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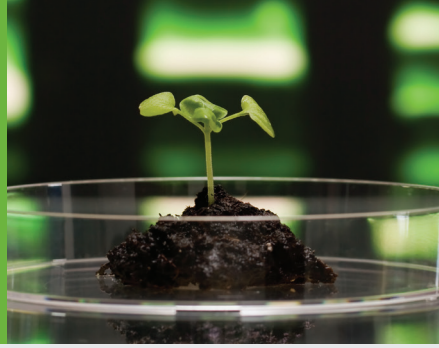
FDA Regulatory and Compliance Monthly Recap



NOVEMBER 2015

KEY FINDINGS

Bill that refines marketing exclusivity for DEA scheduled drugs becomes law

The Improving Regulatory Transparency for New Medical Therapies Act (H.R. 639) was passed in the House of Representatives and was sent to President Obama, who signed the bill into law on Nov. 30.

The House of Representatives agreed to a Senate amendment to H.R. 639 on Nov. 16, the final step before the bill was presented to the president. The amendment was substitutive in nature. On Nov. 30, President Obama signed the law into effect.

The bill amends the Controlled Substances Act (CSA) in an effort to expiate drug scheduling by the Drug Enforcement Agency (DEA), redefining "approval" for certain products. Under current law, drugs subject to the CSA need to be scheduled by the DEA before they reach the market, even after FDA approval. Industry members have raised concerns about the system, as the DEA, in some cases, can take more than a year to schedule products, preventing them from reaching the market.

To address the gap between FDA approval and DEA scheduling, H.R. 639 is designed to standardize and accelerate DEA scheduling; it calls on the agency to make a scheduling decision within 60 days of FDA approval. The 60-day guarantee won't necessarily speed up the DEA review process for all drugs, but it will provide drugmakers with a more predictable and transparent framework. Additionally, the bill provides patent extensions to make up for the time it takes for DEA review.

H.R. 639 also makes it easier to provide patients with drugs during a clinical trial, by setting a timeline for the DEA to review applications to manufacture a controlled substance for clinical trials. Under the bill, the DEA has 180 days to review such applications, though this does not include a notice and comment period as well as a 90-day application window.

FDA, industry stakeholders advance MDUFA IV reauthorization negotiations, agree to three priorities

The FDA and members of the medical device industry agreed to limit their focus in MDUFA reauthorization discussions to three priority areas — incorporating patient perspectives into FDA review, better utilization post- and pre-market evidence, and FDA cross-center collaboration. The final recommendations will head to Congress in January 2017.

As they look ahead to the fourth iteration of the Medical Device User Fee Agreements (MDUFA) for 2017, the FDA and industry stakeholders came to terms on three priority areas.

Although both sides say the program has improved and is heading in a positive direction, they identified three priorities for the 2017 iteration, which is required by law — patient engagement and the science of patient input, use of evidence for post-market and pre-market purposes, and cross-center coordination.

The first priority area focuses on incorporating patient perspectives into FDA reviews, with both regulatory authorities and industry members agreeing to discuss limitations in the use of scientific data on patient preference (PP) and patient reported outcomes (PRO). Specifically, the pair said they will address resource constraints that stymie the use of scientific data on PP and PRO, as well as limitations of getting devices to market using such data. In order to overcome the issue, they called for an expansion in the use of patient registries. The FDA also emphasized the importance of demographic subgroup data and discussed section 907 of the Food and Drug Safety and Innovation Act, which calls on the agency to examine specific demographic data for inclusion in clinical trials.

The second priority focuses on how post- and pre-market device evidence can be better utilized. The industry and FDA acknowledged the need to find the right balance between pre-market and post-market evidence collection and the need for more efficient collection and use of data from various sources, such as device and patient registries, particularly because data collection is beginning to shift, in certain cases, from pre-market to post-market. They encouraged the FDA to adopt a total product life cycle approach in which pre- and post-market are not separate from one another.

The final priority area focuses on how FDA centers can better coordinate in areas such as combination products and companion diagnostics, emphasizing the need to identify areas for efficiencies and consideration of how to ensure adequate user fee funding.

At the next negotiation meeting, the FDA and industry will present final proposals. They hope to reach an agreement that can go into clearance by mid-2016, after which the FDA will conduct the public process for review of draft recommendations by fall 2016. Final recommendations will be delivered to Congress on Jan. 15, 2017.

In response to stakeholder feedback, FDA stays parts of IND application guidance related to conventional foods, health claims

In an effort to encourage scientific research into the relationship between diet and health, and in response to industry feedback, the FDA issued a stay on certain parts of its 2013 guidance on IND applications. The stay applies to trials of conventional foods, as well as studies intended to support health claims.

The FDA decided to stay certain parts of its final guidance on Investigational New Drug Applications, called “Investigational New Drug Applications-Determining Whether Human Research Studies Can Be Conducted Without an IND,” which is designed to clarify when researchers or sponsors are required to file IND applications prior to conducting human research trials.

After publishing the final guidance in 2013, the FDA received comments requesting further opportunity for comments related to studies involving cosmetics and foods. In response, the agency reopened the comment period on those subsections in February 2014. During the comment period, the agency said it received feedback from trade organizations, individual companies, scientific associations, public interest organizations and individuals, raising concerns about the application of the IND requirement to studies of conventional foods, dietary supplements and cosmetics being studied for uses covered by the drug definition in section 201(g)(1)(B) or (C) of the FD&C Act.

In response to comments from industry stakeholders, the regulatory authority has now decided to stay parts of the subsection on conventional foods (subsection VI.D.2) as well as the subsection on trials intended to support health claims (subsection VI.D.3).

The stay excludes clinical trials that include children under one year of age, people with compromised immune systems, and those with serious or life-threatening medical conditions. The FDA noted that "the stay does not affect investigations of conventional foods or dietary supplements studied for use in the diagnosis, cure, mitigation, treatment, or prevention of disease."

During the time the partial stay is in effect, researchers and sponsors of studies designed to support new or expanded health claims conducted in healthy individuals over the age of one year are not required to obtain an IND. Also during the stay, an IND is not required for trials of non-nutritional effects of conventional foods on the structure or function of the body. Trials under the stay that do not require an IND include those evaluating whether conventional foods or dietary supplements may reduce the risk of disease, studies investigating the nutritional effects of conventional foods, and trials assessing a dietary supplement's effects on the structure or function of the body.

The agency said the goal of the stay is to encourage research into the relationship between diet and health, as it considers comments received in response to the final guidance.

The agency republished the final guidance in order to identify the stayed portion to avoid confusion about which parts of the guidance are stayed and which will remain in effect.

FDA data reveals uptick in foreign medical device inspections, decrease in warning letters

The FDA released its 2014 data on inspectional observations and warning letter citations issued to medical device manufacturers, citing an increase in foreign inspections, particularly in China, as well as a decrease in overall warning letters sent to medical device manufacturers.

The FDA's Center for Devices and Radiological Health released data on FDA Form 483 Observations and warning letter citations issued to medical device manufacturers in 2014, citing an increase in foreign quality system surveillance inspections and a decrease in warning letters.

The "2014 Annual FDA Medical Device Quality System Data," which included data from Jan. 1, 2008, to Dec. 31, 2014, showed a jump in foreign inspections from 460 in 2013 to 594 in 2014, coinciding with a decrease in domestic inspections from 1,741 to 1,619. China saw the most inspections, at 190, followed by Germany (72), Japan (37), Taiwan (29) and Switzerland (25). The U.S.'s neighbor to the north, Canada, saw 24 inspections in 2014.

Voluntary action was required in slightly more foreign inspections than domestic inspections, at 43% compared with 40%. Similarly, official action was taken in 15% of foreign inspections, but only 8% of domestic inspections.

The agency found that 58% of foreign-based device manufacturers were not fully compliant with the Quality System Regulation, compared with 48% of domestic manufacturers. Corrective and preventive action (CAPA) violations and production and process controls (P&PC) were the top areas cited by the agency. In 2014, P&PC violations were cited in 1,197 inspectional observations, up from 1,151 in 2013. CAPA violations were cited in 1,148 inspectional observations, compared with 1,085 the prior year. P&PC made up 32% of 483 observations, while CAPA made up 31%.

The 2014 data also showed a decrease in warning letters, from 144 in 2013 to 121 in 2014. These included 21 CFR 820 (Quality System Regulation) deficiencies. In contrast to the uptick in foreign inspections, domestic manufacturers saw an increase in warning letters, while foreign companies received fewer warning letters in 2014. Foreign companies received 45 warning letters in 2014, compared to 74 in 2013, while domestic manufacturers saw 76 in 2014, up from 70 in 2013.

Crackdown on dietary supplement industry continues as FDA, other agencies take action against 117 companies

After a yearlong sweep, the FDA, along with several other government agencies, took action against more than 100 dietary supplement makers for tainting or falsely marketing their products. The FDA says the actions should serve as a warning to the rest of the industry that the agency will continue to crack down on manufacturers as it looks to protect consumers.

The FDA, along with other agencies, filed civil injunctions or took criminal actions against 117 dietary supplement makers for falsely marketing dietary supplements, as the result of a yearlong investigation. The investigation was spearheaded by the Department of Justice, with help from the Internal Revenue Service's Criminal Investigation Division, the Federal Trade Commission, the U.S. Postal Inspection Service, the Department of Defense and the U.S. Anti-Doping Agency, as well as the FDA.

Among the charges is a criminal case against USPlabs, a manufacturer of weight loss and workout supplements Jack3d and OxyElite Pro, and several of its corporate officers. The Dallas-based company was served with an 11-count indictment, contending that it took part in a conspiracy to import ingredients from China using false certificates of analysis and false labeling. The indictment states that the company lied about the source and nature of the ingredients after adding them to its products. The company also told retailers and wholesalers that it used natural plant extracts, despite the fact that it was using a synthetic stimulant from China, the indictment states.

The indictment further finds that USPlabs sold some products despite the fact that it knew research had linked the products to liver toxicity. After its product OxyElite Pro was implicated in an outbreak of liver injuries, USPlabs told the FDA it would stop distributing the product, but instead engaged in what the indictment calls "a surreptitious, all-hands-on-deck effort to sell as much OxyElite Pro as it could as quickly as possible."

In addition to the action taken against USPlabs, the DOJ filed a complaint on behalf of the FDA against Bethel Nutritional Consulting and the company's president and vice president. The complaint, filed in federal court in the District of New Jersey, contends that Bethel and its officers distributed adulterated and misbranded supplements, as well as unapproved new drugs. Under a consent decree of permanent injunction, the company agreed to cease operations until it is in compliance with dietary supplement manufacturing, labeling and distribution laws.

The FDA's deputy commissioner for global regulatory operations and policy, Howard Sklamberg, said the actions should serve as a message to the industry

that the agency will continue to crack down on products that are a threat to public health. In the past year, the agency has warned of more than 100 products containing hidden ingredients and has sent warning letters to manufacturers selling BMPEA- and DMBA-containing supplements as well as to makers of pure powdered caffeine products.

Despite the crackdown, experts say stricter controls of the market are needed. Dr. David S. Seres, director of medical nutrition and associate professor of medicine at Columbia University Medical Center, went so far as to call the Dietary Supplement Health and Education Act "one of the worst frauds ever perpetrated on Americans under the guise of protecting their health." Although they disagree on what's needed, experts seem to agree that more tools are needed to bolster DSHEA and the FDA's ability to regulate the market.

FDA releases 20 case studies to support further oversight of laboratory developed tests

The agency makes its case for further regulatory control of laboratory developed tests (LDTs) in 20 case studies linking the products to harm to patients. The agency says the current regulatory requirements are inadequate, citing the fact that all the problematic LDTs described in its case study met minimum regulatory requirements.

The FDA published a report on the need for regulatory oversight of LDTs, describing 20 case studies to bolster its contention that more oversight is needed. The report, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies," shows that when these products don't comply with FDA requirements, they can cause harm to patients.

Although labs that offer LDTs are subject to the FD&C Act, the FDA has historically exercised enforcement discretion toward such tests, and as a result, most follow only the regulatory requirements of the Clinical Laboratory Improvement Amendments (CLIA). The agency says CLIA is not designed to regulate in vitro diagnostic devices.

The case studies describe LDTs the FDA considers problematic, despite the fact that they meet the minimum requirements of CLIA. The FDA's process is more comprehensive than that of the CLIA program. A routine CLIA survey doesn't include a review of the clinical validation of an LDT, whereas FDA review focuses on safety and effectiveness as well as clinical validity.

The FDA details false-positives resulting in patients being told they have conditions they in fact do not have, resulting in distress and unneeded medical treatment, as well as false-negatives in which life-threatening illnesses go undetected, leaving patients without treatments. The agency also describes LDTs based on disproven scientific concepts, as well as tests that provide information with no proven application to the disease or condition they are designed to be used for. It says the case studies highlight the need for regulation beyond CLIA.

Among CLIA's issues, the FDA cites the failure to ensure the safety and effectiveness of LDTs, examine the quality design and manufacture of products, ensure adequate and truthful labeling, allow for the removal of unsafe devices from the market, and require manufacturers to report adverse events.

The agency calls for device adverse reporting requirements, pre-market review of LDTs, verification of manufacturer claims and assurance of proper product labeling. Without oversight, the agency says labeling may fail to provide adequate information for patients and providers, including information pertaining to how to interpret test results. The agency further explains that manufacturers that do the research needed to validate their devices and seek pre-market review are at an unfair advantage when other LDT competitors don't follow the same standards. This provides incentive for manufacturers not to pursue FDA clearance. The failure to maintain a comprehensive list of all LDTs in use also prevents an overall assessment of the market.

FDA oversight should be complementary to CLIA's, and should promote access to LDTs that provide benefits to patients and the healthcare system, the agency concludes.

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

Loeb & Loeb's FDA Regulatory and Compliance Practice comprises an interdisciplinary team of regulatory, corporate, capital markets, patent and litigation attorneys who advise clients on the full spectrum of legal and business issues related to the distribution and commercialization, including marketing and promotion, of FDA-regulated products. Focusing on the health and life sciences industries, including pharmaceuticals, biologics, medical devices, wellness products, dietary supplements and organics, the practice counsels clients on regulatory issues, compliance-related matters and risk management strategies; advises on laws and regulations related to product advertising and labeling; counsels on FDA exclusivity policies and related Hatch-Waxman issues; and provides representation in licensing transactions and regulatory enforcement actions.