The Focal Point: Advocacy & Legislative Update
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Government Shutdown Impact on CBER

During the government shutdown, the Food and Drug Administration (FDA) will continue vital activities that are critical to ensuring public health and safety in the United States, consistent with the law and to support activities funded by carryover user fee (BSUFA, PDUFA, MDUFA & GDUFA) balances.

FDA is only able to perform user fee-funded activities using carryover user fee balances and is unable to accept new user fees assessed in the current fiscal year until new appropriations or a Continuing Resolution is passed.

For Investigational New Drug Applications (INDs) covered by PDUFA carryover, CBER will continue review of existing INDs and accept new INDs, amendments, annual reports, etc. For INDs not covered by PDUFA user fees, FDA will suspend review of existing INDs and associated submissions, and will not review any newly submitted INDs, except for emergency INDs and new IND amendments that relate to the safety of human subjects.

Both the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) will also stop performing certain non-user fee funded activities during the shutdown. These include non-emergency work on whole blood, blood components for transfusion, allergenic extracts and human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated solely under Section 361 of the *Public Health Service Act*.

FDA Finalizes Guidance on Changes to Device Manufacturing Sites

The FDA has released final guidance on determining requirements for changes to medical device manufacturing sites.

The guidance explains the following:

1. What constitutes a manufacturing site change (including a change to the processing, packaging, or sterilization site) of your legally marketed PMA-approved device;
2. What documentation you should submit in a PMA supplement for a site change; and
3. The general factors FDA intends to consider when determining whether to conduct an establishment inspection prior to approval of a site change supplement.

Requirements include a 180-day premarket approval application supplement for use of a different site that has an impact to a product's safety or effectiveness and either a PMA annual report or a 30-day notice for process changes that are not directly tied to the facility change.

FDA Finalizes Guidance on Breakthrough Devices

The FDA finalized guidance detailing its breakthrough devices program, which finalizes the draft version released in October 2017 and includes clarifications to address comments received during the public consultation.

The breakthrough devices program was created by the *21st Century Cures Act* and supersedes and combines several of the agency's earlier programs to speed access to promising new devices that treat or diagnose "life-threatening or irreversibly debilitating diseases or conditions."

Breakthrough designation can be applied to devices subject to FDA's premarket approval (PMA), *de novo* and 510(k) pathways and provides guaranteed priority review status for designated devices. However, unlike FDA's priority review program for drugs, devices granted priority review are placed at the top of the review queue and are assigned additional review resources but are not guaranteed a faster review.

The final guidance clarifies that devices granted designation under the agency's previous expedited access pathway (EAP) are considered to be part of the breakthrough devices program.

FDA Updates Final Guidance for PMAs and Device BLAs

The FDA made minor revisions to a 2017 final guidance on user fees and refunds for premarket approval applications and device biologics license applications, incorporating information on device biologics license applications from a superseded guidance.

The purpose of this guidance document is to identify: (1) the types of PMAs and BLAs subject to device user fees; (2) exceptions to user fees; and (3) the actions that may result in refunds of user fees that have been paid.

FDA's Regenerative Medicine Framework and Enforcement Discretion Period for HCT/Ps

FDA notified producers of regenerative medicine products, including stem cell products, that FDA is currently applying a risk-based approach to enforcement. In order to lawfully market an HCT/P that is also a biological product and a drug, a valid biologics license must be in effect.

Such licenses are issued only after a showing of safety and efficacy for the product's intended use. While in the development stage, such products intended for clinical use in humans, generally require an investigational new drug application (IND).

FDA also made clear that the 36-month period during which the agency plans to exercise enforcement discretion will end in November 2020. You can read the letter here.

FDA also released a warning letter to Genetech of San Diego for processing umbilical cord blood into unapproved human cellular products to treat a variety of orthopedic conditions. These products were then distributed by Liveyon, LLC.

The warning letter comes as FDA and the Centers for Disease Control and Prevention have received numerous reports of safety issues including those involving microbial contamination and are aware of 12 patients who received Genetech products and subsequently became ill due to bloodstream and joint infections caused by a number of Gram negative bacteria.

FDA investigators also identified significant deviations from current good manufacturing practice (CGMP) and current good tissue practice (CGTP), including deficient donor eligibility practices; unvalidated manufacturing processes; uncontrolled environment; lack of control over the components used in production; and a lack of defined areas or a control system to prevent contamination and mix-ups.

FDA Finalizes Rule to Simplify Medical Device Classification Procedures

The FDA issued a final rule that brings its medical device classification requirements in line with current medical device regulations, so that they are consistent with the provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA). The rule entitled Medical Device Classification Procedures: Incorporating FDA Safety and Innovation Act Procedures, will be effective starting March 17, 2019.

The rule provides for classification of devices in the lowest regulatory class consistent with the public health and the statutory scheme for device regulation. The rule takes advantage of the authority FDA received through 2012 amendments to the *FD&C Act* for changing device classification by administrative order rather than by rulemaking. This makes it easier for the agency to make changes on a classification based on new or changing information to better reflect the risk associated with the use of a device.

The final rule also eliminates some paperwork filing requirements.

Medical Device Classification Procedures: Incorporating Food and Drug Administration Safety and Innovation Act Procedures

FDA Finalizes Guidance on Data Integrity and Compliance with Drug CGMP

FDA finalized its questions and answers guidance on complying with data integrity requirements under current good manufacturing practice (CGMP) for drugs and biologics. The guidance has been developed in response to an increase in findings of data integrity lapses in recent inspections that have resulted in warning letters, import alerts and consent decrees.

FDA expects that all data be reliable and accurate. CGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues. Firms should implement meaningful and effective strategies to manage their data integrity risks.

FDA says the guidance was developed in response to an increase in data integrity violations observed during inspections that have resulted in warning letters, import alerts and consent decrees in recent years.

EMA Releases Final Guideline on Clinical Trial Master File

The EMA's Good Clinical Practice (GCP) Inspectors Working Group has adopted a final revised guideline on the content, management and archiving of the clinical trial master file (TMF). The essential documents and data records stored in the TMF enable the operational staff as well as monitors, auditors and inspectors to evaluate compliance with the protocol, the trial's safe conduct and the quality of the data obtained. The guideline is expected to come into effect in six months.

The guidance is meant to help sponsors comply with European legislation (Directive 2001/20/EC and Directive 2005/28/EC), as well as ICH E6 Good Clinical Practice (GCP). The guideline spells out what should be considered essential documents, including statistics and data management documentation, superseded documents, and correspondence.

In terms of security and control of the TMF, the guideline also explains how access to the TMF should be managed, how storage areas should be appropriate and how electronic TMFs should ensure that the loss, alteration or corruption of data and documents does not occur.

The TMF should provide for document identification, version history, search and retrieval. The ICH GCP guideline requires that "copies in the eTMF that irreversibly replace originals should be certified copies of the original." The TMF shall be archived in a way that ensures that it is readily available and directly accessible upon request, to the competent authorities of the Member States.

FDA Names Amy Abernethy As Principal Deputy Commissioner

The FDA announced that Dr. Amy Abernethy will replace Rachel Sherman as Principal Deputy commissioner of Food and Drugs – the highest position at the agency that is not a political appointee.

Abernethy is currently the chief medical officer, chief scientific officer and senior vice president of oncology at Flatiron Health, which is a unit of Roche. Prior to that she was a professor of medicine at Duke University School of Medicine and ran the Center for Learning Health Care in the Duke Clinical Research Institute and Duke Cancer Care Research Program in the Duke Cancer Institute.

She will replace Rachel Sherman, who oversees clinical, scientific, regulatory, and operational medical programs and initiatives across the agency. Sherman is retiring after 30 years of service at FDA.

FDA Issues Draft Guidance on Patient Experience Data in Effort to Advance Drug Development

FDA issued a draft guidance entitled "Developing and Submitting Proposed Draft Guidance Relating to Patient Experience Data." The draft guidance, which is in a Q&A format, provides information on sampling methods, analysis, and dissemination of patient experience data that will be used to inform the development and evaluation of drugs for consideration by the FDA.

Patient experience data could help enhance regulators' understanding of the course of disease over time, identifying demographic, genetic, environmental, and other factors that correlate with its development and outcomes in the absence of treatment. Additionally, this information could be used to inform clinical trial designs and future research.

CMS Issues Correction to the 2019 ASC Final Rule

CMS issued a technical correction to the 2019 Hospital Outpatient and ASC Final Rule and corrected several typos. CMS had made an error in calculating the ASC weight scaler which is now recalculated to be 0.8800, when it was previously 0.8792. In addition, CMS also made errors in calculating the wage index budget neutrality factor and has corrected it to be 1.000, when it was previously 1.004. These corrections result in a change to the 2019 ASC conversion factor to $46.532 for ASCs meeting quality reporting requirements and $45.621 for ASCs not meeting quality reporting requirements.