FDA Regulatory and Compliance Monthly Recap

MAY 2016

KEY FINDINGS

FDA draft guidance provides recommendations on use of electronic health record data in clinical trials

The draft guidance provides recommendations on deciding whether and how to use EHRs as a source of data in clinical studies and using EHRs that are interoperable with electronic systems supporting clinical studies, while ensuring EHR data quality and integrity and making certain that data used meets the FDA's inspection, record-keeping and record-retention requirements.

The FDA published draft guidance designed to help sponsors, clinical investigators, contract research organizations, institutional review boards and other interested parties on the use of electronic health records (EHRs) in agency-regulated clinical investigations. Although the FDA doesn't intend to evaluate compliance of EHRs, its acceptance of data from clinical studies for decision making purposes requires that it's able to verify the quality and integrity of data. EHRs generally aren't under the control of FDA-regulated entities, as they often belong to health care organizations and institutions, but it is the responsibility of sponsors to examine the validity, reliability and integrity of data used to support a marketing application for a medical product.

The guidance therefore outlines the agency's expectations when EHRs are used as a source of data in clinical studies to facilitate the use of such data and promote the interoperability of EHRs and electronic systems supporting clinical trials. The guidance applies to the use of EHR data in clinical studies of human drugs and biological products, as well as medical devices and combination products, including foreign clinical trials not conducted under an investigational new drug application or investigational device exemption. It does not apply to the use of EHR data in Postmarketing observational pharmacoepidemiologic studies evaluating the risk associated with a drug exposure to test prespecified hypotheses, or use of EHR data as a recruitment tool for clinical investigations.

When using EHRs as a data source, the FDA suggests sponsors use source data that are attributable, legible, contemporaneous, original and accurate (ALCOA) and use EHRs that are certified by the Office of the National Coordinator for Health Information Technology (ONC) Health IT Certification Program. It states that this would give the agency confidence that the data is reliable and that the technical components of privacy and security protection have been met. However, the agency acknowledges that EHRs not certified by ONC can provide adequate data to inform regulatory decisions, so long as proper controls are in place to ensure confidentiality, integrity and reliability of the data. It outlines the security safeguards EHRs should meet, such as audit trails and identifiable authors.

The draft guidance also suggests that sponsors incorporate into trial protocols or data management plans information about the intended use of the EHR during the study, as well as a diagram of the electronic data flow between the EHR and the sponsors' electronic system. Additionally, sponsors should assess the extracted data for consistency and completeness with the source data derived from the EHR and should ensure software updates to the electronic system or the EHR don't affect the reliability and integrity of the EHR data. They must also make sure the informed consent for clinical trials in which EHRs will be used includes a statement defining the extent to which confidentiality of records identifying trial subjects will be maintained and clearly identifying all entities that may gain access to the EHR.

The agency also calls on sponsors to ensure that there are proper methods in place to monitor, track and document changes made to information in the EHR related to the conduct of the clinical investigation. The FDA must also be given access to records so it can inspect and copy all records related to the clinical study.

FDA releases 'leapfrog' draft guidance on 3D printed medical devices

The FDA published draft guidance providing recommendations for medical devices developed using additive manufacturing, or 3D printing. The long-awaited guidance describes the agency's initial thinking on the emerging technology and provides technical considerations and guidance on characterizing and validating 3D printed medical devices.

The FDA released draft guidance for manufacturers and FDA staff titled "Technical Considerations for Additive Manufactured Devices." The guidance outlines technical considerations associated with additive manufacturing (AM), or 3D printing, processes, and recommendations surrounding the testing and characterization of devices that include at least one AM fabrication step. Defined as a "leapfrog" document, the guidance is intended to highlight the FDA's initial thoughts regarding the emerging technology. Although the agency acknowledges that 3D printing provides benefits such as allowing manufacturers to create devices personalized based on a patient's own medical imaging, it notes that the unique aspects of the 3D printing process, coupled with the relative lack of medical device history of devices manufactured using this process, pose challenges to assessing and validating these devices.

The guidance is based on a public workshop in which medical device manufacturers, 3D printing companies and academics discussed technical considerations such as materials, design thinking and post-printing validation; printing characteristics; and assessments and biological considerations of final devices. It outlines what technical considerations manufacturers should address as part of Quality System (QS) requirements for 3D printed devices, but does not provide a comprehensive list of all regulatory QS requirements. It states that manufacturers of Class II and Class III devices and select Class I devices must establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met.

The draft guidance only addresses manufacturing considerations specific to the 3D printing process, though it's anticipated that 3D printed devices will generally follow the same requirements as those applicable to non-3D printed devices of the same type. The guidance doesn't address the use or incorporation of biological, cellular or tissue-based products in AM, which may necessitate additional regulatory and manufacturing process considerations. It outlines technical aspects of a 3D printed device that should be considered through the phases of development, production, process validation and final finished device testing.

It also describes the type of information that should be provided in premarket notification submissions, premarket approval (PMA) applications, humanitarian device exemption (HDE) applications, de novo requests and investigational device exemption applications for a 3D printed device. The gudiance indicates that 3D printed devices should, in general, be tested for the same performance characteristics as non-3D printed devices. Though the type and amount of data needed to support substantial equivalence determination or approval will vary from device to device, it suggests that applications in general include a device description, mechanical testing, dimensional measurements for each 3D printed measurement component and characterization of the materials used during the 3D printing process. The FDA notes that the nature of 3D manufacturing is expected to increase the difficulty of cleaning and sterilization, and suggests manufacturers establish and describe how the cleaning process ensures proper removal of residual manufacturing material. It also recommends that patient-matched 3D printed devices provide additional labeling and include information such as a patient identifier, details classifying use, and information on the final design or version used to produce the device.

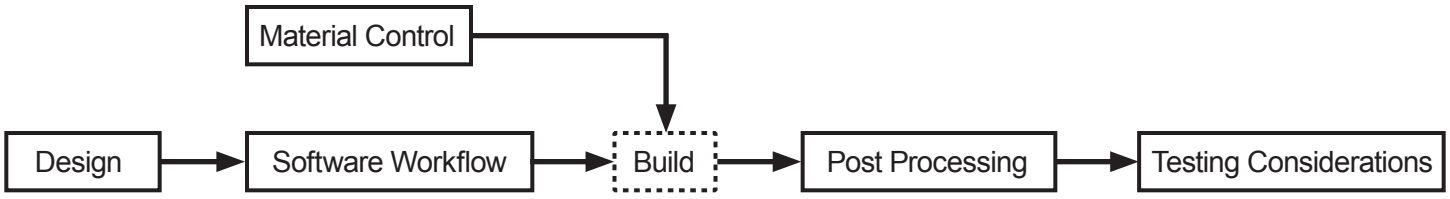

Figure 1: Flow chart of the additive manufacturing process

Graphic Source: Technical Considerations for Additive Manufactured Devices – FDA

FDA sends warning letter to Indian API manufacturer Polydrug Laboratories for quality issues, incomplete compliance records

The FDA sent a warning letter to Polydrug Laboratories calling out significant issues with quality and record keeping. Polydrug joins a growing list of Indian API manufacturers called out by the agency for data integrity issues.

The FDA sent a warning letter on April 14, 2016, to India-based Polydrug Laboratories after an inspection at its Mumbai drug manufacturing facilities revealed significant violations of current good manufacturing practice (CGMP) for the development of active pharmaceutical ingredients (APIs), making its drugs adulterated. The letter follows an FDA ban in September 2015 preventing the company's products from entering the U.S.

The warning letter cites Polydrug for failing to properly record and investigate customer complaints related to quality, noting that the inspector found a ripped sheet of paper titled "Product Quality Complaints" on the floor and discovered that only two of 17 complaints on

the sheet were recorded in the official complaint log. Complaints that went uninvestigated alleged APIs were either subpotent or contained filth, including insects and dirt. The FDA notes that Polydrug's subpar compliant practices and inability to effectively mitigate product quality defects are indicative of major lapses in the company's quality system. The letter also calls out the manufacturer for failing to review and investigate production deviations, citing a torn page from a batch production record for a lot of API in the garbage and discrepancies between the page and the complete batch production record assigned to the official record for that lot. Polydrug failed to investigate the issue or its possible effect on drug quality prior to releasing the lot.

Polydrug also failed to implement adequate controls in its computerized system to prevent unauthorized access to or changes to data, the letter states. During an inspection of one of the computers, a manager showed the inspector how results on already finished certificates of analysis (CoA), which document whether a drug meets specifications, could be changed after formal quality unit approval. The letter also calls out Polydrug for failing to use appropriate test procedures to make sure APIs align with established standards of quality or purity, citing multiple "invalid" moisture content results, which indicate a quality problem or inadequate moisture content test method.

Polydrug had previously responded to FDA concerns, but the agency determined that its response was inadequate, particularly given its failure to retrospectively investigate complaints and data issues. The company reportedly said this warning letter was published after Polydrug had asked for a re-inspection. The FDA suggests Polydrug engage with a third-party consultant having CGMP expertise, and requests that the API manufacturer investigate the extent of inaccuracies in data, conduct a risk assessment of potential effects of the observed failures and provide a management strategy that outlines a corrective action and prevention action.

FDA finalizes guidance on 522 orders for postmarket device surveillance

The FDA finalized guidance initially released in August 2011 describing its interpretation of the law governing postmarket surveillance of certain Class II and III medical devices. The guidance is designed to help manufacturers effectively respond to 522 orders for postmarket surveillance and describes what needs to be included in postmarket surveillance submissions.

Nearly five years after releasing the draft version, the FDA has finalized guidance on postmarket surveillance for certain Class II or Class III medical devices. The finalized guidance provides an overview of Section 522, along with information on how to fulfill 522 requirements and recommendations on the format, content and review of postmarket surveillance plan submissions.

The FDA has the authority under Section 522 of the Federal Food, Drug, and Cosmetic Act to require manufacturers of Class II and III devices to conduct postmarket surveillance. It also has authority under Section 212 of the Food and Drug Modernization Act (FDAMA) to mandate a prospective surveillance period of up to 36 months. The agency is authorized to request surveillance for Class II and III devices that are any of the following:

- Reasonably likely to have negative health effects should they fail.
- Expected to have significant use in pediatric populations.
- Designed to be implanted in the human body for more than one year.
- Intended to be life-sustaining or life-supporting devices used outside a user facility.

It can issue a postmarket surveillance order at any time during device approval or clearance, or anytime thereafter. The agency may identify device issues

that require postmarket surveillance at any time throughout a device life cycle, through means such as adverse event reports, post-approval data and reports from other government bodies or scientific data. If the statutory requirements for a Section 522 order have been met, the agency will establish a cross-center team comprising epidemiologists, clinicians or other experts to assess the issue further in order to decide whether an order should be issued.

Each 522 order will include a postmarket surveillance number for manufacturers to cite when submitting a proposed postmarket surveillance plan, the guidance states. Plans must be submitted within 30 days of receiving the order, with surveillance starting no later than 15 months after the issuance of the 522 order. A postmarket surveillance submission should include general and specific content such a description of the device, its regulatory history and indications of use. It should address the plan's objectives and hypotheses, as well as surveillance design, sample size calculation and endpoints. It should also describe follow-up plans, data collection procedures and time lines. The FDA will assess the proposed plan to determine whether it is complete and will result in the collection of data that will effectively answer the surveillance questions. If a manufacturer would like to change an approved plan such that it would affect the nature or validity of data collected, it first needs to obtain FDA approval in writing.

The guidance calls on manufacturers to submit an interim report every six months for the first two years of the surveillance and every year thereafter. These interim reports will be assessed by the FDA based on completeness of the report content, the anticipated versus actual status of the study and adherence to agreed-upon methodology. Manufacturers must also submit a final report of a terminated 522 order no later than three months after study completion. These reports should describe the methodology and results and explain how it fulfills the 522 order, the guidance recommends.

Agency epidemiologists will review the report to determine whether it meets the requirements of the 522 order, with a goal of responding within 90 days. If the findings spur new questions, additional actions may be called for, such as labeling changes, a new order for postmarket surveillance or administrative or regulatory actions.

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.