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Regulatory Pathway for Drug-Device Combination Products in US

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1. Introduction

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) was enacted on October 26, 2002 (1). Among other things, this act created the Office of Combination Products (OCP). One of OCP's functions is to develop and implement policies and processes to streamline the review and regulation of drug-device, drug-biologic and device-biologic combination products. In addition, there can also be "cross labeled" and "co-packaged" combination products.

Under 21 CFR 3.2(e), a combination product includes:

- A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (a "single entity" combination product, such as a prefilled syringe or drug-eluting stent);
- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (a "co-packaged" combination product, such as a surgical or first-aid kit);
- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved, individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose) (a "cross-labeled" combination product, as might be the case for a light-emitting device and a light-activated drug); or
- Any investigational drug, device, or biological

product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (another type of cross-labeled combination product) (2).

2. Regulatory Pathway for Combination Products

OCP is also responsible for implementing regulations for Combination Products (CP) as well as the issuance of Guidances to help both FDA reviewers and industry sponsors expedite the development and approval of CPs. Starting in 2006, Guidance documents began being issued and now total 16 Guidances with most of these being published in only the last three years (3). These Guidances attempt to cover the many issues faced by sponsors attempting to develop and gain approval of CPs.

The laws and regulations governing drugs (Food Drug and Cosmetic Act), medical devices (Medical Device Amendments to the FD&C Act), and biological products (Public Health Services Act) originated from different Congressional actions. As a result, the marketing application process, review, approval and GMP requirements all differ from one another. These differences resulted in many unforeseen issues with the implementation of CP regulation such as deciding which FDA Center conducts the product review, how primary mode of action (PMOA) is determined, post marketing safety reporting requirements, labeling and cross-labeling issues, regulatory exclusivities and cGMP compliance to name a few.

The Office of Combination Products encourages sponsors developing a CP to formally contact the Office in order to determine the lead Center assignment for the CP. FDA Guidance "How to Prepare a Pre-Request for Designation" (4) details this process. OCP makes their decision on Center

assignment based on the Primary Mode of Action (PMOA) of the CP defined as:

“The single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product” (5).

For example, in the simplest case, epinephrine injectable contained in an autoinjector is assigned to CDER and the product filed for approval as a New Drug Application (NDA) with the Center for Devices and Radiological Health (CDRH) participating in the review of the autoinjector device. The FDA determined that the PMOA is the drug (epinephrine) and the device is acting as a convenient way to deliver the drug. Determining the PMOA is not always as easy as in this epinephrine case. For example, Antibody/Drug Conjugates (ADCs) are CPs where the role of the antibody is to deliver a drug (e.g., a cytotoxin) to specific cells harboring an antigen to which the antibody binds. FDA has determined, as a therapeutic class, ADCs are to be regulated as biologics and not drugs and such products are submitted for approval as a Biological License Application. However, a consult CMC review of the linker and drug portion of the ADC are conducted by the reviewing chemists in the Office of Pharmaceutical Quality (OPQ) within CDER.

In the case of drug eluting stents, the FDA has decided that “the uncoated stent functions to physically maintain vessel lumen patency, while the drug component has played a secondary role in preventing restenosis, augmenting the safety and/or effectiveness of the uncoated stent. In these cases, FDA has concluded that the primary mode of action for the combination product is that of the device component and has assigned the Center for Devices and Radiological Health (CDRH) primary responsibility for premarket review and regulation” (6). Thus, a Premarket Approval Application (PMA) would be filed to CDRH for such products.

Imaging agents and detection devices are also drug/device Combination Products and present unique challenges in terms of PMOA. Some of these CPs have been assigned to CDER with the imaging agent being considered the PMOA while others have been assigned to CDRH where the detection device is considered the PMOA.

For sponsors developing a drug/device CP, it is critical that the September 2017 Guidance entitled

“Classification of Products as Drugs and Devices & Additional Product Classification Issues” be consulted (7). The vast majority of CPs under development are drug/device CPs and this Guidance attempts to greater clarity and explain the decision-making process for determining whether the CP is developed and approved through CDER or CDRH. One of the problems that the FDA is faced with is that the statutory definition of a “drug”. Conceptually, all FDA-regulated medical products meet the definition of “drug” under section 201(g) of the FD&C Act, due to the broader scope of the drug definition. For a medical product also to meet the more restrictive device definition under section 201(h) of the FD&C Act, it must (i) be “an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article,” and (ii) “not achieve its primary intended purposes through *chemical action* within or on the body of man or other animals” and (iii) “not [be] dependent upon being *metabolized* for the achievement of its primary intended purposes” (emphasis added) (8).

3. Regulatory (data) Exclusivity Issues

Regulatory exclusivity determinations continue to be a challenge for the FDA when it comes to Combination Products. Drugs, Devices and Biologics all have different regulatory exclusivities. For example, for a New Chemical Entity (NCE) the exclusivity period is as much as 5 years, for Devices it is as much as 6-years and for a new biologic 12-years. These exclusivities are not automatic and were created under different laws and at different times by the US Congress. The laws did not take into consideration combination products so it is still not clear, for example, what exclusivities would be available for an NCE imaging agent combination product with a new detection device and approved as a PMA in CDRH. Would it be 6 years (device), 5 years (drug), 11 years (both), or none (no exclusivity category for a CP). For sponsors of such products, early engagement with OCP and the assigned Center on this topic is strongly advised.

4. Dealing with differences in GMP requirements

As mentioned earlier, drugs, devices, and biologics all have different cGMP requirements as the regulations governing each of these categories of

medicinal products were developed under different laws passed by the US Congress. Although the category of Combination Product was first established in 2002, it wasn't until 11 years later in January 2013 that FDA issued regulations governing GMP compliance for CPs (9). It wasn't until four years later that the FDA finally issued a final Guidance for following these new CP GMP requirements entitled "Current Good Manufacturing Practice Requirements for Combination Products" (10). This Guidance wasn't finalized until 4 years later in January 2017 (11). The Guidance is comprehensive, and it does recognize the challenges for sponsors to comply with both categories of GMPs for a combination product. In fact, the Guidance offers a "streamlined" approach to GMP compliance. Until the regulations were issued in January 2013, sponsors of combination products were required to comply fully with the respective GMPs for each constituent part of the CP. In the "streamlined" approach, the FDA is requiring that the sponsor complies fully with the GMP requirements for one of the CP constituent part while also complying to an abbreviated listing of GMP requirements for the other constituent part.

5. Post Marketing Safety Reporting (PMSR)

Although the PMSR regulations for drugs, devices, and biological products share many similarities, each set of regulations establishes distinct reporting requirements, including reporting triggers and timeframes. In December 2016 FDA issued new regulations for post marketing safety reporting requirements for CPs and in July 2019

issued a Guidance on this topic giving the Agency's current thinking on how this reporting can be accomplished for CPs (12). Like the GMP requirements for CPs above, a "streamlined" approach for safety reporting is discussed in the Guidance. The reporting requirements generally are in line with what is required for drug products. However, an additional requirement is that information on safety reports must be shared with the individual constituent part applicants. For example, an unexpected adverse event or product failure in the field for a prefilled syringe drug/device product must be shared with the syringe supplier even if the syringe was not responsible for the adverse event. There are many nuances and requirements in this regulation and requires thorough reading and understanding for safety reporting especially for drug/device CPs.

6. References:

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