FDA Regulatory and Compliance Monthly Recap

OCTOBER 2016

KEY FINDINGS

FDA sends warning letters to two N.J. companies for insufficient PADE reporting

The warning letters raise issues with the standard operating procedures in place to monitor, receive, evaluate and report postmarketing adverse drug experiences, submitting adverse drugs reports on time and in the proper format. The warning letters following Form 483s for which the FDA determined the companies' response was inadequate.

The FDA issued warning letters to two separate companies for violating Postmarketing Adverse Drug Experience (PADE) reporting requirements under section 505(k) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations 314.80 and 314.98, including failures to submit Periodic Adverse Drug Experience Reports (PADERs).

Elite Pharmaceuticals, a New Jersey based company, was issued a warning letter for violations uncovered during an inspection conducted between January and February 2016. The FDA found the company's standard operating procedures (SOPs) failed to outline how the company monitors, receives and assesses postmarket adverse drug experiences (ADEs). The FDA took issue with how the SOPs describe certain aspects of adverse event reporting, including how the company identifies the existence of ADEs and how it handles ADE information provided from business partners. The SOPs also failed to describe how Elite assesses ADEs for seriousness, expectedness and reportability to regulatory authorities. They also didn't describe how Elite reports ADEs, including PADERs, in the right format.

Inspectors found that Elite had failed to investigate at least half of the 15-day Alert Reports it had received. Although the drugmaker had an agreement with a contractor for such activity, the agency says it retains the onus of ensuring ADEs are adequately investigated and that follow-up information is submitted to the agency within 15 days. Inspectors also found that nearly half of the 15-day Alert Reports were submitted late.

Although Elite responded to an initial Form 483, the FDA determined that its response was insufficient, as it failed to address the root causes of the issues and failed to outline how the company will monitor and review its actions to make sure the corrective measures are effective and the issues do not recur. The response also failed to include evidence of the corrective and preventive actions, including proper SOPs.

A second New Jersey-based company, Navtina, was chided for similar issues following an investigation in May 2016. Inspectors identified similar issues with SOPs for monitoring and reporting ADEs, including a failure to describe how the company prepares and reports post marketing safety information, individual case reports and PADERs in electronic format and how it investigates ADEs for missing data elements. Navinta staff provided FDA inspectors with a written agreement with a marketing partner regarding reporting, but the FDA found the agreement failed to ensure Navinta would receive all ADEs, which are required to be submitted to the agency in PADERs. The FDA found Navinta has also failed to submit PADERs for six approved abbreviated new drug applications.

Navinta sent the issue a written response to an initial Form 483, but the agency deemed it to be inadequate as newly established SOPs failed to describe important aspects of ADE reporting, including how the company would document and investigate ADEs that are both serious and unexpected. The response also included an SOP on PADER preparation from a third-party service provider, but the FDA said SOPs from other companies don't compensate for deficiencies in and omissions from Navinta's SOPs.

FDA issues final rule to update definition, regulatory requirements for custom medical devices

The final rule functions as a technical amendment to update the current existing custom device exemption to align the regulations with the FD&C Act. It includes several requirements that need to be met in order for a device to be considered a custom device, as well as certain limitations. The rule takes effect immediately.

The FDA issued a final rule amending its regulations on custom devices to include new statutory requirements for custom device exemption under the Federal Food, Drug, and Cosmetic Act, as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), and to introduce new concepts and procedures for the products. As with the original custom device exemption, devices that meet the qualification of a custom device are exempt from 510(k) and Premarket Approval (PMA) submissions. Due to amendments to section 520(b) of the FD&C Act, however, the current regulatory definition for a custom device doesn't align with the statute. The final rule therefore updates the regulations by adjusting the definition of a custom device.

Regulatory requirement to be considered a custom device include:

- Created or adapted to comply with an order from, or to meet the particular needs of, a physician, dentist or other specially qualified person;
- Not generally available in the U.S. in finished form through labeling or advertising by the manufacturer, importer or distributor;
- Designed to treat a unique pathology or physiological condition for which no other device available in the U.S. is intended to treated;
- Made for an individual patient named in the order of a physician, dentist or other specially qualified person;
- Assembled from parts or manufactured and finished on a case-by-case basis to meet the particular needs of individuals, physicians or dentists; and
- May have common, standardized design characteristics, compositions and manufacturing processes as commercially distributed products.

The provisions for custom device exemption include three limitations:

1. The device is intended to treat a condition rare enough that conducting a clinical study on the device would be unreasonable;

2. The production of the device is limited to no more than five units each year for a particular device type;

3. Manufacturers need to submit an annual report to the FDA on the custom devices it supplied.

The FDA issued the final rule without notice and comment, as it represents only a technical amendment to correct the implementing regulation to restate the statute and simply incorporate requirements of the FC&C Act. Guidance issued in 2014, Custom Device Exemption, describes the FDA's interpretation of devices that qualify for custom device exemption and outlines what information should be submitted in the mandated annual reports. The amendments are effective immediately.

FDA publishes draft harmonized IMDRF guidance on software as a medical device

The guidance supplements finalized IMDRF guidance on risk categorization for software as a medical device and provides input on the clinical assessment and principles to establish the safety, efficacy and performance of such software. The FDA is seeking input before submitting a final version to the IMDRF management committee in February.

The FDA published draft guidance, developed by the International Medical Device Regulatory Forum, outlining the principles of clinical assessments for software as a medical device (SaMD), defined as software designed to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device. The guidance provides recommendations to help manufacturers establish how a SaMD meets clinical needs by demonstrating analytical validity and, when needed, the scientific validity and clinical performance. The guidance outlines the applicable clinical evaluation methods and processes to study SaMDs, as well as the required level of evidence for different categories of SaMDs.

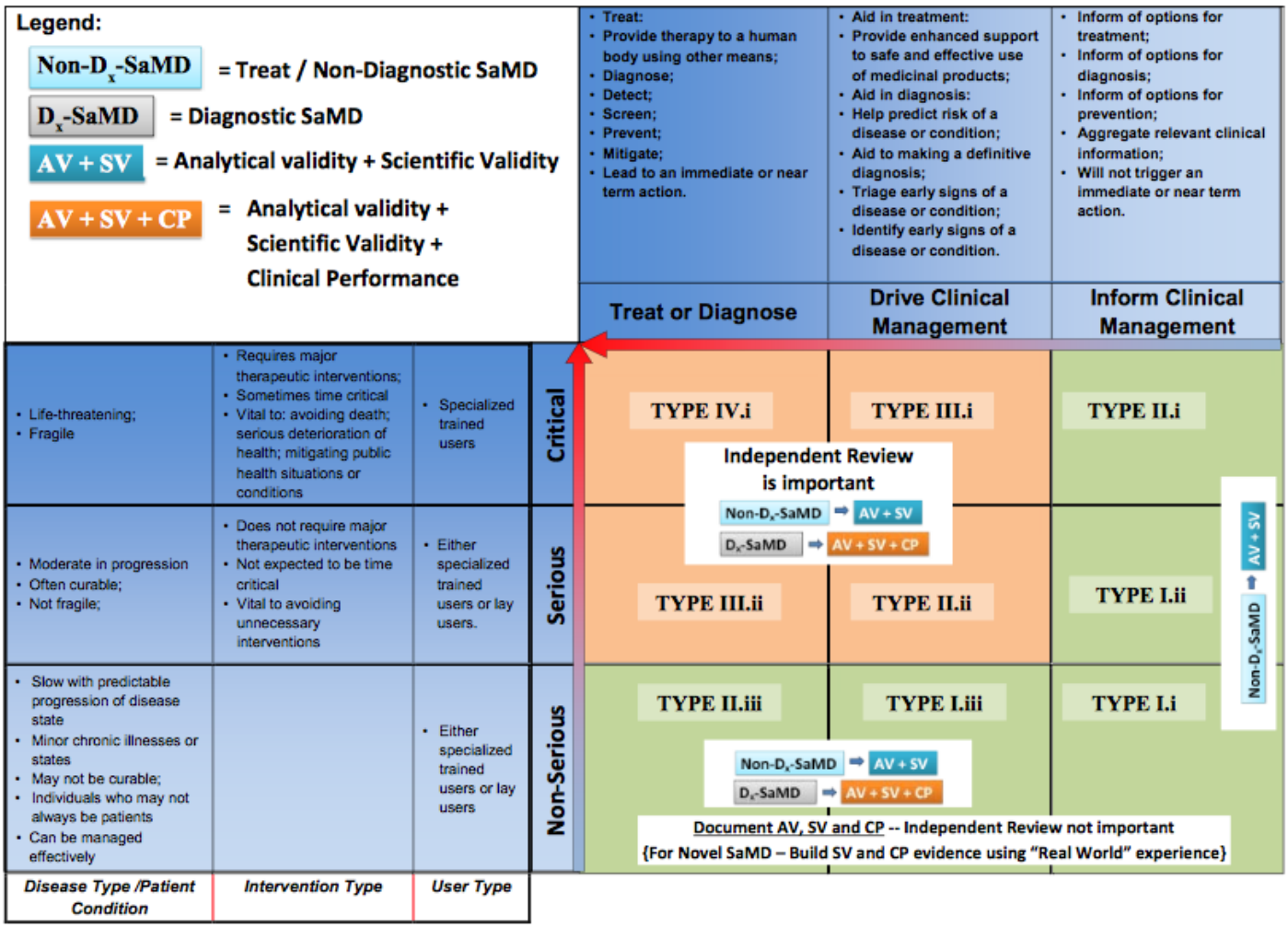
To demonstrate the SaMD's clinical validity for its intended use and indications, a systematically planned clinical assessment approach that yields sufficient evidence is required. Evaluations of SaMDs should examine how well the information provided by the product meets the clinical needs in the healthcare situation and condition it is to be used in. The scope of the clinical evaluation depends on the intended use established by the manufactures through product claims and the SaMD definition statement. SaMDS are categorized into four categories based on the significance of the information provide to healthcare decision making and the impact of the information provided to the healthcare situation or condition. Category I and II are considered lower risk. Certain categories may require independent review of the evidence to provide confidence in the software's clinical validity.

The guidance defines analytical validity as the SaMDs ability to provide accurate output for a given input, while scientific validity is defined as the SaMDs ability to provide an output associated to the intended clinical condition or physiological state. The overall clinical validity is expressed differently depending on the type of device:

- **For those intended to treat a disease of condition:** Evidence of effectiveness of the output to the treatment or prevention;

- **For non-diagnostic software:** Evidence of scientific validity that demonstrates usefulness of the output in clinical care;

Summary of SaMD Clinical Evaluation recommendation



Graphic Source: Software As A Medical Device (SaMS): Clinical Evaluation - FDA

- **For diagnostic software:** Evidence of scientific validity and clinical performance.

Analytical validity is always required for a SaMD and includes measures to demonstrate:

- **Accuracy:** Degree of closeness of measurements of a quantity to the quantity's true value;
- **Precision:** Degree to which repeated measurements under different conditions yield the same results; and
- **Analytical sensitivity:** Degree to which the algorithm's output is impacted by the input data.

Scientific validity is generally demonstrated through studies objectively showing the clinical association of the SaMD's use of inputs, algorithm and outputs compared to a recognized reference standard, another SaMD or medical device, a well-established method, the current clinical practice or a composite reference standard. Scientific validity also explores whether the association of the product's intended use to a clinical condition is well established, based on existing research. After validity is assessed, a SaMD can be divided into two general categories:

- **Well-known association:** The product has an output with a well-known association to identified clinical guidelines, reference materials and clinical studies.

- **Novel association:** Products involve new inputs, algorithms or outputs, new intended target populations or a new intended use and are not know well-known.

Clinical performance is the SaMD's ability to provide output that yields a clinically meaningful association to the target use. Clinically meaningful is defines as a having a positive impact on the health of an individual through measurable, patient-relevant clinical outcomes. Clinical performance can be established using real world data in instances in which data is helpful in identifying less common use situations. The guidance recommends manufacturers take advance of the SaMD's unique ability to capture real world data to form an agile clinical evidence gather approach to generate clinical evidence, which could possible result in modification of the impact category.

CBER strategic plan for FY 2017–2019 outlines plan to enhance regulatory decision-making, guidance

The strategic plan includes initiatives to improve regulatory guidance and standards to reflect new technologies and innovations, while enhancing international collaboration and regulatory harmonization. The plan includes objectives to meet the FDA's enhanced authority under FDASIA to monitor drug safety.

The FDA's Center for Biologics Evaluation and Research (CBER) published its interim strategic plan for FY 2017–2019, building on six overarching goals outlined in the previous strategic plan published four years ago. The plan outlines the center's plans for working toward the goals in light of internal and external changes since the previous strategic plan was published, including new legislative mandates from the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). Several strategies required adjustment from the previous plan to reflect these new legislative mandates and the center's enhanced role in addressing global health needs, as well as innovations in regulatory science and technology. The plan also reflects enhanced opportunities for collaboration and partnership following the relocation and consolidation of CBER's eight offices and laboratories to FDA headquarters.

One of the goals is to improve global public health via international collaboration and by addressing the unique regulatory pathways and challenges associated with new paradigms emerging to address unmet product development needs, such as nongovernmental organizations and product development partnerships. To enhance its role in global public health, CBER will not only promote research and information sharing, but will work towards regulatory harmonization using two primary strategies: engagement with other regulatory agencies on topics such as post-marketing product safety signals; and recommending strategic means to achieve greater harmonization in the interpretation and application of ICH guidelines. The CBER will also engage with international scientific efforts and standards-setting bodies, National Institute for Biological Standards and Control, to establish reference materials and standards for biologics.

A second goal is to leverage scientific and technological advances in the development of biological products, including in the development of technical standards and criteria to address issues related to biosimilars. The CBER plans to integrate advances such as innovative clinical trial designs and technologies such as genomics and proteomics into its regulatory oversight. To achieve these goals, the CBER will collaborate with other FDA centers, the NIH and industry, while incorporating new knowledge into new regulatory guidance.

The CBER is also planning to advance regulatory science research and updates its policies to take into consider new assessment tools and products. The center will continue to update standards, guidance and policy for biosimilars in collaboration with CDER,

while developing collaborative programs to assess new approaches to facilitate the development of novel therapies. It will also augment the biological drug compliance program by integrating inspection of new therapies and updating the review training program to include new technology for inspectors, compliance officers and reviewers.

In a step to meet its goal of ensuring the safety of biological products, the CBER will use the authority granted under FDASIA to monitor drug shortage and reduce the risk of counterfeit products entering the market by expanding the use of healthcare data to monitor licensed products. For safety monitoring, the CBER will expand the use of large databases from providers, insurers and other partners to generate patient use and health outcomes data, while building capabilities to use real world data to determine product safety and efficacy both pre- and post-market. It will also use new tools such as bioinformatics and new models of statistical analysis to generate data and methods to assess safety signals.

To enhance regulatory science and research, the center will, on advisement from the Regulatory Science Council, undertake research to enhance the existing knowledge of biologics to form the basis of improved guidance and more informatized regulatory decisions. It will also explore new approaches for clinical development and evaluation, including new uses of healthcare data and improved benefit-risk assessment of regulated products. The CBER will take a proactive approach to emerging regulatory needs, with for-ward looking priority setting and ongoing reviews to ensure regulatory impact and accountability to stakeholders.

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.