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Jurisdiction and Regulatory Pathway

Introduction

Chapter 4 will provide an overview of how the United States Food and Drug Administration (FDA) assigns jurisdiction of combination products. This chapter will also discuss how to request a designation for a potential combination product. Lastly, this chapter will briefly introduce a few of the different pathways for combination products to be marketed. Regulatory professionals need to understand how to determine the jurisdiction of a combination product in order to understand the potential regulatory pathways that are available to bring the product to market.

Introduction

How do you know which FDA center will have primary jurisdiction for your combination product? How can you determine which constituent part of your combination product is the driver for the product? There are several avenues available to make the determination.

To ascertain which FDA center has the primary responsibility for review of a premarket application for a combination product, a regulatory professional must first determine the mode of action including the primary mode of action (PMOA). Why is this important? It is important because FDA is required to assign a combination product to a lead center based on its PMOA. As published in the 25 August 2005 edition of the *Federal Register*,¹ FDA promulgated a final PMOA Rule to describe the principles of how combination products are assigned to an agency

center. The regulation defined mode of action (MOA) and PMOA and provided an algorithm for how FDA would assign combination products for which the PMOA cannot be determined with “reasonable certainty.” The rule became effective 23 November 2005.²

Constituent Parts

FDA defined MOA as the means by which a product achieves an intended therapeutic effect or action. For purposes of this definition, “therapeutic” action or effect includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease or affect the structure or any function of the body. Because combination products are comprised of more than one type of regulated article (biological product, device, or drug), they typically will have more than one identifiable MOA. Specifically, each regulated article of the combination product, referred to as “constituent part” per 21CFR3(k)(1–3) and 21CFR4.2,^{3,4} will contribute either a biological product, device, or drug MOA. The definitions of biological product, device, and drug MOAs are closely related to the following statutory definitions of a biological product, device, and drug respectively. See **Chapter 1** What are combination products?

- A constituent part has a biological product MOA if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic

product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings, as described in *Public Health Service Act (PHS Act)* Section 351(i).⁵ (**Note:** While not currently reflected in the biological product MOA definition, the statutory definition of a biological product was amended in 2010 to include proteins (except any chemically synthesized polypeptide).

- A constituent part has a device MOA if it meets the definition of device contained in *Federal Food, Drug and Cosmetic Act (FD&C Act)*, Section 201(h)(1)–(3),⁶ does not have a biological product MOA and does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and is not dependent upon being metabolized for the achievement of its primary intended purposes.
- A constituent part has a drug MOA if it meets the definition of drug contained in *FD&C Act* Section 201(g)(1) and does not have a biological product or device MOA.⁷

21CFR3(m) defines the PMOA as the single MOA of a combination product that provides the most important therapeutic action of the combination product. The regulation further clarifies PMOA as “the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.”⁸ For example, if a drug-device combination product’s PMOA is attributable to its device constituent part, CDRH would have primary jurisdiction, whereas if a drug-device combination product’s PMOA is attributable to its drug constituent part, CDER would have primary jurisdiction. If a biological-device combination product’s PMOA is attributable to its biological constituent part, CBER would have primary jurisdiction.

For some combination products, it is a relatively simple exercise to determine the MOA and, subsequently, the PMOA. For some products, however, the PMOA is not readily apparent to either FDA or the product sponsor at the time the request for assignment is submitted.

Determining the PMOA of a combination product is also complicated for products that have two completely different MOAs, neither of which is subordinate to the other. In close cases, assignments may turn on subtle distinctions related to the determination of whether a MOA is “primary” or not.

What is the remedy if there is confusion regarding which constituent part is the PMOA? What happens if FDA is unable to determine the PMOA?

When FDA is unable to determine the most important therapeutic action with reasonable certainty, the assignment algorithm defined in 21CFR3.4(b) is used to determine the product’s assignment.⁹ First, FDA looks at historical precedents to assign the combination product to the agency component that regulates other combination products presenting similar safety and effectiveness questions regarding the combination product as a whole. When no other combination products present similar safety and effectiveness questions regarding the combination product as a whole, FDA makes the most appropriate assignment based on the new combination product’s safety and effectiveness questions. FDA assigns the product to the center with the most expertise related to the combination product’s most significant safety and effectiveness questions. For example, if the most significant safety and effectiveness issues a drug-device combination product presents in this scenario were attributable to the drug constituent part, the combination product likely would be assigned to CDER as the lead center. This process is explained in more detail below.

Request for Designation (RFD)

Understanding the regulatory pathway early in a combination product’s development phase is essential for the sponsor to establish a realistic regulatory strategy. There are two ways in which a manufacturer can seek FDA feedback to determine product jurisdiction: informally or formally. Informal processes involve seeking advice from the appropriate center or Office of Combination Products (OCP) staff, typically by telephone, email, meeting, or submitting a pre-request

for designation (Pre-RFD). These procedures generally are appropriate where the combination product's most important therapeutic action is clear, or when FDA has experience in jurisdiction decisions for similar combination products. However, one disadvantage of the informal approach is that the advice is not binding on FDA and may be subject to change.

Formal designation of a combination product is achieved by submitting an RFD or an applicant's letter of request, which is a written submission to OCP requesting designation of the center with primary jurisdiction for a product. An RFD submission is not necessary for every product but generally is indicated when a combination product's jurisdiction is unclear or in dispute.¹⁰

The RFD process also may be used by a sponsor or applicant to figure out the classification of a product (i.e., drug, medical device, biological, or combination product).¹¹ At the end of the RFD process, the sponsor or applicant will receive a formal classification determination. However, as part of the RFD process, the sponsor or applicant must recommend a classification in order for the application to be reviewed. Basically, if a sponsor or applicant is uncertain of their product's classification and jurisdiction, the RFD process will provide a remedy for both.

FDA action on an RFD is a binding jurisdictional determination with respect to center assignment and is subject to change only under conditions specified in 21CFR3.9 and *FD&C Act* Section 563.^{12,13} However, while a designation is binding for a particular product's assignment, such assignment pertains only to the product described in the RFD. For example, if the product's configuration, composition, modes of action, intended use, or any other key aspect changes after the designation letter is issued, it may be necessary to submit a new RFD to determine the modified product's appropriate assignment.

Before submitting an RFD, the sponsor or applicant should contact OCP if it is unsure of the information required in the RFD, has any questions regarding the RFD process, or would like to provide OCP with details on how the product works. OCP will provide general information regarding the RFD process and respond

to questions about the process. Additionally, a sponsor or applicant may request a meeting with OCP. The meeting request can be mailed or emailed (combination@fda.gov) to OCP. If the meeting request is mailed, the cover letter should prominently state "Meeting Request." OCP generally will not grant a meeting after a sponsor or applicant has already submitted the RFD. The meeting request should include an explanation of any issues the sponsor or applicant would like to discuss in the meeting. OCP makes the final decision on whether a meeting is granted. Currently, there is no statutory timeframe for either acceptance or rejection of a meeting request. The sponsor or applicant should call OCP to establish, if possible, a timeframe for responding to the meeting request.

According to 21CFR3.7(c), an RFD is limited by regulation to 15 pages, including attachments.¹⁴ FDA expects that a well-thought-out and well-written RFD should not require more than 15 pages. Additionally, FDA does not expect to receive large attachments with extensive data, since the RFD is likely to be submitted early on in the development process. Any attachment should be supportive information for the classification chosen or to bolster the choice of FDA center with jurisdiction for review. An RFD should be submitted prior to submitting an investigational or marketing application. As described in 21CFR3.7(c), the following information is required in an RFD submission. FDA has issued *How to Write a Request for Designation: Guidance for Industry*,¹⁵ which further elaborates on these requirements:

- Sponsor identity, including company name and address, establishment registration number, company contact person, and telephone number
- Product description, including:
 - Classification, name of the product, and all component products, if applicable
 - Common, generic, or usual name of the product and all component products
 - Proprietary product name
 - Identification of any product component that has received premarket approval already, is marketed as not being subject to

- premarket approval, or has received an investigational exemption
- o Identity of the sponsors and the status of any discussions or agreements between sponsors regarding the product's use as a component of a new combination product
- o Chemical, physical, or biological composition
- o Status and brief reports of developmental work results, including animal testing
- o Manufacturing process description, including all component sources
- o Proposed use or indications
- o Description of all known modes of action, sponsor's identification of the PMOA, and the basis for that determination
- o Schedule and duration of use
- o Drug or biologic dose and route of administration
- o Description of related products, including the regulatory status of those related products
- o Any other relevant information
- Sponsor's recommendation on which agency component should have primary jurisdiction, with accompanying statement of reasons

If any aspects of the requirements are not known, they should be stated in the RFD in the applicable section. As an example, proprietary name requests can only be submitted under an IND or a marketing application and are not approved until the marketing application is approved. An RFD would be submitted prior to an IND or marketing application. Therefore, the proprietary name would not be known at the time of an RFD application.

The following discussion will focus on best practices for the major sections of the RFD, keeping in mind that the regulation dictates 15 pages maximum. The description of the product should contain detailed diagrams, with an explanation of how the sponsor or applicant intends to market the combination product. For chemical, biological, or physical composition, the sponsor or applicant should identify all the components or ingredients, the purpose of each, and their concentration or amount. Tabular format is preferable and will save space. If preclinical or

clinical studies have been conducted, they should be summarized succinctly in the status and brief reports of developmental work section. Emphasis should be placed on studies that support the PMOA of the product. Manufacturing information can be provided in a process flowchart with a brief description. The proposed use or indications is a critical section, and the information should be stated as concisely and clearly as possible. The information in this section should be relevant to both the classification and the assignment of the product, especially if the RFD covers both topics. It is critically important for OCP to understand the MOAs and the PMOA. The RFD should contain a clear and concise description of all the known MOAs along with the determination of the PMOA. For each MOA, one should include a description, how the MOA is achieved, and which component or ingredient is responsible for each MOA. The manufacturer should explain which MOA contributes either a drug, biological, or device MOA and provide the basis for this conclusion. Published literature may be cited; however, the cited reference should not be provided in the RFD. Additionally, the section of the RFD containing information on the development of work or testing completed to support the chosen MOAs should be referenced. A rationale also must be provided to explain and defend the choice of the PMOA. OCP looks at the following in determining the PMOA from the RFD:

- Proposed use(s) or indication(s)
- How the combination product achieves its overall intended therapeutic effect(s)
- Relative contribution of each constituent part of the proposed use(s) or indication(s), and to the overall intended therapeutic effect(s)
- Duration of the contribution of each constituent part toward the intended therapeutic effect(s)
- Data or information provided or cited scientific literature that describes and supports the MOA expected to make the greatest contribution to the overall intended therapeutic effect¹⁶

The regulatory professional should ensure the MOA and PMOA sections contain this information. The sponsor or applicant should attempt to use the assignment algorithm to determine if another similar product is on the market when providing the rationale for the PMOA and jurisdictional center recommendation.

If OCP cannot determine the PMOA based on the data provided in the RFD, OCP will assign the combination product based on the assignment algorithm found in 21CFR3.4(b), discussed earlier in this chapter.

Assignment Algorithm

The assignment algorithm used by FDA has two steps. The first step is to check for other combination products that present similar questions of safety and effectiveness as a whole, compared to the unclassified combination product. The second step occurs if there are no combination products with similar questions of safety and effectiveness. In this case, OCP will assign the combination product to the center with the most expertise related to the most significant safety and effectiveness questions presented by the combination product. Some factors FDA weighs when evaluating a product for classification or assignment to a center are:

- Does the device constituent part incorporate a novel or complex design or have the potential for clinically significant failure modes?
- Does the drug have a narrow therapeutic index?
- Is the biological constituent part fragile?
- Which constituent part poses the greatest risks?
- Is the drug constituent part a new molecular entity or new formulation?¹⁷

How to Write a Request for Designation (RFD): Guidance for Industry contains an RFD screening checklist in the appendix that the regulatory professional can use to ensure the RFD contains the relevant required information. It should be noted that an RFD is submitted electronically via email to combination@fda.gov as a PDF, with two copies sent via mail to the OCP physical address

with “Request for Designation” clearly visible on the outside of the package or envelope. In other words, the RFD is not an eCTD submission.

FDA generally reviews an RFD for completeness within five working days of receipt. An incomplete RFD is “not filed,” and the applicant is notified of the information needed for OCP to undertake a substantive review. If an RFD is filed, the sponsor or applicant is sent an acknowledgement letter with the filing date and the date by which OCP will respond. Within 60 days after the RFD is filed, OCP issues a letter specifying the agency component with primary jurisdiction for the product’s premarket review and regulation. The designation letter also usually identifies any consulting agency components and sometimes describes the regulations (e.g., *FD&C Act* device or drug provisions) to which the product will be subject. Under 21CFR3.8(b), if FDA does not provide an answer within 60 days of the RFD filing date, the sponsor’s recommendation for classification or assignment is granted.¹⁸

Request for Reconsideration

If the sponsor or applicant disagrees with the designation, it may request that an OCP product jurisdiction officer reconsider the decision. The Request for Reconsideration (RFR) must be submitted within 15 days of receiving the designation letter. The RFR cannot include new information and must not exceed five pages. The OCP product jurisdiction officer will consider an RFR over five pages as a new RFD, subject to all the requirements of an RFD. The product jurisdiction officer at OCP, in turn, will review the RFR and respond in writing within 15 days of receipt.

Pre-Request for Designation

OCP was approached by sponsors and applicants searching for more flexibility in interacting with OCP and the three medical product centers when obtaining feedback prior to submitting a marketing application to FDA. These informal methods for obtaining feedback became customary to sponsors and applicants, and for some, more preferable than the RFD process.

The Pre-RFD program was the result of FDA enhancing transparency and consistency of the informal, flexible process. FDA introduced *How to Prepare a Pre-Request for Designation (Pre-RFD): Guidance for Industry*, dated February 2018, to provide clear recommendations to sponsors and applicants on how to submit a Pre-RFD.¹⁹

The Pre-RFD process provides an informal, non-binding preliminary assessment regarding the regulatory identity or classification of a medical product as either a drug, device, biologic, or combination product. The Pre-RFD process also provides information on the non-combination or combination product's assignment to an appropriate FDA center. There are similarities and differences between the Pre-RFD and RFD process (see **Table 4-1**).

The main similarities between the two processes are the basic information provided, such as a product description, proposed use or indication, and a description of how the product achieves its intended therapeutic/diagnostic effects. The most striking differences between the Pre-RFD and RFD are the length of the submission and the depth of the regulatory analysis required. A Pre-RFD does not have a page limit. Of course, the sponsor or applicant should strive to provide

a succinct summary of all required information in the Pre-RFD but will not be penalized for a lengthier application. Regarding the regulatory analysis, in the RFD, a sponsor or applicant must provide an analysis of the product's classification, PMOA, and a recommendation for the center with jurisdiction. This information is optional in the Pre-RFD. OCP will still conduct a PMOA analysis but will not have the sponsor or applicant's recommendation. A Pre-RFD should contain the following basic information:

- Contact information, including sponsor or applicant name, company's name, email address, and telephone number.
- A complete description of the product and, if applicable, the following information:
 - 510(k), Premarket Approval (PMA), New Drug Approval (NDA), Abbreviated New Drug Approval (ANDA), Biologics License Application (BLA), or any other FDA regulatory submission number associated with the product.
 - Name of the product and all component products.
 - A photo/diagram of the product.
- For products sourced from biologically derived materials, a description of how the

Table 4-1. RFD and Pre-RFD Comparison^a

| Submission Type | RFD (Information Required) | Pre-RFD (Information Recommended) |
|---|-------------------------------|--|
| Description of product | Yes | Yes |
| Proposed use or indications for use | Yes | Yes |
| Description of the manufacturing processes, including the sources of all components | Yes | Optional (if available; recommended if it is a human cell, tissue, or cellular- or tissue-based product (HCT/P) or a biological product) |
| Supportive data/studies | Yes | Optional (if available) |
| Description of how a product achieves its intended therapeutic/diagnostic effects | Yes | Yes |
| Analysis of classification, primary mode of action (PMOA), if it is a combination product, and jurisdictional assignment | Yes | Optional (if available) |
| Description of related products | Yes | Optional (if available) |
| Sponsor recommendation | Yes | Optional (if available) |
| Page limit | Yes | No |
| <p>a. <i>How to Prepare a Pre-Request for Designation (Pre-RFD): Guidance for Industry</i>. February 2018. Final. FDA website. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-prepare-pre-request-designation-pre-rfd. Accessed 19 March 2021.</p> | | |

- material was processed and a characterization of the identity of the final product.
- An explanation of how the product works. And, though optional, additional information describing details (i.e., study conditions/methods, identification of controls, results, and conclusions) of relevant testing that supports how the product works may be included. Please be aware that comparisons to other products or biocompatibility testing results are typically not helpful in understanding how the product works.
 - An explanation of how the product will be marketed. For instance, will the product have separately marketed constituent parts that are to be labeled for use together, or will it have components that either will be physically or chemically combined to make a single entity, or will be co-packaged?
 - A listing of all components/ingredients, including the amount and reasoning for including each component/ingredient, in the product. If the product contains a solution/liquid/gel/powder, please provide a listing of all ingredients (active and inactive), their amount/concentration, and the reason for including the ingredient in the product.
 - Proposed use/intended use/indications for use statement.
 - Instructions for use/conditions of use.
 - All known methods of action and the mechanism(s) by which each is achieved.
 - For products that might be combination products, any information that might support the relative contribution of different components to the overall intended therapeutic/diagnostic effects of the combination product. Though optional, a detailed description of any supporting tests/studies if such information is available may be provided for FDA to consider.
 - A list of claims the sponsors intends to make or has made regarding the product.²⁰

Additional information may be provided if it will aid OCP in determining classification or PMOA for assigning jurisdiction. As with the RFD, specific attention should be given to providing clear and concise information on the

indications or intended use(s); all of the MOAs for the product; a comprehensive description of the product, including detailed information on the composition; claims that have been made or plan on being made about the product and, of course, any information or data that would elucidate the PMOA. The Pre-RFD guidance contains a screening checklist to assist the regulatory professional in providing all pertinent data or information to OCP. As with the RFD, the Pre-RFD is submitted to OCP via email in PDF or Microsoft Word format. No paper copies are required to be submitted.

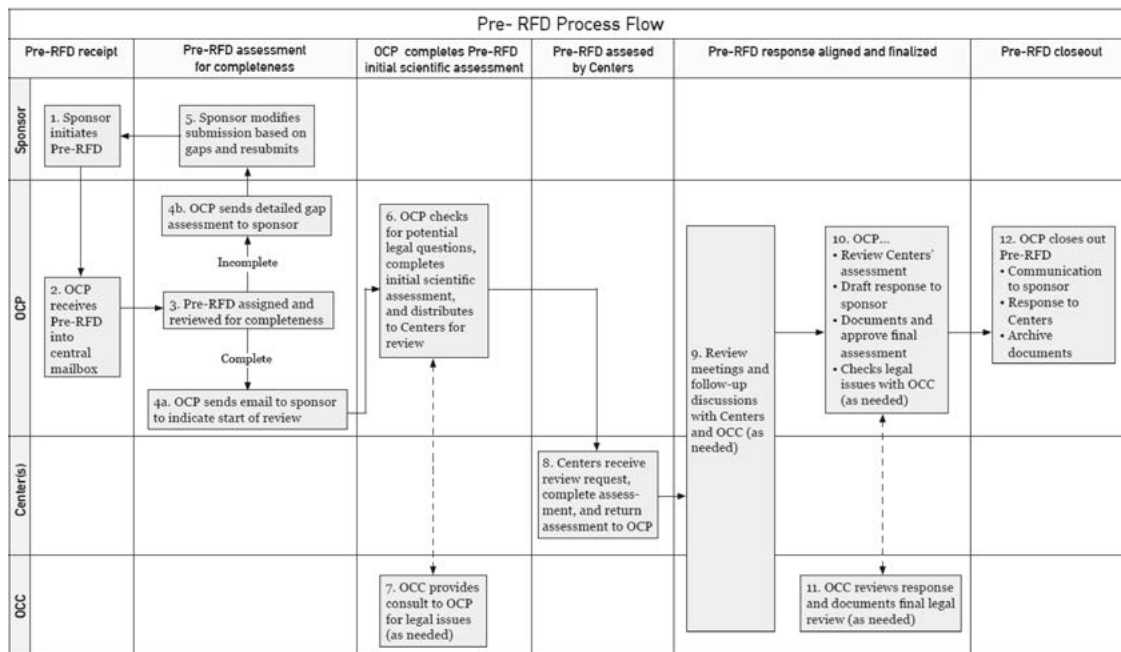
OCP follows the same process and timing as with the RFD in reviewing the Pre-RFD for adequacy and providing an acknowledgement letter within five days of receipt. OCP will strive to provide feedback within 60 calendar days after receipt of the Pre-RFD information. However, the review could take longer than 60 calendar days if the Pre-RFD contains a large amount of data or if the quality or adequacy of the information submitted slows down the review time.²¹ Therefore, even though no page limit is provided, it is best to minimize the size of the Pre-RFD in order to receive a preliminary response within 60 calendar days.

Unlike the RFD, there is no request for reconsideration process for the Pre-RFD. If the sponsor or applicant does not agree with the preliminary assessment by OCP, the sponsor or applicant should contact OCP to discuss the assessment findings. If new or additional information is available, the sponsor or applicant should discuss this with OCP prior to submitting another Pre-RFD. Providing new information or data will result in a new Pre-RFD, and a new assessment will be started. Alternatively, the sponsor or applicant can submit an RFD and receive a binding determination.²²

Pre-RFD Meetings

Meetings for a Pre-RFD are not necessary, but OCP is willing to meet if the sponsor or applicant believes it will help OCP better understand how the product works. A meeting can be requested either before or after the submission of the Pre-RFD to OCP. If the meeting

Figure 4-1. Pre-RFD Process Flow



Source: How to Prepare a Pre-Request for Designation (Pre-RFD): Guidance for Industry. February 2018. Final. FDA website. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-prepare-pre-request-designation-pre-rfd>. Accessed 19 March 2021

is requested after submission of the Pre-RFD but prior to OCP’s feedback, the meeting could potentially extend the review timeline for the Pre-RFD. OCP will require four weeks prior to the meeting to review any data or information submitted as part of the meeting request.²³ A comprehensive background package provided at the time of the meeting request is imperative for a timely and thorough OCP review. The background information package should be clear, concise, and focused, without extraneous and irrelevant information or data. OCP cannot provide meaningful feedback during a meeting if the background package is inadequate; this will cause unnecessary delays. See **Figure 4-1** for a diagram of the Pre-RFD process.

Intercenter Agreements: Jurisdiction

Many resources are available to help sponsors understand a combination product’s jurisdiction. The original resources were the three intercenter

agreements (ICAs) established in 1991 between the following:

- CBER and CDER
- CDER and CDRH
- CBER and CDRH

The ICAs’ usefulness has decreased over time due to agency organizational realignments, the development of new products not envisioned in the original ICAs, new uses of existing products, and laws enacted since 1991. In the 2006 *Federal Register* the agency announced it had reviewed these agreements and preliminarily proposed continuing to use the CBER-CDRH and CDER-CDRH ICAs, as they provide helpful, nonbinding guidance, with the understanding that they should not be relied upon as the agency’s most current, complete jurisdictional statements. Due to the transfer of many therapeutic biological products from CBER to CDER in 2003, the agency stated the CBER-CDER ICA was out of date.

The 2006 notice also explained that while FDA does not plan to update the existing ICAs, it believes transparency in jurisdictional decision making should result in greater predictability and reduce ambiguity on FDA perspectives. The agency has implemented a number of mechanisms to provide this transparency. For example, it has used its website to disseminate information concerning product jurisdiction. Some examples include:

- Jurisdictional determinations: Approximately 250 capsular descriptions of selected RFD decisions have been posted on OCP's website.²⁴
- Jurisdictional updates: Detailed statements on updated classification and assignment of specific product classes are available on OCP's website.²⁵

The OCP website also includes RFD jurisdictional determination letters²⁶ for more than 65 approved or cleared products covered by an RFD, redacted to remove trade secret and confidential commercial information in accordance with the *Freedom of Information Act*.²⁷ The information from these three sources can be used by sponsors or applicants to compare their product to other approved or cleared products to ascertain if any are similar enough to leverage for classification or jurisdiction, or if any of the information can be supportive in a Pre-RFD or RFD submission.

Regulatory Pathway

The regulatory pathway for a combination product is dependent on the classification and center jurisdiction assigned based on the PMOA. Once the PMOA has been identified as belonging to the drug constituent part (CDER), biological constituent part (CBER), or medical device constituent part (CDRH), a sponsor or applicant can begin figuring out the testing needed, identifying any applicable product-specific guidance, and in general, mapping out the regulatory strategy for the product. Understanding the applicable regulatory pathway early in a combination product's development phase is essential for the sponsor to establish a realistic regulatory strategy.

This chapter will not cover all possible regulatory pathways for combination products; only the major regulatory pathways are discussed. For example, to obtain authorization to legally commercialize regulated medical products in the US, there are three types of applications for drugs, one for biologics, and two for medical devices.

FD&C Act Section 505²⁸ identifies the following three different regulatory pathways for drugs:

1. 505(b)(1)²⁹ is for an NDA with full safety and effectiveness data; typically, an NDA is submitted for new chemical or molecular entities.
2. 505(b)(2)³⁰ is for an NDA that requires full safety and effectiveness data, but some of the data can come from published literature or by cross-referencing an approved, off-patent NDA or ANDA. This is used for modifications of drugs (e.g., dosage form, route of administration) that are off patent where an ANDA is not appropriate, but duplicative studies are not necessary.
3. 505(j)³¹ is for an ANDA for a drug that is identical to an already marketed drug (innovator drug). This means all characteristics of the generic drug are the same as that of the innovator drug. CMC data and a bioequivalence studies are usually required to support the ANDA.

PHS Act Section 351(h)³² establishes the BLA for biologic (or biological) and biosimilar products, which are established per section 351(k) of the *PHS Act*.³³

Section 510(k) of the *FD&C Act* provides for a premarket notification (510(k)) for medical devices.³⁴

This pathway is for medical devices that can show substantial equivalence to a medical device that is already on the market. Section 515 of the *FD&C Act* established the PMA application for Class III medical devices.³⁵ The NDA, BLA, 510(k), and PMA are the main regulatory pathways that will be discussed in subsequent chapters.

Generally, for any of the regulatory pathways, the same types of questions need to be asked to move towards the goal of a premarket

submission. What testing is needed? Is analytical testing required? What standards and guidance are applicable to my combination product? Which are specific to each constituent part? Are biocompatibility studies needed? How many clinical trials will be required? When should human factors testing be started? Will an investigational application be needed?

Conclusion

OCP provides guidance to both industry and FDA centers on combination products. OCP provides multiple mechanisms for sponsors and applicants to assist in determining if a product is a combination product or noncombination product. Both the pre-RFD and RFD provide an opportunity for the sponsor or applicant to put forth a justification for how their product should be designated and receive a preliminary or final decision on the designation. Sponsors or applicants that are sure of the designation of their products as combination products have a number of regulatory pathways depending on the PMOA.

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5

Combination Product Development and Meetings

Introduction

Now that the jurisdiction of the combination product has been established (see **Chapter 4** Jurisdiction and Regulatory Pathway), the sponsor or applicant can move to implement a comprehensive regulatory strategy for the product. Many cutting-edge combination products are being introduced with innovative technologies (e.g., new technological delivery systems, on-body wearable pump infusion systems, mobile health technologies, and digital health innovations). All combination products present some developmental challenges, especially if the sponsor or applicant is more accustomed to developing and manufacturing only one of the two or three constituent parts. Another complexity of combination product development is the fact that no single regulatory pathway has been prescribed by the US Food and Drug Administration (FDA).

As with other medical products, combination product development typically focuses on the scientific and technical issues raised by the particular product being developed. For a combination product, these scientific/technical issues will ordinarily reflect the combination product itself as well as its constituent parts. When combining products, such as drugs or biologics and devices that are usually developed using different regulatory pathways, certain critical developmental issues, including the interaction of the drug/biologic and device constituents, may not be readily apparent.

From the regulatory perspective of product development, the regulatory professional should begin by reviewing the data and information accumulated for each constituent part of the combination product to determine if any relevant regulations, existing guidance documents, or standards are available. These documents can be used to gather information on the types of issues that may be raised by the constituent parts of the combination product. In consultation with subject matter experts (SMEs) in different functions or departments in the company, the regulatory professional can determine whether the guidance can be followed as written or if any changes will be needed to accommodate the specific constituent parts. If the combination product has constituent parts that share some of the same regulatory requirements, such as a drug-biologic combination product, adapting the guidance document recommendations may be easier or simpler to implement. However, for a combination product, such as a biologic-device, with each constituent part having vastly different regulatory requirements, it could be more difficult to adapt the guidance recommendations. The bottom line is that the regulatory professional needs to work with the development team to implement an approach that addresses the technical or scientific issues without duplicative or redundant studies. One other aspect that should not be forgotten is to address issues that could occur because of the type of combination product, e.g., issues that could arise for a single-entity combination product will differ vastly from the issues for a