Third Phase of Transparency Initiative Covers Guidances, Reviews and Regulations

Industry may see an end to indefinite waits for major guidances as the FDA could develop timelines for producing the documents. That proposal is included in a set of 19 action items and five draft proposals announced Thursday as part of the third phase of the FDA’s Transparency Initiative, meant to increase openness with drugmakers.

The agency “heard very clearly” industry’s concerns about the agency working on a guidance while nobody knows the status of that document, Principal Deputy Commissioner Joshua Sharfstein said during a media call Thursday.

Two of the action items also relate to guidance development. For example, FDA Commissioner Margaret Hamburg has formed a cross-agency workgroup to identify best practices for improving work on guidances.

Additionally, the FDA will describe how to provide input to the agency about guidance topics. Links to a list of guidance documents that have been withdrawn during the past year, as well as possible topics for future guidance development or revision, will be made accessible on the FDA website.

These and other items are contained in a 46-page report, “FDA Transparency Initiative: Improving Transparency to Regulated Industry,” which outlines how the agency intends to shed light on its operations and decisionmaking processes (DID, May 20, 2010). Comments on the proposals are due March 8. The agency also wants input on which draft proposals should be given priority.

Some of the action items deal with improving communication about FDA procedures. For example, the FDA will:

- Launch a web-based resource, FDA Basics for Industry, to provide basic information and answers to frequently asked questions about regulatory processes;
- Update the agency’s organizational charts and senior leadership personnel changes on its website at least quarterly;
- Provide links to the processes for industry to submit general regulatory questions to each center;
- Aim to respond to emailed general questions about an existing policy, regulation or regulatory process within five business days or provide an estimated time for response; and
- Issue a final version of the “Strategic Priorities FY 2011-2015” by March 2011.

The FDA also will post on its website slide presentations given by FDA employees at events sponsored or cosponsored by the agency. One of the draft proposals suggests posting a list of other presentations, such as those given at private conferences, so that industry can request them, Sharfstein said.

Transparency During Application Review

Four action items focus on improving transparency during the application review process. The FDA plans to compile all center guidance and standard operating procedures for meeting with sponsors about applications on FDA Basics for Industry. It also will describe the types of notifications it provides with respect to the review process and give general expectations about when it is appropriate to use secure email between the FDA and a manufacturer for a question about a product.

FDA Basics was first announced in January 2010 in the first phase of the Transparency Initiative (DID, Jan. 13, 2010).

The agency will explain how a sponsor is informed about whether a review is on track to meet its target action date. The agency is willing to hold further discussions with industry about possible implementation of an application tracking system.

Five of the action items focus on improving transparency to the importing community. To reach this goal, the FDA will:
• Provide contact information within each district for questions about the import regulatory process;
• Allow members of the public to receive email notifications when an import alert is posted on the FDA website or an existing import alert is updated;
• Develop a project to promote more uniform processes and procedures across districts, where appropriate;
• Aim to respond to general questions about the import process within five business days or provide an estimated time for response. Frequently asked questions will also be posted on the FDA website; and
• Work with U.S. Customs and Border Protection to explore development of a process for brokers and filers to correct inadvertent data errors submitted about imported products.

Regulations Development Impacted

Two additional action items focus on transparency of the regulations development process. After the FDA issues a final rule, it will conduct outreach to affected stakeholders if the rule imposes substantial new obligations. It will also work with HHS and the Office of Management and Budget to improve the accuracy of the timetables included in the agency’s regulatory agenda.

The report also contains five draft proposals. In addition to the timeline for high-profile guidelines and the online list of FDA presentations, the proposals include informing applicants if an appeal request will be reviewed by the commissioner and when a decision may be expected; reviewing existing procedures to evaluate importers, or third parties working on behalf of importers, who file information electronically about products; and planning for a web-based system to provide information about importing requirements.

The FDA’s new report on the Transparency Initiative is available at www.fdanews.com/ext/files/UCM239088.pdf. — April Hollis

Merck Gets Priority US, EU Review for Hepatitis C Drug Boceprevir

Merck has received priority review in the U.S. and EU for its oral hepatitis C virus (HCV) drug boceprevir.

The U.S. application has a six-month review, the company said Thursday. Additionally, the European Medicines Agency granted accelerated assessment for the marketing authorization application in that region.

Merck is seeking approval for boceprevir, a protease inhibitor, to treat chronic HCV genotype 1 infection, in combination with standard therapy, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

The applications are supported by results from two pivotal Phase III studies that showed sustained virologic response (SVR) in patients on the HCV treatment (DID, Aug. 5, 2010).

When boceprevir was added to a control regimen of peginterferon alfa-2b and ribavirin (Schering-Plough’s PegIntron and Rebetol), both treatment-failure and treatment-naive patients with chronic HCV achieved a greater SVR than those on the control regimen alone.

The results put Merck’s drug candidate on similar footing with Vertex Pharmaceuticals’ telaprevir, which reported strong efficacy results in treatment-naive patients (DID, Aug. 11, 2010).

Vertex asked for priority review in its NDA for telaprevir, submitted in November (DID, Nov. 24, 2010). The company expects an FDA decision on priority review this month, Vertex spokeswoman Amy Pasqua told DID. — April Hollis

J&J Submits NDA, Complete Response for Rivaroxaban

Johnson & Johnson (J&J) has submitted to the FDA an NDA for rivaroxaban as a treatment for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).

The NDA submission, announced Wednesday, was supported by a global Phase III trial known as ROCKET AF that showed Xarelto (rivaroxaban) was superior to warfarin, the longtime standard of care for this indication.

The ROCKET AF trial showed similar bleeding to warfarin, but fewer intracranial hemorrhages, organ bleeds and bleeding-related deaths (DID, Nov. 16, 2010).

Bayer, J&J’s European partner for the drug, also said it submitted a marketing authorization application to the European Medicines Agency.

If approved for AF, rivaroxaban could become a cash cow for J&J. “[Stroke prevention in atrial fibrillation], in particular, is critical to the commercial potential for Xarelto given the size of the atrial fibrillation market and the potential for chronic therapy in this population,” Credit Suisse analyst Catherine Arnold says in a Thursday note.
Rivaroxaban could also potentially compete with Boehringer Ingelheim's Pradaxa (dabigatran etexilate), which was approved by the FDA in October, and Bristol-Myers Squibb and Pfizer's apixaban, an NDA for which was submitted in November on a rolling basis.

Arnold expects the completion of apixaban's ARISTOTLE study, which compares the drug to warfarin in stroke prevention in atrial fibrillation, in the second quarter. Top-line results could be available as early as in mid-year with full results following later in the year.

Complete Response

J&J also said it submitted a complete response to the FDA for approval of rivaroxaban for the prevention of deep vein thrombosis and pulmonary embolism in patients undergoing total hip or knee replacement surgery.

After receiving a complete response letter in May 2009 that requested additional data from completed and ongoing studies of the drug to further assess its risk-benefit profile, J&J met with the FDA twice (DID, July 16, 2009).

The company's response was based largely on data from the Phase III RECORD trial. J&J will most likely receive a decision in six months, according to Arnold. — Molly Cohen

Lawmakers Question FDA’s Understanding of Biosimilars Legislation

As the FDA continues its internal deliberations over how to regulate biosimilars, the principal authors of the bill that created the approval pathway have written to the agency seeking to clarify what they see as an error in the FDA’s interpretation of the law.

In a letter sent Dec. 21, Reps. Anna Eshoo (D-Calif.), Jay Inslee (D-Wash.) and Joe Barton (R-Texas) express concern that FDA officials are confused about the 12-year period of data exclusivity that was granted to manufacturers of brand biologics when President Barack Obama signed the Patient Protection and Affordable Care Act into law last year.

Their concern stems from a Federal Register notice the FDA released prior to its public meeting on biosimilars in November, in which the agency asked stakeholders what factors it should consider to ensure that drugmakers are not granted additional periods of “marketing” exclusivity for minor changes to their products, a process known as “evergreening” (DID, Oct. 5, 2010).

The FDA’s changing of the term “data” to “marketing” is important, because there are “significant and critical differences” between the two types of exclusivity, the legislators say.

"Data exclusivity only prohibits the FDA from allowing another manufacturer to rely on the data of an innovator to support approval of another product,” the letter says. “Importantly, it does not prohibit or prevent another manufacturer from developing its own data to justify FDA approval of a similar [or] competitive product.”

The lawmakers also took issue with the FDA’s notion that such “evergreening” of products could occur under the law, saying that the bill expressly prohibits that from happening (DID, May 21, 2010).

"As authors of the legislation, we took very seriously the concerns about ‘evergreening’ and the legislation is clear that no product, under any circumstances, can be granted ‘bonus’ years of data exclusivity for mere improvements on a product," Eshoo, Inslee and Barton say.

The legislators note, however, that if a product has "significant changes in safety, purity or potency," then it could be considered a "next generation" product and thus receive its own 12-year period of data exclusivity.

The letter highlights the complex task the FDA is facing in implementing its regulations of the biosimilars pathway.

Stakeholders from the brand- and generic-drug industries have stark differences over the actions they want to see the agency take, and as the lawmakers' letter shows, a single word can make an enormous difference in how the biosimilar industry will work.

So far, though, the agency has resisted revealing its thinking, and experts have predicted it could be years before any formal guidance is issued (DID, Oct. 20, 2010). — David Belian

CMS Hit With Suit Demanding Provenge Review Criteria

A government watchdog group has filed a lawsuit against HHS seeking to require the department's Centers for Medicare & Medicaid Services (CMS) to reveal information about its ongoing national coverage analysis of Dendreon’s prostate cancer treatment Provenge.

In a suit filed Monday in the U.S. District Court for the District of Columbia, Judicial Watch accuses HHS of failing to respond to a Freedom of Information Act (FOIA) request filed by the group in November.
The request sought access to all of CMS’ records concerning its review of Provenge (sipuleucel-T), including the criteria the agency is using to analyze the drug.

That criteria has been a source of controversy since CMS initiated its review in July, because such reviews — which determine if the agency adopts a national policy to pay for a product — are uncommon and Provenge’s $93,000 per-treatment cost is not supposed to factor in the agency’s decision (DID, July 2, 2010).

In its suit, Judicial Watch says that CMS was required to respond to the group’s FOIA request by Dec. 15, but it has not produced any records or indicated whether it intends to do so.

The group is asking the court to require the agency to search for and hand over the requested documents.

For CMS though, Judicial Watch is just the latest in a long line of stakeholders who have demanded to know why the agency is reviewing Provenge.

In August, Sens. Arlen Specter (D-Pa.) and John Kerry (D-Mass.) joined the fray, sending a letter to CMS Administrator Donald Berwick asking the agency’s reasoning for conducting the review (DID, Aug. 27, 2010).

Despite the backlash, however, a CMS advisory panel voiced support for Provenge in November, saying that the drug improves survival and lessens the treatment burdens associated with other anticancer therapies (DID, Nov. 18, 2010).

A proposed coverage decision from the agency is due in March and a final determination is expected by June 30. — David Belian