Arrays and the FDA

A new product from Roche Diagnostics is testing the regulatory waters for diagnostic microarrays.

BY DAVID FILMORE

When Roche Molecular Diagnostics introduced the AmpliChip CYP450 in June 2003, Stephen Fodor, CEO of Affymetrix—the company that designed the product's platform technology— said, "The launch of this product heralds the emergence of pharmacogenetics as a medical and commercial reality." The AmpliChip was billed as "the world's first pharmacogenomics microarray for clinical applications." Its availability prominently highlighted that genomics is moving from the research lab to the clinic.

However, the product's launch also highlighted uncertainties over the FDA's role in regulating products such as microarrays.

"We are breaking new ground," says Melinda Baker, a spokesperson for Roche Molecular Diagnostics. "And we are not aware of any other companies that are putting high-density microarrays in front of the agency right now."

As it currently stands, the AmpliChip CYP450—which measures polymorphisms of two genes that play a major role in drug metabolism, *CYP2D6* and *CYP2C19,* to determine the best drug dosage for a patient—is marketed for research use only, not as a diagnostic device approved for clinical decision-making. In fact, the FDA has not yet cleared any microarray as an "in vitro diagnostic device" (IVD), the status Roche is now pursuing for the AmpliChip.

Par for ASR?

At the time of its launch, Roche said it would initially sell the AmpliChip to clinical laboratories as a so-called analyte-specific reagent (ASR), exempt from premarket FDA review.

"Basically, the intention [of an ASR] is that it is used as a component in a home-brew diagnostic test," Baker says. A "home brew" is an assay designed in-house by a clinical laboratory. The ASR typically has been an antibody, nucleic acid, or some other reagent purchased by the lab as an assay building block.

ASRs must fulfill certain FDA requirements to make their way into home-brew tests. For instance, they must be produced using standardized "quality system" practices; also, they can be sold only to "high-complexity" labs as designated by the Centers for Medicare & Medicaid Services (CMS). By and large, unless the reagent is involved in either blood screening or diagnostics for a life-threatening contagious disease, companies need not notify the FDA before bringing ASRs to the market.

Once a lab purchases an ASR, it takes complete responsibility for the assay incorporating the reagent. The ASR manufacturer isn't even allowed to provide instructions or performance claims with the product, because that might be viewed as evidence it is being marketed as a kit—which would require FDA notification.

Home-brew assays for patient diagnostics are regulated not by the FDA but by the CMS under the Clinical Laboratory Improvement Act of 1988 (CLIA). CLIA essentially defines analytical standards that clinical labs must meet to receive Medicare and Medicaid reimbursements for the tests they perform; it doesn't, however, provide a process for outside review of the performance and clinical validity of individual test systems.

Soon after Roche introduced the AmpliChip, the FDA questioned the company's ASR designation of the product. By November 2003, the agency decided the microarray would need to undergo FDA review to be sold as a diagnostic. "The technological characteristics of the AmpliChip cause it to differ from existing or reasonably foreseeable ASRs such that the AmpliChip would not be exempt from premarket notification," wrote Steven Gutman, the director of the FDA's Office of In Vitro Diagnostic Device Evaluation and Safety, in a letter to Roche explaining this decision.

"They basically told Roche that they think their product is somewhat ambiguous," says Thomas Tsakeris, president of Maryland-based Devices and Diagnostic Consulting Group and former director of the FDA's Division of Clinical Laboratory Devices. "They said they don't know whether it is an ASR or not," he explains, "but it is a product that has substantial importance to public health and therefore ought to be regulated more actively than a traditional ASR."

Microarrays have actually been sold as ASRs in "lots of situations," Tsakeris says.

PHOTO: ROCHE DIAGNOSTICS

Clinical array? Roche's AmpliChip CYP450 may soon be the first DNA microarray approved as an in vitro diagnostic device.

The difference in this case is that Roche made a particularly public case of it.

ASRs, Tsakeris says, are "clearly a gray area for which the agency has not been very responsive up until the time Roche made it very public." He suggests Roche might have been looking for clarification on the regulatory issue since microarray diagnostics are expected to be a rapidly expanding area in which Roche sees itself as a major player. "Some people think that Roche did this purposely to see what the FDA reaction might be," he says.

Array reagents

The FDA has not yet explicitly indicated if commercial microarrays can be considered ASRs or if they must be approved as diagnostic devices in their own right. One major question is whether microarrays like the AmpliChip CYP450 can realistically be supplied to a lab as a reagent without instructions or claims about its application. The ASR regulation "wasn't really promulgated with a DNA microarray in mind. It was really intended for one reagent, one analyte, and not for a whole battery of analytes," Tsakeris says.

An important issue hindering acceptance of DNA microarrays as diagnostic reagents is platform standardization. "I would say the number one concern right now is the variability from platform to platform," says Isaac Meek, an industry analyst at Frost & Sullivan. In other words, he explains, on a gene-per-gene basis there are significant inconsistencies between, say, an Affymetrix chip, an Agilent Technologies chip, and a home-brew chip.

Another issue is variability from lab to lab. Microarray analysis, Meek says, "is not a shake-and-bake type of experiment. It is pretty involved."

Tsakeris says "unstandardized testing" is a large concern for the FDA, not only regarding microarrays but also for all genetics-based tests. It is also a concern of the CMS. Thus, he says, the two agencies are discussing ways to encourage development of all-inclusive, FDA-approved test kits. "They are looking at whether tests cleared by the FDA should be reimbursed at different levels than those not approved by the FDA."

This could be a significant commercial incentive; reimbursement levels will be a major factor in determining the size of the diagnostic microarray market, Meek says. As things stand now, when a microarray diagnostic kit is approved, "you are going to see revenues go up pretty quickly, but then," he believes, "they are going to drop off." The reason for this, he explains, is that companies will have to lower their prices to make up for lower insurance compensations.

IVD direction

Roche stopped marketing the AmpliChip as an ASR, dropping it to research status subsequent to the FDA's November letter, and submitted an official in vitro diagnostic device premarket notification to the agency. But Roche had indicated its plans to take this step even if the product was still being offered as an ASR back when the AmpliChip was launched in June 2003.

This way, the AmpliChip would be assured a more direct role in guiding therapy choice, Baker points out. "If the product is approved for clinical diagnostic use, then it becomes a test a physician can order."

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"The company," Baker says, "is in regular discussions with the FDA about this product, and I believe they have set a clear path for how they are proceeding." Essentially, the FDA will classify the AmpliChip on the basis of its intended use and its similarity to existing IVDs. This will determine the nature of the review process and the extent and type of data Roche needs to submit.

There is really nothing special about microarrays from a regulatory review standpoint, Gutman says. "The microarray is just another device. How it is regulated depends on what it actually does. If it's being used for a very novel application for the diagnosis of prostate cancer, for example, it might be regulated as a Class III device," a category requiring a full-fledged approval process with extensive clinical data. But if there is not as much of a safety implication or there is a more established precedent already on the market, a less intensive review might be warranted.

The cytochrome P450 enzyme genes included on the AmpliChip are, in fact, one of the few genetic classes the FDA considers to be fully validated pharmacogenomics biomarkers (*www.fda.gov/cder/guidance/5900dft.pdf*). Thus, IVD approval of the AmpliChip might be more a matter of proving analytical validity than clinical validity.

Nonetheless, the AmpliChip could be an important learning case as the agency attempts to fit microarray technology into its regulatory framework. It currently has a draft guidance to industry in circulation (*www.fda.gov/cdrh/oivd/guidance/1210.html*) on the assessment of multiplex diagnostic assays including microarrays. This hints at greater complexities to come, such as clinical measurements based on more subtle changes in global RNA expression.

Gutman stresses that the agency is approaching microarrays as they do any new technology. "The FDA is only interested in two things: Does the test actually work, and can you label the product so it can actually be used in some plausible manner?" he says.

However, the agency has indicated in a recent report (*www.fda.gov/oc/initiatives/criticalpath/whitepaper.html*) that development of microarrays, which can be predictors of drug safety and efficacy, will be essential to bringing innovative drugs to market at a more efficient pace. In this light, the stakes for bringing microarrays and related technologies to full-fledged clinical status extend beyond those of just a device-related issue to ones that might call for a more comprehensive regulatory strategy.

As Alice Till, vice president of science policy and technical affairs of the Pharmaceutical Research and Manufacturers of America, writes in the organization's comments on the FDA's microarray draft guidance: "Given the likelihood that studies in clinical drug development using microarrays will be coordinated with development of clinical test applications based on microarrays, a shared regulatory framework seems not only desirable but necessary." ■