The Focal Point: Advocacy & Legislative Update

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FDA Drafts Guidance on Bridging Data for Combination Product Applications

The FDA issued draft guidance explaining how drug-device and biologic-device combination product sponsors can bridge data from earlier stages of development or other development programs to support an application.

The guidance addresses two scenarios where information may be bridged: when the device constituent of the product is different but the drug or biological product constituent is the same, and when the drug or biological product constituent is different but the device constituent is the same.

FDA defines bridging as "the process of establishing the scientific relevance of information developed in an earlier phase of the development program or another development program to support the combination product for which an application is seeking approval."

According to FDA, once a sponsor has bridged information about a combination product, it may be able to "leverage that information to streamline the development program." For certain types of applications, the use of information from another development program may require that the applicant own the information or have the rights to reference that information.

FDA specifies that the guidance only applies to combination products subject to an investigational new drug (IND) application, new drug application (NDA) or biologics license application (BLA) and does not extend to products covered in a final or tentative over the counter (OTC) monograph.

FDA Requests Comments on the Burden of Deviation Reporting

FDA is requesting comments on the collection of information extension that has been submitted to the Office of Management and Budget (OMB) for Reporting of Biological Product Deviations and Human Cells, Tissues, and Cellular and Tissue-Based Product (HCT/P) Deviations in Manufacturing. The deadline to submit comments is January 27.

FDA estimates that the average time to complete a deviation report is 2 hours, which includes a minimal one-time burden to create a user account for those reports submitted electronically. The availability of the standardized report form, Form FDA 3486, and the ability to submit this report electronically to CBER further streamlines the report submission process.

CBER has developed a Web-based addendum to Form FDA 3486 (Form FDA 3486A) to provide additional information when a BPD report has been reviewed by FDA and evaluated as a possible recall. This information is requested by CBER through email notification to the submitter of the BPD report. The additional information requested includes information not contained in the Form FDA 3486 such as: (1) Distribution pattern; (2) method of consignee notification; (3) consignee(s) of products for further manufacture; (4) additional product information; (5) updated product disposition; and (6) industry recall contacts.

CBER estimates that 5 percent of the total BPD reports submitted to CBER would need additional information submitted in the addendum. CBER further estimates that it would take 15 minutes to complete the addendum.

Activities such as investigating, changing standard operating procedures or processes, and follow-up are currently required under 21 CFR parts 211, 606, 820, and 1271 and, therefore, are not included in the burden calculation for the separate requirement of submitting a deviation report to FDA.

CMS Revises OPO Conditions for Coverage

This proposed rule would revise the Organ Procurement Organization (OPO) Conditions for Coverage (CfCs) to increase donation rates and organ transplantation rates by replacing the current measures with new transparent, reliable, and objective measures. Comments should be received by February 21, 2020.

They are proposing to revise the outcome measures for re-certification at § 486.318 to replace the existing outcome measures with two new outcome measures that would be used to assess an OPO's performance: ''donation rate'' and ''organ transplantation rate'' effective for CY 2022.

The ''donation rate'' would be measured as the number of actual deceased donors as a percentage of total inpatient deaths in the DSA among patients 75 years of age or younger with any cause of death that would not be an absolute contraindication to organ donation; and the ''organ transplantation rate'' would be measured as the number of organs procured within the DSA and transplanted as a percentage of total inpatient deaths in the DSA among patients 75 years of age or younger with any cause of death that would not be an absolute contraindication to organ donation.

The first measure, ''donation rate'', would demonstrate the OPO's percentage of possible deceased donors who become actual donors and the second measure, ''organ transplantation rate'', would demonstrate the percentage of organs transplanted after procurement.

Requesting FDA Feedback on Combination Products

The FDA released a draft guidance for industry entitled ''Requesting FDA Feedback on Combination Products.'' The purpose of this guidance is to discuss ways in which combination product sponsors can obtain feedback from FDA on scientific and regulatory questions and to describe best practices for FDA and sponsors when interacting on these topics.

These interactions can occur through application-based mechanisms, such as the pre-submission process used in the Center for Devices and Radiological Health (CDRH) and the Center for Biologics and Research (CBER) and the formal meetings used in the Center for Drug Evaluation and Research (CDER) and CBER, or through Combination Product Agreement Meetings (CPAMs), as appropriate.

FDA Extends TRIP Program for HCT/P Manufacturers

FDA extended the agency's TRG Rapid Inquiry Program (TRIP) to help manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps) obtain a rapid, preliminary, informal, non-binding assessment from FDA regarding how specific HCT/Ps are regulated. The program will operate until March 31. Instructions for submitting a TRIP request are available online.

FDA Drafts Guidance on Demonstrating Substantial Evidence of Effectiveness

The FDA has drafted a guidance that provides expectation of details to support clinical evidence of effectiveness for human drugs and biologics. The agency now allows a single adequate and well-controlled study and confirmatory evidence to be used to support the approval.

Although randomized superiority trials with a placebo- or active-control design generally provide the strongest evidence of effectiveness, this guidance discusses the circumstances

under which trials not using a placebo control, superiority design, or randomization may be acceptable. In addition, this guidance also discusses situations in which human efficacy trials are not ethical or feasible, and the animal rule may be applied.

The guidance discusses when different amounts of evidence are appropriate to support approval, including two adequate and well-controlled clinical investigations or a single adequate a well-controlled large multicenter trial.

Additionally, the guidance provides examples of approaches based around a single adequate and well-controlled study:

- One adequate and well-controlled clinical investigation on a new indication for an approved drug, supported by existing adequate and well-controlled clinical investigation(s) that demonstrated the effectiveness of the drug for its other, closely related approved indication(s);
- One adequate and well-controlled clinical investigation supported by data that provide strong mechanistic support;
- One adequate and well-controlled clinical investigation with compelling results, supported by additional data from the natural history of the disease; and
- One adequate and well-controlled clinical investigation of the new drug supported by scientific knowledge about the effectiveness of other drugs in the same pharmacological class.

FDA Wants to End Quarterly Reporting of Device Decisions

The FDA is proposing to amend its medical device regulations to end its practice of publishing quarterly lists of its approval or denial decisions for premarket approval applications (PMAs) and humanitarian device exemptions (HDEs) in the *Federal Register*.

FDA will continue to post approval and denial notices for PMAs and HDEs on FDA's home page on the internet and will also continue to make available on the internet and place on public display summaries of safety and effectiveness data (SSED) for PMAs. FDA says the rule will improve efficiency and eliminate duplication in publishing PMA and HDE decisions.

The proposed rule would also revise regulations for requesting copies of current PMA approvals, denials and SSEDs to direct requests to the agency's Freedom of Information staff rather than the Division of Dockets Management.

FY 2019 Report from the CBER Director

Peter Marks, MD, PhD, Center for Biologics Evaluation and Research Director summarized the product approvals, research and guidance documents released in FY 2019 to protect and improve public health globally.

These included a novel gene therapy, vaccines, treatments for immune deficiencies, and tests for protection of the blood supply, among other products. The report also highlighted CBER's efforts to advance biologic and human cells, tissues, and cellular and tissue-based product (HCT/P) development through the establishment of the CBER Advanced Technologies Team (CATT) and the Tissue Reference Group (TRG) Rapid Inquiry Program (TRIP).

Read the FY 2019 Report from the Director here.

CMS Corrects HOPPS and ASC Payment Systems Final Rule

The Centers for Medicare & Medicaid Services (CMS) released a correction of the final rule of the Hospital Outpatient Prospective Payment System (OPPS) and Ambulatory Surgical Center (ASC) Payment Systems.

CMS is correcting the standard wage index conversion factor budget neutrality adjustment from 0.9990 to 0.9991, which also results in the overall wage index budget neutrality factor changing from 0.9981 to 0.9982. This affected both the conversion factor, which changes from $80.784 to $80.793, as well as all CY 2020 OPPS payment rates included in the final rule.

CMS had also inadvertently omitted a discussion of the reestablishment of Comprehensive Ambulatory Payment Classification (C– APC) 5495 (Level 5 Intraocular Procedures) in the description of additional C–APCs that are finalized for calendar year (CY) 2020.

Guidance for Using Rapid Diagnostic Tests for Ebola in the United States

The Centers for Disease Control and Prevention (CDC) issued a Health Advisory regarding Ebola testing in the U.S. The FDA allowed marketing of the OraQuick® Ebola Rapid Antigen Test, a rapid diagnostic test (RDT) for detecting Ebola virus in both symptomatic patients and recently deceased people in October 2019. This is the first Ebola RDT that FDA has allowed for marketing in the United States.

The RDT should be used only in cases where more sensitive molecular testing is not available. All OraQuick® Ebola Rapid Antigen Test results are presumptive; all test results (positive and negative) must be verified through real-time reverse transcriptase polymerase chain reaction (rRT-PCR) testing at a Laboratory Response Network (LRN) laboratory located in 49 states and at the Centers for Disease Control and Prevention (CDC).

NIH Launches Patient-derived Stem Cell Trial for Geographic Atrophy

Researchers at the National Eye Institute (NEI) launched the first U.S. clinical trial testing the safety of a patient-specific stem cell-based therapy for the treatment of geographic atrophy, the advanced “dry” form of age-related macular degeneration (AMD).

The therapy involves taking a patient’s blood cells and converting them into induced pluripotent stem cells (iPSC), which have the potential to transform into any type of cell in the body. They program them to become retinal pigment epithelial cells. The cells will be grown in sheets that are one cell thick, replicating the structure within the eye, before they are transplanted into one eye of each of the 12 study patients.

The phase I/IIa study will closely monitor the patients for at least 1 year to establish safety. A concern with any stem cell-based therapy is its oncogenic potential: the ability for cells to multiply uncontrollably and form tumors. In animal models, the researchers genetically analyzed the iPSC-derived RPE cells and found no mutations linked to potential tumor growth.

The use of an individual's autologous blood cells is expected to minimize the risk of the body rejecting the implant.

ASAE Urges Government to Halt Sale of .ORG Registry

ASAE asked the federal government to intercede and stop the pending sale of the .org domain registry to the private equity firm Ethos Capital LLC in a letter to the Justice and Commerce departments and the Federal Trade Commission. ASAE said the sale of the .org registry to a for-profit firm would risk exposing nonprofit organizations to drastically higher costs to maintain their online presence.

In late November, Public Interest Registry said it had reached an agreement to be acquired by Ethos for an undisclosed price. Public Interest Registry has managed the .org domain registry since 2002. There are roughly 10 million .org domains in operation, including most web addresses used by associations, including almost all EBAA-member eye banks.

ASAE voiced its concern that Ethos' interest in acquiring Public Interest Registry is to increase .org registration and renewal fees. Doing so would subject millions of associations and nonprofit organizations to what would most likely be an unstable pricing environment, forcing them to divert valuable resources from their exempt purpose in order to protect their online presence.

The concern that Ethos will raise the fees to register and renew domain names has heightened since the Internet Corporation for Assigned Names and Numbers (ICANN), a global entity that manages the internet's address system, took steps this past June to remove the longstanding price cap of 10 percent for renewal of .org domain names.
In response to public outcry from the .org community, ICANN this month delayed the sale of PIR to afford PIR time to provide .org stakeholders answers to questions about the recently announced acquisition.

FDA Proposes Allowing Importation of Certain Prescription Drugs from Canada

FDA issued a proposed rule that, if finalized, would allow for the importation of certain prescription drugs from Canada. Specifically, the proposed rule seeks to implement "Section 804 Importation Programs" (SIPs) through the Food Drug and Cosmetic Act (FDCA). A SIP would be approved by FDA and managed by states or certain other non-federal governmental entities, and could be co-sponsored by a pharmacist, a wholesaler, or another state or non-federal governmental entity.

To be eligible for importation, prescription drugs must be sold legally on either the Canadian market or the American market with appropriate labeling; and currently be marketed in the United States. Biological products are excluded from the definition of "eligible prescription drug" due to safety reasons. All intraocularly injected drugs are excluded from importation due to significant risks associated with route of administration. FDA proposes to consider the importation of ophthalmic drugs on a product-by-product basis.

The FDA also released a new draft guidance, "Importation of Certain Food and Drug Administration-Approved Human Prescription Drugs, Including Biological Products," that describes procedures drug manufacturers can follow to facilitate importation of prescription

drugs, including biological products, that are FDA-approved, manufactured abroad, authorized for sale in any foreign country, and originally intended for sale in that foreign country.