FDA Regulatory and Compliance Monthly Recap

JANUARY 2015

KEY FINDINGS

FDA's CDER, CDRH and CBER put out 2015 guidance agendas

The regulator's Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER) released lists of guidances set to be issued this year.

The CDER's agenda, which is intended to outline the agency's workload relating to pharmaceutical and biological products, shows that it plans on publishing 90 guidance documents in 2015.

In its guidance agenda, the CDER included several guidances of particular note. The agency said it intends to release four guidance documents covering biosimilarity in 2015, including one on labeling of biosimilar products. The agenda also shows plans to release or finalize six advertising guidance documents, including one on the use of healthcare economic information and one on direct-to-consumer TV ads, which the FDA also announced as the subject of a study this month. The regulator is also set to issue social media guidance, with the latest document to come down the regulatory pipeline covering the use of links to third-party sites on social media, which the CDER bumped from 2014 to 2015. Under the Food and Drug Administration Safety and Innovation Act, the FDA was required to create social media guidance within two years — meaning in 2014. Drafts for four different social media topics were issued on the 2014 agenda, but the FDASIA action was marked as completed following the third draft guidance's release.

It also appears that manufacturing is an area of particular focus for the FDA in 2015, with planned guidances on modernizing the pharmaceutical manufacturing base with the use of emerging technologies, on "quality metrics and risk-based inspections" and on data integrity.

According to the agenda, the CDER also intends to issue or finalize six guidance documents covering track and trace as part of the Drug Supply Chain Security Act. Other noteworthy guidances include one describing "common issues in drug development for rare diseases," one on the inclusion of pregnant women in clinical trials, several on risk evaluation and mitigation strategies, and one gauging the effect of a drug on a patient's driving ability, which was issued this month.

The Center for Devices and Radiological Health also put out lists of medical device guidance documents it is planning on developing and publishing this year, including ones concerning accelerating device submissions, regulation of lab-developed tests and decision support software.

The FDA's announcement includes three lists. The A-list consists of prioritized documents the agency "fully intends to publish," while the B-list is composed of guidances the CDRH intends to publish as resources permit, and the third includes final guidance documents issued in 1985, 1995 and 2005 that may require retrospective review.

A few of the CDRH's highest-priority guidance documents are familiar to longtime industry watchers. The FDA is planning on releasing or finalizing two documents as part of its effort to more closely regulate lab-developed tests after issuing a draft guidance regulatory framework in August.

The guidance agenda also shows the agency's plans to finalize guidance on its new expedited approval program for high-need devices, following the release of a draft guidance document establishing the Expedited Access Premarket Approval program in April.

The FDA's agenda also shows that it was planning on publishing new guidance covering general wellness products and medical device accessories, both of which were issued this month. Other high-priority guidance documents set to see issuance include ones that cover medical device decision support software, direct marking under the unique device identification program, adaptive designs for device studies and informed consent policies.

The FDA's B-list includes draft guidance topics, including medical device interoperability, use of symbols in labeling and 3D printing.

Another FDA guidance agenda issued this month came from the Center for Biologics Evaluation and Research. The agenda contains a list of 11 documents the agency intends to release, on topics for which the CBER has issued drafts as well as topics that currently have no guidance associated with them. The list is composed of three categories: blood and blood components; cellular, tissue and gene therapy; and "other." Among the planned documents topics are how blood banks should treat patients who may have been exposed to the Ebola virus or the Chikungunya virus, as well as regarding the homologous use of human cell and tissue products.

FDA to study limiting major risk statements in direct-to-consumer (DTC) TV ads amid concern that information is getting lost on consumers

The regulator will study whether consumers would benefit from DTC TV advertising containing a shorter list of major side effects rather than the currently lengthy list of nearly all of them, looking into whether it would promote improved consumer perception and understanding of serious and actionable drug risks.

The study, which the FTC first proposed in February 2014, is intended to address the concern that people who are bombarded with a long list of side effects may have a tough time deciding between drugs. In its Federal Register notice, the FDA said there's concern that the major statement — as it's currently implemented in DTC ads — is often too long, potentially leading to "reduced consumer

comprehension, minimization of important risk information and, potentially, therapeutic noncompliance due to fear of side effects." However, the FDA said there's also concern DTC TV ads don't contain adequate risk information or they exclude important information. As a potential resolution to these conflicting viewpoints, the regulator said the risks in the major statement could be limited to those that are serious and actionable, with the inclusion of a disclosure alerting consumers that there are other product risks not included in the ad. Through empirical research, the OPDP will investigate the effectiveness of this "limited risks plus disclosure" strategy.

The FDA's primary hypothesis is that, in relation to the inclusion of the full major statement, providing limited risk information in conjunction with the disclosure about additional risks will promote improved consumer perception and understanding of serious and actionable drug risks. Other questions such as whether overall drug risk and benefit perceptions are impacted by these changes will also be probed.

The agency's proposed study will have patients 18 years or older who self-identify as having been diagnosed with depression, high cholesterol or insomnia view one of four versions of a DTC ad, each with various disclosures of risk. The FDA said it will modify an ad already in the marketplace, as it would be considerably cheaper for it to use, and that it wouldn't fictionalize any of the drug's risks.

Cegedim Strategic Data shows drug makers spent nearly $4 billion in 2013 on DTC advertising, but the future of TV advertising has become ambiguous in recent years as viewers are increasingly on their smartphones during commercial breaks or fast-forwarding through commercials altogether.

FDA opens Office of Pharmaceutical Quality (OPQ) as it seeks to standardize and centralize how regulatory officials oversee drug quality

The regulator launched its new office in the hope that the integration of functions performed by staffers reviewing drug applications and inspectors visiting manufacturing plants will lead to fewer glitches as medicines come to market.

The FDA first announced the creation of the OPQ in 2012, during a broader reorganization of the CDER by longtime director Janet Woodcock, who said the agency needed to have systems established to identify and address quality issues before they become problems.

Lawrence X. Yu, Ph.D., acting director of the CDER's OPQ, said the office is looking to be a global benchmark for the regulation of pharmaceutical quality, and that it's aiming to achieve the goals described in the FDA's 21st Century Quality Initiative by streamlining the drug quality work that is currently being undertaken in multiple parts of the center to deliver seamless assessment and surveillance over the product life cycle. The new office will closely incorporate review, inspection, surveillance, policy and research in a bid to provide one unified view on pharmaceutical quality. It is working on establishing risk-based measurements to identify quality issues more quickly and enable a quick response before they become major, systemic problems. Yu said the OPQ will use performance measures to determine the current state of quality of both facilities and products so that it can make better decisions on when to conduct surveillance or take regulatory action if a firm shows a pattern of being unable to achieve quality standards.

The office is also intended to tackle a number of endemic problems in the pharmaceutical sector, such as chronic drug shortages and a lack of manufacturing modernization, with Yu saying manufacturing and quality issues are the most frequently cited causes for drug shortages.

With the launch of the OPQ, all new drug applications are being reviewed by the office under its new "unified approach to quality," which Woodcock said will mean some changes to how the regulator accepts and reviews data about how a drug is made. "Quality scorecards" will be used, and they will include information generated by a sponsor to demonstrate that their operations conform to good manufacturing practices and that they are keeping a keen eye out for potential problems. The idea is to match known or potential issues to quality metrics.

While guidance on what the FDA will be looking for concerning the data companies will need to provide during the review process is under development, no release date has yet been confirmed. Woodcock also said sponsors will eventually be required to submit quality metrics data in a standardized form so that information technology systems can make better use of the information provided.

A potential hurdle for the OPQ could be the number of decisions it will have to process. By consolidating the quality functions of new drugs and generic drugs, including post-approval supplemental applications, the office will need to make more than 10,000 decisions each year, possibly causing backlogs if the center isn't able to recruit adequate staff.

However, Woodcock stressed the potential benefits to industry if it complies with the FDA's new quality approach. Firms that have better approaches to quality should see more predictability in their drug applications, more manufacturing "uptime" and even fewer inspections by the regulator.

FDA issues guidance proposing not to regulate wellness products; defines when they become medical devices

The regulator proposed to not enforce regulatory compliance for products exclusively intended for general wellness, in a draft guidance document defining low-risk products promoting health management and when such products cross into the territory of medical devices.

The agency issued a draft policy document on low-risk general wellness devices, in compliance with actions outlined in its FDASIA Health IT Report, writing that it will likely not regulate most mobile apps or wearables. The document states that the CDRH doesn't plan on examining those types of products to determine whether they're devices or are in compliance with premarket review or post-market regulatory requirements for medical devices, defining a "low-risk general wellness" product as one exclusively meant for a general wellness use and that presents "a very low risk to users' safety."

The FDA said the issuance of "General Wellness: Policy for Low Risk Devices — Draft Guidance for Industry and Food and Drug Administration Staff" is aimed at clarifying CDRH's policy on general wellness products, thus improving the predictability, consistency and transparency on regulation of these products.

Elaborating on the scope of its definition of a general wellness product, the FDA wrote that such a product has intended use related to the maintenance or encouragement of a general state of health or a healthy activity, or an intended use claim associated with the role of a healthy lifestyle, with helping reduce the risk or effect of certain chronic diseases or conditions, and where it is well understood and accepted that healthy lifestyle choices may strongly influence health outcomes for the disease or condition.

The guidance outlines two different categories for general wellness devices that don't fall into FDA regulation.

The first category includes devices that "do not make any reference to diseases or conditions," instead making claims that are more general, including claims related to weight management, physical fitness,

relaxation or stress management, mental acuity, self-esteem, sleep management or sexual function. The guidance also contains examples of general wellness claims, including claims to promote or maintain a healthy weight, encourage healthy eating or help with weight-loss goals; to promote relaxation or manage stress as long as there's no reference to anxiety disorders or other reference to a disease or condition; to promote sleep management, such as to track sleep trends; and to increase or improve the flow of qi.

The second category of general wellness devices includes those that do make reference to specific diseases or conditions, but do so only in two specific ways. They either claim to help users reduce the risk of certain diseases or conditions or that they may help users better live with specific diseases or conditions. The FDA provided examples of these types of claims, including that a given product promotes physical activity, which, as part of a healthy lifestyle, could help reduce the risk of high blood pressure; and that it tracks activity sleep patterns, promoting healthy sleep habits, which, as part of a healthy lifestyle, may help reduce the risk for developing type 2 diabetes.

The FDA said the guidance doesn't cover any product whose intended uses go beyond general wellness intended uses. Therefore, a general wellness product becomes a medical device when it refers to its use for a specific disease or condition and its applications are invasive or exceed the general purposes of most wearables. Any device or an app claiming to treat or diagnose conditions such as obesity, anorexia, autism, anxiety, erectile dysfunction, or any other disease or condition would conflict with the FDA's policy and be regulated as a medical device.

The guidance document also states that in order for a wellness product to fall outside of FDA regulation, it must be deemed "low risk." The device can't be invasive, involve an intervention or technology that may pose a risk to a user's safety in the event that device controls aren't applied, raise novel questions regarding usability or raise questions of biocompatibility.

The FDA provided examples in its document of wellness devices that are low risk, some of which were mobile apps, including an app that plays music to "soothe and relax" a person and to "manage stress," and an app that monitors and records food consumption to "manage dietary activity for weight management and alert the user, healthcare provider or family member of unhealthy dietary activity."

FDA guidance outlines framework for the classification and approval of medical device accessories

The agency issued the draft document to provide guidance on its regulation of medical device accessories, aiming to clarify and modify the policy on the classification of accessories as well as to go over the application of that policy to specific categories of devices commonly used as accessories to other medical devices.

The general framework for medical device accessories has prompted some confusion for makers of medical device accessories. Because accessories function in conjunction with another device, called a "parent device," which is often cleared or approved as a separate device, there are now questions about how the FDA should evaluate each device accessory. For example, should an accessory be evaluated on its own merits or should it be attributed its parent device's same risk status?

With "Medical Device Accessories: Defining Accessories and Classification Pathway for New Accessory Types — Draft Guidance for Industry and Food and Drug Administration Staff," the regulator attempts to clarify some of the uncertainty in this space.

Traditionally, the FDA determined the classification of device accessories, which it defines as a device meant to "support, supplement and/or augment" the performance of a parent device, in one of two ways — either by its inclusion in the same classification as the parent device, which can be through 510(k)

Premarket Notification clearance, PMA approval, or by express inclusion in the classification regulation or order for the parent device, or by a separate, unique classification regulation or order.

The FDA wrote that while it's appropriate to classify an accessory in the same class as its parent device when the accessory meets the class criteria, some accessories have a lower risk profile than the parent device and therefore could be regulated in a lower class.

In view of this, the agency developed the document to make clear how its risk- and regulatory control-based framework applies to accessories. The FDA noted that a fundamental consideration in its valuation of risk is the accessory's relationship with its parent device. Certain accessories are critical to the proper function of a device, like a rechargeable battery for an AED. However, other accessories enable the parent device to perform new functions, or perform some function better or more safely, but aren't necessary to its core functions. The regulator said it plans on determining the risk of accessories and the necessary controls based on their intended use "in the same way that is used to determine such for devices that are not accessories." The FDA further explains that it will determine the risk of a device "when used, as intended, with the parent device," but that it doesn't intend to simply superimpose a parent device's risk classification to its accessory, because it's possible that the risk profile of an accessory differs significantly from that of the parent device.

The guidance also encourages manufacturers to use the de novo classification process to enable them to get their products to market more rapidly.

Ultimately, the document shows the FDA's position that device accessories aren't automatically as risky as their parent devices and thus might be able to win approval along a less grueling regulatory pathway.

For more information on any of these FDA regulatory and compliance updates, please contact Scott S. Liebman at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

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