FDA Regulatory and Compliance Monthly Recap

MARCH 2016

KEY FINDINGS

FDA warning letter calls out exoskeleton device manufacturer for repeatedly avoiding FDA requests for postmarketing surveillance

The FDA sent a warning letter to Argo Medical Technologies after the company averted multiple attempts to ensure an adequate plan for postmarketing surveillance (PS) was in place for its exoskeleton device.

After Argo Medical Technologies avoided FDA requests on multiple occasions, the agency sent a warning letter to the company for failing to conduct PS for its ReWalk exoskeleton device. In June 2014, the FDA approved the device to help patients with spinal cord injuries, at which time it issued an order under Section 522 of the Federal Food, Drug, and Cosmetic Act (the Act) for PS due to concerns that device failure could cause serious user injuries or death. The FDA was unable to resolve the surveillance issues with Argo despite multiple attempts to contact the company.

In July 2014, the agency received Argo's initial proposed 522 PS study plan, which the agency determined was missing information. Argo failed to respond to the FDA's request for additional information. The FDA notified the device maker that its response was overdue, and Argo subsequently responded, but the revised PS plan was still missing information needed to complete the review. The agency again waited for response, but Argo failed to respond, so the FDA sent yet another notification regarding the PS plan. Although Argo said it intended to submit a response, no response was received. After another request from the FDA, Argo indicated that it was prepared to respond to all but one issue and asked the FDA for a meeting to discuss the issue. Despite multiple attempts at contact, the FDA was unable to contact Argo to coordinate a teleconference to resolve the issue.

Argo then responded one more time, saying it was planning significant changes to the methods and study plan and asked the FDA for an in-

person meeting. The FDA reviewed Argo's proposed changes and provided feedback recommending that the company submit a revised PS study plan addressing the feedback and previously identified deficiencies. Argo never responded.

As per the 522 order, Argo was required to begin surveillance within 15 months of receiving the order. Argo's time frame closed on Sept. 28, 2015. Failure to comply with a 522 order is prohibited under Section 301(q)(1)(C) of the Act and renders a device misbranded under Section 502(t)(3) of the Act. As such, the FDA classified the ReWalk device as misbranded and requested that Argo respond to these violations. The FDA warned that failure to take corrective action could lead to regulatory action, including seizure, injunction or civil money penalties.

FDA revises guidance on initial pediatric study plans required under PREA

In response to public comments, the FDA revised draft guidance on pediatric study plans. The revised guidance clarifies aspects of the original guidance released in 2013 and information on what constitutes an incomplete initial pediatric study plan (iPSP) and addresses the contents and timing of requested amendments to an iPSP.

The FDA published updated draft guidance to direct pharmaceutical sponsors through the submission and amendment of iPSPs as required under the Federal Food, Drug, and Cosmetic Act and the Food and Drug Administration Safety and Innovation Act (FDASIA). It aligns with the 2003 Pediatric Research Equity Act (PREA), which was reauthorized under the FDASIA and requires sponsors looking to submit an application for a drug subject to PREA to submit an iPSP early in development.

The revised guidance, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans, updates draft guidance published in July 2013. It outlines the agency's current thoughts on iPSP requirements and incorporates feedback received on the 2013 guidance. The guidance is intended to address ongoing issues of inadequate testing of drugs in pediatric populations and insufficient pediatric use information in drug and biological product labeling.

The guidance addresses the following key areas:

1. **Who needs to submit an iPSP:** The guidance states that iPSPs are required for sponsors planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form or regimen, or new route of administration unless it has been granted orphan drug designation for the proposed indication. For biosimilars, those that have not been designated interchangeable are considered to have a new active ingredient under PREA.

2. **When an iPSP should be submitted:** Sponsors are required to submit the plan before the date it plans to submit the required assessments and no later than 60 days after the end-of-phase 2 meeting. Should no end-of-phase 2 meeting be held, sponsors should submit the plan as early as practicable and before starting any phase 3 or combined phase 2/3 trial. Sponsors should not submit marketing applications or supplements until an agreement has been reached on an iPSP. The FDA has 90 days to review an iPSP and respond to the sponsor.

3. **What should be included in an iPSP:** Plans should include an outline of planned pediatric studies, including study objectives and designs, age groups, endpoints, and statistical approach; any request for a deferral, partial waiver or waiver, as well as supporting information; and information specific to FDA regulations. The guidance provides an iPSP template for sponsors. It also states that iPSPs will be considered materially incomplete if a sponsor doesn't address all pediatric age groups and indications. If there isn't enough information for the agency to assess the plan, the FDA will consider the iPSP complete, even if it disagrees with it.

4. **What should be included in requested amendments to an iPSP:** Sponsors can request to amend an agreed iPSP at any time. These requests should include specifications of the desired changes, justification for those changes, a copy of the agreed iPSP with requested changes highlighted in red and a clean copy of the amended version. Amendments are not considered agreed until the agency sends a letter stating the amendments have been deemed acceptable.

5. **The relationship between an agreed iPSP and requirement to submit a pediatric study plan with a marketing application:** For NDAs, BLAs or supplemental applications subject to PREA, the FDA says sponsors need to include an iPSP in the application when a deferral of pediatric studies is requested. An agreed iPSP or amended agreed iPSP will serve as that plan and needs to be included in the application.

6. **What a non-agreed iPSP is:** An iPSP will be considered non-agreed when the FDA and sponsor are unable to come to terms on an IPSP by the end of the 210-day review period.

7. **Processes to reach an agreement with the FDA on a non-agreed iPSP:** To resolve nonagreement, the agency will work with sponsors to address the areas of disagreement. There is no statutory timeline for this process. Sponsors that disagree with the FDA's recommendations are allowed to request a meeting with the agency to discuss the issues.

FDA's annual medical device quality system data shows uptick in foreign inspections but no change in warning letters

The FDA's annual medical device quality system (QS) data shows a decline in overall QS inspections, despite an increase in foreign inspections as it bolsters enforcement in countries such as China. The number of warning letters remained flat.

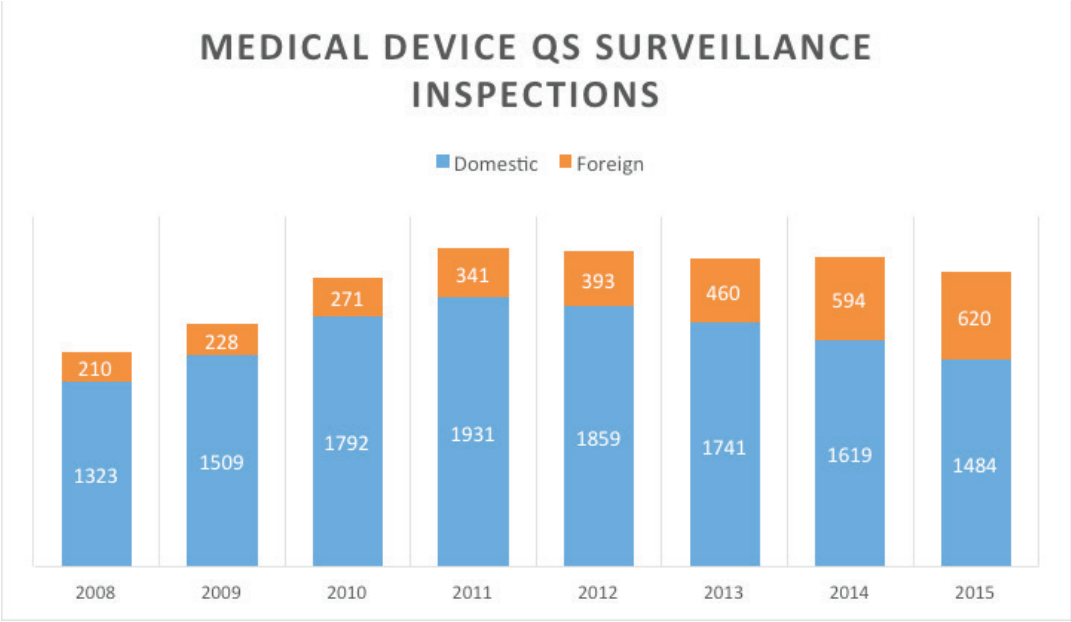
In support of its Transparency and Case for Quality Initiatives, the FDA's Center for Devices and Radiological Health published annual data on medical device inspections, inspectional observations and warning letter citations issued in 2015.

The QS data from Jan. 1, 2015, to Dec. 31, 2015, shows the FDA conducted 2,104 medical device inspections in 2015 – a slight decline from 2,213 in 2014. Notably, the share of domestic inspections fell (1,484 vs. 1,619), while there was an uptick in foreign inspections (620 vs. 594). The share of foreign inspections has been steadily increasing in recent years as the FDA bolsters its efforts. China continued to account for the most inspections, though inspections in the country declined (126 vs. 190) and other countries such as Germany (90 vs. 72), Japan (44 vs. 37) and Canada (42 vs. 24) saw increased inspections.

Nearly half (45 percent) of the inspections resulted in no official action, with only 11 percent resulting in official action and 42 percent calling for voluntary action. Markedly, the number of inspections resulting in official action increased from 9 percent in 2014 to 11 percent in 2015. China accounted for the most inspections yielding official action (19), followed by the U.K. (10), Germany (10) and Japan (7).

During the period, the FDA issued 924 Form 483s, which included 3,525 observations citing 21 QS regulation deficiencies. Of these, production and process controls (P&PC) tied corrective and preventive action (CAPA) for the largest share, at 32 percent each. The top CAPA observations related to corrective and preventive action (34 percent), complaint files (29 percent), and nonconforming products (14 percent). The top P&PC observations related to process validation (16 percent), purchasing controls (12 percent), and inspection, measuring and test equipment (7 percent).

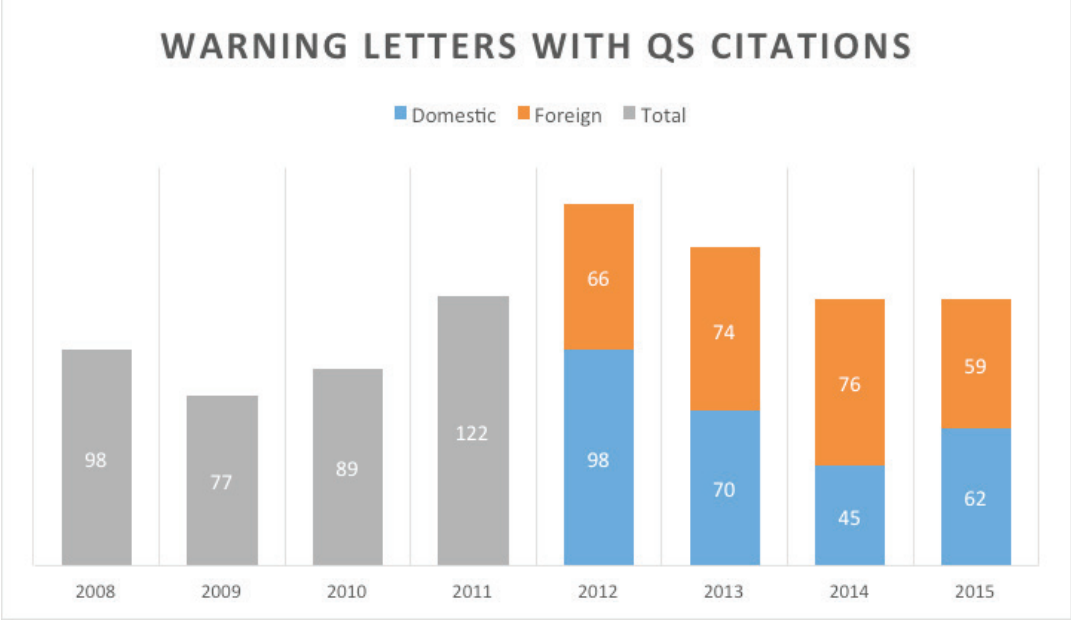
Throughout the year, the agency also issued 121 warning letters – the same number issued in 2014 and down from 144 in 2013 and 164 in 2012. These



Source: Re-created using FDA data

cited 21 QS regulation deficiencies. In line with the trend observed for inspection, the share of warning letters issued to foreign companies increased, accounting for 59 letters in 2015, versus 45 in 2014.

Of these, CAPA accounted for 220 citations and P&PC accounted for 227 citations. Citations related to similar issues observed in Form 483s.



Source: Re-created using FDA data

FDA kicks off initiative to standardize clinical trial protocols with template for NIH-backed studies

The FDA teamed up with the National Institutes of Health (NIH) to create a draft protocol template to increase the efficacy of clinical trial protocol reviews for NIH-backed studies. The FDA is planning to collaborate on similar standardization efforts beyond NIH-backed studies.

In its strategic plan for 2016-2020, the NIH committed to promoting approaches to bolster the speed and efficiency of clinical trials. As part of that commitment, the NIH, in collaboration with the FDA, published a draft clinical trial protocol template for NIH-backed studies.

The template, developed by the NIH-FDA Joint Leadership Council, is designed for phase 2 and phase 3 clinical trials supporting new drug applications or investigational device exemptions. The template is designed to help investigators establish consistent protocols that contain all the required information to ensure efficient and timely reviews. It supplements guidance on the content that needs to be included in clinical trial protocols to protect patients and ensure data quality.

Peter Marks, director of the Center for Biologics Evaluation and Research, said standardization is needed because the majority (85 percent) have participated in only one clinical trial in their careers and may lack experience in protocol development. He said the template will help fill a gap left by international standards such as the ICH E6 Good Clinical Practice guidance and ISO Good Clinical Practice guidance. He said the FDA is hoping to collaborate on similar efforts to ensure consistency in medical product development.

The NIH and FDA are looking for feedback on the utility of the template, as well as comments on the accompanying instructional guide. In particular, they are soliciting feedback from investigators, sponsors, institutional review board members and stakeholders interested in the development of clinical trial protocols.

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.