FDA pushes for control over laboratory-developed tests

The US Food and Drug Administration (FDA) has told Congress that it intends to enforce its oversight over laboratory-developed tests (LDTs). On July 31, the agency announced that it will publish draft guidelines on how it will regulate LDTs. The FDA has sidestepped bringing laboratory tests under its control for years, but the rapid expansion of genotyping technology and widespread genomic testing, among other things, have increasingly brought the existing regulatory framework into question. FDA now plans to subject laboratory services firms to similar rules as those currently governing *in vitro* diagnostics sold as kits.

Reaction to the FDA proposal was predictably divided. AdvaMed, a medical technology trade group, "welcomes the publication of the draft framework on a risk-based approach to the regulation of LDTs," says executive director Andrew Fish. On the other hand, the American Clinical Laboratory Association (ACLA) expressed concern that "another layer of regulation could stifle diagnostic innovation and ultimately jeopardize patient access to timely and effective treatments," and urged the agency to exercise caution.

Debate over regulation of LDTs—tests developed by and performed in laboratories, as opposed to tests manufactured and distributed as kits—has raged since the early 1990s, when FDA first claimed the authority to regulate them. At the time, the agency said it would exercise "enforcement discretion" and declined to act. Since then, laboratory tests have mainly fallen under the Clinical Laboratory Improvement Amendments (CLIA) pathway. But CLIA rules, implemented in 1988, focus on a laboratory's processes for performing tests; not on the nature of the tests themselves. They do not assure an LDT's safety and effectiveness, require adverse event reporting or provide a means for removing a test from the market if it is deemed unsafe.

Laboratory-developed tests have become increasingly complex, propelled by sequencing and bioinformatics. Tests now include cancer therapy selection, for instance. This is a higher-risk use similar to that of *in vitro* diagnostics, Jeff Shuren, director of the FDA's Center for Devices and Radiological Health, noted in a press briefing on the guidance. The new rules aim to level the playing field for *in vitro* diagnostics manufacturers, whose diagnostic products are expected to undergo a premarket review process to determine safety and effectiveness. "Numerous stakeholders have claimed that the current system of uneven oversight has a negative effect on innovation," Shuren said.

Among the first class of LDTs to be reviewed will be those with the same intended use as FDA-approved companion diagnostics. Laboratories running such tests will have to submit a premarket application 12 months after the final guidance date (which would be sometime after October 1, 2014, following a public comment period). FDA will set up advisory panels to assist it in classifying other LDTs into risk-based categories, with other high-risk devices phased in over the next four years, followed by another four-year phase-in for moderate-risk devices. Low-risk LDTs, those for purely forensic use, and certain tests for transplantation are exempt from the new rules. FDA will also require only notification rather than review for some tests, including LDTs for rare diseases, otherwise unmet needs, and those used in hospitals or clinics for diagnosing or treating their own patients.

Regulating LDTs that compete with FDA-approved companion diagnostics (a category that now includes cancer tests around KRAS, EGFR, BRAF, ALK and Her2) is a significant undertaking by itself, says Danielle Pambianco Showalter of the health care consultancy ADVI in Washington, DC. "Think of how many labs across the country are running KRAS tests," she says. "Then extrapolate to other companion diagnostics." With the *in vitro* diagnostics road becoming a more popular route for developing companion diagnostics, "by the time this plays out there will be a fair number more on the market," she says.

FDA has "made a big splash" and put "a lot of momentum" behind the guidance, says Bruce Quinn of the law firm Foley Hoag in Boston. But with a definite proposal now on the table, Congress could weigh in on FDA's authority or attempt to curtail implementation through its control of the FDA budget. "It's definitely not a done deal," Quinn says. "It could be that only a few segments of this survive, or that [implementation] is delayed for several years while FDA regroups and tries another approach," he says.

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Laboratory directors have long opposed FDA regulation of their operations.

Mark Ratner *Boca Raton, Florida*

Bioelectronics SPARC at NIH

The US National Institutes of Health (NIH) plans to allocate $248 million to explore bioelectronics therapeutics. The seven-year program—stimulating peripheral activity to relieve conditions (SPARC)—will aim to produce proof-of-concept studies supporting the use of new modulatory therapies to regulate visceral organ functions. GlaxoSmithKline has also backed more than 30 academic projects in bioelectronics, set up a $50-million fund, and an innovation challenge with a $1-million prize to develop a rodent research platform. The purpose of NIH's and GlaxoSmithKline's programs is to identify diseases that can be treated by modulating electrical signals in peripheral visceral nerves, and develop technologies that will enable neural regulation using miniature, implantable devices.

First biosimilars trickle into US pathway

Novartis subsidiary Sandoz became the first company to file for approval under the newly created US biosimilars pathway. The company is seeking the go-ahead to market biosimilar filgrastim as Zarzio, a granulocyte-colony stimulating factor, a copy of Amgen's Neupogen, indicated for nonmyeloid malignancies in patients receiving myelosuppressive anticancer drugs. Zarzio, approved in the EU since 2008, became the first biosimilar to overtake its reference product. In August, the first application for a monoclonal antibody under the US biosimilar pathway was made by South Korea's Celltrion. Remsima is a biosimilar of Janssen Biotech's original reference drug Remicade (infliximab). As part of the application, Celltrion submitted pharmacokinetic and pharmacodynamics equivalency and safety data obtained for the originator products sold in the US and EU and for Remsima. Celltrion already markets Remsima in 50 countries.

"**Even if one believes the need for California to devote $3 billion to a narrow, extremely speculative field of science, the Trounson case and other CIRM [California Institute for Regenerative Medicine] administrative missteps have made clear that Proposition 71 created the wrong framework to manage a complex research effort. The initiative left the public with no way to tell if its money has been well spent, and no accountability if it hasn't.**" Columnist Michael Hiltzik on the announcement that the CIRM's former president Alan Trounson accepted a seat of the board of a company that receives funds from the institute. (*Los Angeles Times,* 18 July 2014)"