, it explains why a toxic response might be species-dependent. "In general, results intended to influence the course of the clinical development process will be considered part of the safety and efficacy evaluation," says Woodcock. The agency does not plan to consider data used solely for research purposes. The FDA hopes to have new guidelines in place in the next 16 months and is currently planning a workshop for the fall.

Industry representatives were happy with what they heard. "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," said Harold Davis, vice president of preclinical safety assessment at Amgen (Thousand Oaks, CA, USA).

While big pharma sees pharmacogenomics as a toxicology exercise, other, smaller biotechs like Millennium Pharmaceuticals (Cambridge, MA, USA) and Genaissance Pharmaceuticals (New Haven, CT, USA) list treatments for genetically defined populations as a drug discovery priority. Still, few (if any) representatives from small biotechs showed up at the meeting, and none returned calls asking for comment.

Such disinterest could be because the discussion is still in the early stages, says Gillian Woollett, vice president for science and regulatory affairs at the Biotechnology Industry Organization (Washington, DC). "The little guys are going to have to judge where their equities are best spent. There's no question in my mind that it's incredibly important that the industry as a whole work with the FDA. If the outcome is good for bigger companies, it will be good for little companies."

One development that may help smaller biotech firms hoping to develop medicines and diagnostics based on pharmacogenomic data is the potential creation of an Interdisciplinary Pharmacogenomic Review Group that would evaluate data that does not have a regulatory effect. The FDA wants access to research information so that its reviewers can bring themselves up to speed on the new technologies and their implications. "We need product developers and researchers to share their results with us so we can incorporate it into what we're doing," says McClellan. By familiarizing themselves with such data as soon as possible, FDA reviewers should be prepared to properly evaluate similar information when products based on pharmacogenomic data start making their way through the clinic.

Woodcock says FDA considers the proposal a blueprint for other emerging technologies. "It could also be applied to proteomics by extrapolation. Really, these issues (of what do with data from emerging fields of research) apply to all of the techniques in the development and regulation of drugs."

Jim Kling, Washington, DC, USA

India dawdles over *Bt*-cotton

The Indian agbiotech industry suffered multiple blows at the hands of the government in late April, calling into question whether genetically modified (GM) crops have a future in the country. Not only has the entry of additional GM crops into the Indian marketplace been delayed, but the marketing of Mahyco Monsanto Biotech's (MMB; Mumbai) approved GM cotton beyond 2004 is also up in the air.

On April 26, a parliamentary committee called for an independent review, the results of which are expected by the end of August, of last year's decision by the Genetic Engineering Approval Committee (GEAC; New Dehli) to give MMB a three-year license to market three insect-resistant GM cotton hybrids (containing the gene for *Bacillus thuringiensis* toxin; *Bt*) in six central and southern states of India (*Nat. Biotechnol.* **20**, 415, 2002). A day earlier, GEAC refused to grant permission to MMB to sell its *Bt* cotton to farmers in northern India, citing sensitivity to curl leaf virus spread by white flies that are rampant in that region. Also on April 25, GEAC called for more field trials and biosafety tests from ProAgro (Gurgaon) for its GM mustard, rejecting the firm's commercial application for a second time since 2001.

All of these setbacks have been influenced by conflicting reports over the performance of *Bt* cotton in the country in 2002, the first year of sowing. MMB claims that *Bt* cotton

farmers obtained 30% higher yield using 65–70% less pesticide. These claims have been called into question not only by Greenpeace (Bangalore) and Gene Campaign (Delhi), a nongovernmental organization headed by a geneticist, but also by the parliamentary committee's report saying that "farmers who have grown *Bt*-cotton have been put to loss in most of the places." MMB spokesperson Ranjana Smetacek disputes the disparity. Out of the 50,000 farmers that sowed *Bt* cotton hybrids in 2002, Smetacek says, "We collected data from 1,090 sites whereas Suman Sahai (of Gene Campaign) talked to just 100 farmers."

E.A. Siddiq, a board member of the International Rice Research Institute (Manila, Philippines) argues that like any new technology, *Bt* cotton will have hiccups at the start. He says there are plenty of Indian farmers who have had great success with *Bt* cotton and will continue to purchase and plant it on their farms as long as the government does not take that choice away from them.

But many feel that the major roadblock to wide commercialization of GM crops in India is inter-ministerial rivalry, specifically between GEAC and the Department of Biotechnology (DBT; New Dehli), which funds agbiotech research in the country. According to a DBT report published in April 2003—Agricultural biotechnology research in India: status and policies—48 transgenic projects involving 15 crops in the public sector and 20 projects involving nine crops in the private sector are currently in various stages of development in India. DBT has earmarked Rs.750 ($15.9) million for crop biotechnology for the period 2002–2007. According to DBT secretary Manju Sharma, "prospects of even higher financial outlays are bright if tangible products come through" from ongoing transgenic research.

Many researchers working on transgenic crops are predictably upset at the appearance of GEAC stifling the prospects that are both envisioned and funded by the DBT. Ironically, the new controversy has come at a time when the country's top agricultural scientists have overwhelmingly endorsed genetic modification as a means to enhance the productivity of 10 out of 12 crops grown extensively in India (*Current Science* **84**, 310–320, 2003). Prasantha Kumar Ghosh, former advisor to the DBT and ex-member of GEAC, told *Nature Biotechnology* the "stupid" decision only demonstrates the power of bureaucrats who outnumber scientists in the committee. "GEAC has no scientific logic for their decision making," says Shantu Shantaram, a scientist with Syngenta that is engaged in promoting transgenic rice in India.

A farmer inspects GM cotton in a field in India. Disconnects between different governmental agencies have put in jeopardy the future of all agbiotech products in the country.

Asis Datta, director of the National Center for Plant Genetic Research (New Delhi), says that other than causing confusion, the GEAC's actions will not affect DBT-funded projects. But that is not necessarily the case for industry. "After having once embraced GM technology, it seems India is putting transgenic research in the reverse gear," says Arvind Kapur, managing director of Nunhems Seeds (Gurgaon), a sister company of ProAgro. "Whenever we want to release a variety, GEAC says data is not sufficient. My company has already aborted our work on GM vegetable crops and now ProAgro is thinking of going slow on mustard. I wonder why the government is spending money researching transgenic crops if GEAC is going to stop their cultivation?" says Kapur.

Industry leaders say that a national biotechnology policy and an autonomous single window regulatory commission with complete transparency and a scheme that allows the industry to use the facilities, infrastructure and human resources of publicly funded institutions on attractive terms are crucial. A new forum called the Association of Biotechnology Led Enterprises (ABLE; Bangalore) launched in April 2003 expects "to build close links between academia, industry and government." ABLE has appealed to the government to establish a $1 billion venture fund for all fields of biotechnology and also create new national institutions of biotechnology where industrial research and academic work can go hand in hand.

K.S. Jayaraman, New Delhi, India