



From Genome Exploration to Drug Development

Jill Wechsler

Without discouraging research, FDA wants to establish new policies for incorporating genomics information into the regulatory process.

In April 2003, scientists around the world celebrated the 50th anniversary of the discovery of the double helix by announcing the successful completion of the Human Genome Project (HGP). As the nearly finished version of the human genome sequence was unveiled, leaders of the landmark project outlined plans for tackling the next stage: translating genomic research into

medical treatments to improve public health. This task involves identifying variations in DNA sequences that contribute to disease and defining how the proteins are produced by each gene control cellular operation.

HGP accomplished a great deal beyond producing a 99.9% accurate sequence. HGP mapped the genome of comparative organisms (rat, mouse) and developed new technologies that facilitate further exploration and development. The project also identified more than 1400 disease genes and studied the ethi-

cal, legal, and social issues raised by expanded knowledge of the human genetic makeup. The next stage of using genome-based discoveries in product development will involve pharmaceutical manufacturers more directly and will require FDA and other government agencies to address pertinent regulatory and legal issues.

New vision

In marking the completion of HGP's stated task, Francis Collins, director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH), declared it was time to move from large-scale DNA sequencing to more specific research projects. Collins and other HGP leaders outlined new research and development opportunities in "A Vision for the Future of Genomics Research" (1). This blueprint for future genomics research describes the resources and technological developments that are

critical to developing "powerful new therapeutic approaches to disease" (see sidebar, "Turning the genomics vision into reality").

An ongoing issue is the need to balance timely access to new discoveries with the protection of intellectual property. Without an understanding of how complex patent and licensing policies influence private sector investment in new technologies, many diagnostic and therapeutic advances based on genomics may never reach the clinical setting where they can benefit patients (see sidebar, "Patent protection versus public access").

Pharmacogenomics (PG) policies

Manufacturers are mainly concerned that gathering more genomic data will affect policies governing the testing and approval of new drugs and medical products. The industry already is investing more resources in PG to better understand how and why individuals respond differently to pharmaceuticals, which is a key issue in identifying candidate compounds and testing them for safety and efficacy. This information promises to streamline animal and human studies by

- developing new sets of biomarkers for toxic responses in animals and humans
- predicting who will respond to a drug on the basis of genetic differences in pathogenesis
- predicting who will have serious side effects on the basis of toxicogenomic analysis
- rationalizing drug doses through the use of genetic-phenotypic tests for metabolizer status.

Such analyses have the potential to revolutionize drug development processes and can lead to faster and more efficient production of more-effective, less-toxic drugs, commented Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER), at the April 2003 meeting of FDA's Science Board. However, agency officials are concerned that companies are not presenting PG analysis to the agency for fear that it may lead to requests for even more data and tests, which would further delay new product approval. Woodcock wants to clarify FDA regulatory policies to encourage PG analysis and to gain access

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FDA guidances aim to overcome the industry's reluctance to disclose data from pharmacogenomics studies.

to information that could advance scientific discovery.

Manufacturers' concern that innovative research will complicate product regulation is similar to the don't-use-and-don't-tell attitude hindering industry adoption of new manufacturing technologies. Manufacturers worry that installing on-line methods to control pharmaceutical production and drug quality will raise new questions from plant inspectors and FDA

staffers who review chemistry, manufacturing, and controls data. To overcome these obstacles, FDA has launched the process analytical technology (PAT) initiative. PAT aims to encourage manufacturers to install more-efficient production systems to reduce costs and better ensure product quality.

Similarly, Woodcock seeks to develop several PG guidances to clarify agency approaches for using PG information. The objective is to overcome industry reluctance to disclose data from exploratory PG studies used by researchers to identify target compounds and to evaluate cellular and animal responses to drug candidates. The guidances will address

- when PG data will have a regulatory effect
- codevelopment of drugs and diagnostic tests
- general PG standards and techniques.

FDA's first step will be to develop concept papers on these topics, followed by draft and final guidances, which FDA hopes to issue by the end of 2004. A main

goal of the envisioned guidances will be to distinguish between PG data that may affect product regulation and should be submitted to FDA and data that will not be required in filings for investigational drugs (INDs) and new drugs (NDAs). One threshold for submission might be genomic information that represents a valid biomarker with known predictive characteristics. FDA is likely to request that certain PG information is filed in applications such as

- studies supporting enrollment in clinical trials by genotype used to enrich responders or avoid bad outcomes
- dose selection data that are based on metabolizer genotype
- animal genomic data that indicate why a toxic finding is unique to that species
- data that may influence the course of the clinical development process.

Alternatively, FDA wants to define a research information package that manufacturers would share with FDA but would not affect application review. Such data would be discussed separately by a new

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Interdisciplinary Pharmacogenomic Review Group (IPGRG) composed of representatives from all FDA centers. Data collected for research use that would not affect regulatory and approval decisions might include

- evaluation of new transporter gene diversity versus the response in clinical subjects
- genomic single nucleotide polymorphisms data collected in clinical trial subjects
- gene expression microarray screen in trial subjects or in animal toxicology studies.

Industry wary

Woodcock anticipates plenty of public discussion of PG issues through the guidance development process, beginning with a public workshop this fall. Manufacturers already are expressing concerns about new FDA rules in this area. Brian Spear, director of pharmacogenomics at Abbott Laboratories (Abbott Park, IL), told the Science Board that most pharma companies are exploring how PG analysis may help design clinical trials and interpret study data. Gene expression studies can help scientists predict the toxicity of candidate compounds and identify biomarkers for toxicity and drug response. Analyzing patient genotypes may help define study populations and avoid overloading trials with inappropriate patients. Although such approaches may reduce potential patient injury and make studies safer, they also may be challenged as attempts to merely improve study results. A prime challenge is to establish sound methods for validating conclusions derived from modern microarray and genomic analysis, which the industry fears could be misinterpreted by regulatory officials.

Spear supported FDA's idea of establishing a central group of experts to review PG studies outside of the usual review process but emphasized the need for clearer definitions of pharmacogenomic data and research exemption. Without a more explicit policy, manufacturers worry that FDA and other regulatory authorities could later expand requirements for product registration studies and data analysis. Although clarification of research approaches may appear useful, increased

Turning the genomics vision into reality

Pharmaceuticals on the market target less than 500 of the 30,000 or so human genes, leaving an enormous untapped pool of human gene-based targets for therapeutic intervention, according to "Vision for the Future of Genomics Research" (1). Further success in defining genetic networks and protein pathways and how they contribute to cellular and organismal phenotypes will contribute fundamentally to the design of new therapies. For example, the publication notes that the success of Novartis's Gleevec (imatinib mesylate) to treat leukemia relies on a "detailed understanding of the disease's genetic cause."

One approach to further incorporate genetic factors in disease and in drug response may be to explore gene variants that promote good health and disease resistance. This approach could involve identifying individuals with unusually good health for comparison with cohorts of individuals with disease to determine genetic variants linked to disease. Scientists also are exploring ways to develop genome-based techniques to predict disease susceptibility and drug response, which eventually may lead to development of individualized preventive medicines. New molecular taxonomy promises to improve early detection of disease, allowing for more-effective and less-costly treatment. Such sentinel methods might involve further analysis of gene expression in circulating leukocytes, proteomic analysis of body fluids, and advanced molecular analysis of tissue biopsies.

Public and private organizations are launching a number of initiatives to use genomic research to

combat disease and improve human health. These initiatives include the

- development of chemical genomics, which involves using high-throughput screening to identify small molecules that can act as positive or negative regulators of gene products, pathways, or cellular phenotypes. NHGRI is exploring the acquisition and/or creation of a public library of organic chemical compounds for scientists to use in charting biological pathways. The ability of such molecules to enter cells enables them to probe gene function, making them useful biological tools for drug development.
- establishment of a reference work for all genes and functional elements of human DNA sequence. A pilot project aims to develop an encyclopedia of DNA Elements (ENCODE) that will help scientists fully use the human genome sequence to predict potential disease risk and develop new strategies for disease prevention and treatment.
- development of a more precise chart of genetic variation within the human genome. The International HapMap Project is in the middle of a three-year effort to make the results of the human genome project more applicable to individuals.
- expanded study of structural genomics to gain a more complete description of all proteins encoded by an organism's genome. The Wellcome Trust may create a nonprofit Structural Genomics Consortium, similar to the SNP Consortium, to generate public databases about genomic structures that are crucial for rational drug design.

standardization also carries the risk of encouraging both regulators and manufacturers to favor certain procedures, which may inhibit innovation in the long run.

Another concern of manufacturers is that PG data could be used to narrow product marketing opportunities. For example, a genetic study showing that 30% of patients could fail to respond to a certain treatment may lead to restrictive product labeling even if the drug appears safe and effective for a general population. Or data indicating that certain patients respond better to a specific treatment might lead to the required diagnostic testing of participants in clinical trials and potential patients. In the end, the industry's willingness to underwrite more PG studies may prompt FDA to require genetic analysis as a regular component of drug development programs.

These are difficult issues, and FDA is building its internal capacity and expertise for analyzing and understanding genomic data, explained Frank Sistare, acting director of CDER's Office of Testing and Research. CDER has established an internal nonclinical pharmacogenomics subcommittee and is expanding reviewer training in this area. The panel will help develop standards for submission, review, and integration of PG data and will work with other government agencies and outside scientists to further develop these initiatives. FDA is seeking input from advisory committees and experts about ways to better understand and assess relevant information as genomics discoveries evolve.

The task of clarifying FDA regulatory policies related to pharmacogenomics is an important challenge for FDA Commissioner Mark McClellan. A key strategy

Patent protection versus public access

Increased industry involvement in genomics research and the development of gene-based therapies raise challenges for protecting intellectual property and proprietary data. A key principle of HGP is to deposit sequence data into public databases that are available to scientists all around the world. This policy contrasts with commercial rival Celera Corporation's (Rockville, MD) more restrictive approach to publishing data. Tensions remain between permitting maximum and early access to data and providing protections to encourage commercialization of new diagnostic and therapeutic advances.

In the article "Lessons from Large-Scale Biology," Collins et al. emphasize the importance of HGP's early data release policy (2). The policy was defined in 1996 as the Bermuda Principles, which call for

rapid release of sequence assemblies to the public domain. The authors note that the difference between the public sequences and the Celera model, which is based on private control of data release, continues to threaten public access to health benefits. In the article, "A Vision for the Future of Genomics Research," Collins et al. emphasize the importance of early and open access to large data sets, as well as the need for policies to protect and reward scientists who share their data (1). The article acknowledges that laws and regulations governing genomics must be consistent with long-established intellectual property principles. In addition, the authors call for new policy options for data access and for patenting, licensing, and other intellectual property issues to facilitate the dissemination of genomics data.

for improving public health is to make new cost-effective therapies available to those patients who can benefit the most from them, McClellan told industry leaders at the recent annual meeting of Pharmaceutical Research and Manufacturers

of America. To this end, FDA is undertaking a concerted effort to use PG information effectively, he said, but needs more help from the industry to better understand the issues and make FDA's regulatory process more efficient.

McClellan made similar remarks at the Science Board meeting in April 2003, calling for action to integrate genomics information into product development and medical practice. He acknowledged that drug developers fear that data from molecular genomics don't fit the regulatory process and may raise red flags with reviewers. McClellan urged the industry to share results with FDA so that these issues can be discussed openly and collaboratively.

References

1. F. Collins et al., "A Vision for the Future of Genomics Research," *Nature* **422**, 835-847 (24 April 2003).
2. F. Collins et al., "Lessons from Large-Scale Biology," *Science* **300**, 286 (11 April 2003).

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On-line discussion forum

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