REPRINT FROM

genomeweb | Pharmacogenomics Reporter

September 07, 2011

At Dx Conference, FDA's Gutierrez Sheds Further Light on Plans for Risk-Based LDT Regulation

By Molika Ashford

Ahead of the US Food and Drug Administration's release of three new guidance documents outlining its plans to regulate laboratory-developed tests, an FDA official recently provided some clarification on how the agency intends to classify such tests in a risk-based manner.

In the year since the FDA first signaled its intent to regulate LDTs (*PGx Reporter 7/21/2010*), the agency has disclosed little detail on how it intends to oversee this segment of the diagnostics industry, which has traditionally been under the purview of the Centers for Medicare and Medicaid Services' CLIA regulations. As a result, labs and manufacturers have been left wondering how the agency plans to classify and regulate LDTs and what this may mean for their operations.

Alberto Gutierrez, deputy director of the FDA's Office of In Vitro Diagnostic Device Evaluation and Safety, addressed some of these concerns at the recent Next Generation Dx Summit in Washington, DC, where he fielded questions from conference attendees and moderator Franklin Cockerill, president and CEO of Mayo Medical Laboratories and Mayo Collaborative Services.

While he was not able to give a timeline for the release of the new guidances and noted that the agency is still exercising "enforcement discretion" over these tests, Gutierrez acknowledged that the uncertainty surrounding its future regulatory path is not ideal for groups developing such tests.

"While we are in the process of putting out guidance, we are actually in a worse place," he said. "We want to put out guidance so it's open and makes sense for everybody."

The agency recently said that it plans to release three guidance documents that will outline its roadmap for regulating LDTs — one that will describe the agency's general regulatory plan for LDTs; one that will lay out how the agency plans to assess the LDT field; and another that will describe the differences and similarities between CLIA and FDA's Quality System Regulations (*PGx Reporter 7/20/2011*).

It was clear from the questions raised to Gutierrez during the session, however, that labs and companies are anxious for further details on how the FDA sees its regulation of LDTs fitting into what many called an already heavy regulatory burden for laboratories, as well as what the agency's description of a "risk-based" classification for tests really means.

Gutierrez told attendees that risk classification for LDTs will mirror largely what the FDA already does for *in vitro* diagnostics. "Anything already defined class III [as an IVD] will stay as class III [if an LDT makes the same claim]," he said.

For example, "a screening test for HPV, that's class III, so if you have an LDT that does the same thing and is making the same claims as that test, you are class III."

Of course, not all tests will fit readily into this paradigm, Gutierrez admitted. But, he said, there are sets of LDTs that will be easier for the agency to classify than others.

Companion diagnostics were one example. "If you

continue on next page

genomeweb
www.genomeweb.com
The GenomeWeb Intelligence Network

are making a claim that your test can determine whether a drug can be given or not, for the most part you clearly would be class III," he said. "Unless someone comes out with a test on whether to take an aspirin or not — that likely would not."

"But a test for a drug to treat late-stage melanoma for example — yes, that would be high risk," he said.

Meanwhile, tests that have an undetermined risk profile will be assessed on a case-by-case basis, in what Gutierrez said is the FDA's normal procedure for IVDs. "We convene a panel of experts, lab people, doctors, experts in the area, to help determine what the risk of that test is," he said.

Cockerill asked about difficult cases, saying that there has been "a lot of concern" among companies and labs about how the agency will deal with tests that aren't linked to a life-saving drug, or designed to diagnose a serious disease. He also mentioned that there is uncertainty surrounding preventative tests, prognostics, and other categories of tests.

"Unfortunately, you can't make generalizations, but you can look at what we've done in the past and that gives you an idea," Gutierrez said. As an example, he cited Agendia's Mammaprint breast cancer recurrence test, which was the first test the FDA cleared as a so-called *in vitro* diagnostic multivariate index assay. "That was classified as class II as a prognostic test, and there are a couple that we've done that way.

"Unless there are some unusual circumstances," he added, "we would do them in the same manner."

But "unusual circumstances" seemed to be a major concern of many conference attendees, who pressed Gutierrez on specific test types and scenarios.

One questioner asked about mass spectrometry technologies.

"If you had a mass spectrometer manufacturer that decided their mass spec does only one thing — for example, detects the difference between c12 and c13 — and they want to use it for breath testing … and make a medical claim, that mass spec would take on the classification of that claim," Gutierrez said. "So it depends on what claim they make."

David Jackson, the senior director of pharmaceutical business development at Qiagen, countered that lab-developed tests often aren't offered with claims but rather as a test for a biomarker. "If a lab offers an LDT [for] a marker that in clinical practice only has one utility, but they don't make any claim, how will you deal with that?" he asked. "Because it seems you are a little gray on this."

"It is a little grey," Gutierrez acknowledged, "but if they are not making a claim, we don't have much of a regulatory [standing]."

Asked about companion diagnostics in a non-life threatening scenario, Gutierrez reiterated his aspirin example and noted that the agency's recently released draft guidance on companion diagnostics (*PGx Reporter 7/13/2011*) illuminates how future steps would be taken with LDTs.

"If you read the companion diagnostic guidance, companion diagnostics are right now defined by the agency as those tests that are essentially used during drug trials to bring a drug to market in which patients were selected based on that test," he said. "The reality is, most of the drugs that are coming to market right now tend to have a higher risk, and in most of these cases that we can think of, you are likely going to end up there [as a class III].

"I understand that there is some angst that in class III we are setting a higher bar," Gutierrez continued, but suggested that premarket approval applications for companion diagnostics should actually be easier than some other PMA scenarios. "If you come through the process with a company that makes a drug, the issue of clinical validity is really a given. So then your problem is more of validation," he said.

Cockerill brought up the issue of risks and benefits and suggested that the cost burdens of meeting additional regulatory requirements from the FDA would eventually transfer to patients. In particular, he asked what the benefits will be for heavily burdened laboratories that are "barely making it" and have "significant regulatory oversight already."

Gutierrez, however, didn't agree with Cockerill's premise on the cost-benefit balance and noted that

Continue on next page

any cost-effectiveness analysis has to include both sides of the equation — namely, "What is the cost of doing the wrong thing — of not regulating?"

The FDA understands "that the regulatory picture is not quite as easy as it looks," he said. "But we try to make sure that overall, we are doing a good job to make sure we protect public health."

FDA officials have said previously that the agency intends to coordinate LDT regulatory activities with CMS to ensure that labs don't have to meet the same requirements for two agencies, and the agency planned to use CMS inspectors (*PGx Reporter 7/21/2010*).

Gutierrez confirmed this at the conference. "In the plan that we are putting together we are looking at the possibility of synergies with other bodies that actually regulate the laboratories," he said, explaining that there is likely to be a proposal for a third party to review PMA applications that are class II or higher, and that proposals have also been made to have "certified bodies" do any third-party inspection for the agency, "so we can leverage some of the things they already do."

"We understand that labs clearly do get inspected [already]," he said. "In fact, they get inspected more often than companies that we already regulate."