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Regulations and Quality Considerations of Drug Device Combination Products in USA

Kommalapati Swathi*, Koushik Yetukuri
Department of Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Guntur, AP
Kommalapati Swathi
Corresponding Author: Kommalapati Swathi
Email: skommalapati99@gmail.com

ABSTRACT
The legal foundation for current USA regulations pertaining to pharmaceuticals, biologics, and medical devices in general will be briefly discussed in this chapter, along with the steps required to get a combination product approved by the Food and Drug Administration (FDA). This section provides background information on how the Food, Drug and Cosmetic Act affects combination products within the various FDA branches, outlines the procedures for assigning the FDA Branch responsible for overseeing product reviews (pre- and post-approval), and briefly addresses the variations in how each FDA branch handles study and approval applications. Depending on the FDA's classification of the combination product (as a medicine, device, or biologic), these can differ significantly. The final section discusses the challenges that the FDA and applicants are facing as the process of regulating new technology develops and changes, providing some insight into the action plans that the FDA is taking to address these intricate challenges.
Keywords: *Combination devices, combination drugs, investigational devices, premarket approval, classification, FDA approval.*

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INTRODUCTION

LEGAL BASIS FOR US REGULATION

Here is a very brief rundown of the main legislative measures that have been passed over time and brought about the current state of food, drug, cosmetic, and medical device regulation by the US Food and Drug Administration (FDA). Since Franklin Roosevelt signed the Food, Drug, and Cosmetic Act (the "Act") on June 25, 1938, food, drugs, and cosmetics have been regulated under US law. The new law controlled drugs and cosmetics and mandated that medication labels include sufficient instructions for safe usage. Additionally, it required premarket approval for all new medications, meaning that before a drug could be sold, a manufacturer had to convince the FDA that it was safe. It unquestionably forbade making false therapeutic claims for medications, even though the Federal Trade Commission was given authority over drug advertising by a different statute. The act also required legally binding food standards and addressed violations in food quality and packaging. The topic of tolerances for some toxic substances was covered. Formally authorizing factory inspections, the law also included injunctions to the agency's arsenal of enforcement instruments. The Act's drug amendments were passed by the US Congress in 1968, and they Among other things, essentially needed strong clinical evidence to demonstrate- assessing new drug safety. Congress passed the Medical Device Act in 1976 Act modifications. In essence, this gave the FDA control over medical gadgets, much like how drugs were regulated in 1962. Numerous other modifications have been made since then; however, they are not covered in this chapter. At the end of this chapter, there are recommendations for further reading for anyone interested in learning more about the history of US food and drug regulations [1]. The FDA regulates, in general, all producers, distributors, and connected parties involved in the promotion and sale of goods subject to FDA regulations; however, two crucial points should be noted:

1. Initially, the amended US Food, Drug, and Cosmetic Act is only applicable to goods that are sold in interstate commerce. This indicates that a product that stays within a state has no direct jurisdiction over the FDA. The US FDA does not have jurisdiction over a medical device, for instance, that is made in Florida and is only marketed or administered there. The regulatory framework for the management

of pharmaceuticals and medical devices must be established by each state independently. Depending on the product (drug, device, or biologic), each state has a different set of regulations, and some have none at all. At the point of embarkation or debarkation, goods that are imported or exported are deemed to have entered the interstate commerce.

2. The FDA is not legally able to control the practice of medicine, according to the Food, Drug and Cosmetic Act, as amended. The FDA does not interfere with medical professionals' use of medications, biologics, or medical devices when it comes to treating their patients. FDA regulations do apply to study conduct when investigators are studying products that are not approved or that are being used for purposes other than those that are approved.

   In general, medical products classified as drugs, devices, or biologics are regulated by the FDA. The Center for Devices and Radiological Health (CDRH) and the Office of In-Vitro Diagnostics were split apart by the FDA more recently, but this move is not expected to cause any problems with combination products.

DRUG DEVICE COMBINATION PRODUCT

Any combination of a drug and a device, a biological product and a device, a drug and a biological product, or a drug, device, and biological product is referred to as a combination product. A combination product is defined as follows under 21 CFR 3.2(e):

1. A product consisting of two or more regulated components, such as a drug and device, biologic and device, drug and biologic, or drug and device and biologic, that are combined, mixed, or produced as a single entity through physical, chemical, or other means;
2. One package or group of two or more distinct products, either device and biological, drug and biological, or device and device packaged together;
3. A medicine, device, or biological product that is packaged separately and that, in accordance with its investigational plan or proposed labeling, is only meant to be used in conjunction with another approved medication, device, or biological product when both are necessary to achieve the intended use, indication, or effect and where the approved product's labeling would need to be altered upon approval of the proposed product, for example, to reflect a change in the approved product's intended use, dosage form, strength, route of administration, or significant change in dose.
4. Any biological product, investigational drug, or device that is packaged separately and, per its proposed labeling, is only to be used in conjunction with another specifically designated investigational drug, device, or biological product when both are necessary to accomplish the intended use, indication, or effect.

Products that are drugs, devices, or biologics do not fit the definition of a combination product as stated in 21 CFR 3.2 (e). The Office of Combination Products was created by the FDA to help with managing the complexity and breadth of the numerous potential combinations. tasks performed in the office include in the designating a primary FDA center for the review of combination products; managing the prompt and efficient premarket review of combination products by supervising reviews involving multiple agency centers; guaranteeing uniformity and suitability of post-market regulation of combination products; settling disagreements about the promptness of premarket review of combination products; revising agreements, guidelines, or procedures particular to the assignment of combination products; and providing yearly reports to Congress on the Office's operations and outcomes[2]. Additionally, the Office has taken over the responsibilities of the FDA Office of the Ombudsman's Combination Products Program, which was started in 2002. Serving as a focal point for internal and external stakeholders on combination product issues is one of these responsibilities, as is collaborating with FDA centers to develop guidelines or regulations that clarify agency regulation of combination products. Combination product developers should take the necessary steps to ascertain whether or not their product will fit in choosing the review division of the FDA, since the corresponding regulations differ greatly depending on the designation.

Designations may fall into the following:

- Device: drug (or biologic): combination device: in this instance, studies, approvals, and evaluations will be primarily handled by the CDRH.
- Drug · Device: combination drug · In this instance, studies, assessments, and approvals will be primarily handled by the Center for Drug Evaluation and Research (CDER).
- The Center for Biologics Evaluation and Research (CBER) will be primarily responsible for studies, evaluations, and approvals in the following scenario: biologic device: combination biologic.

DESIGNATION ASSIGNMENT

An algorithm for designating a combination product has been created by the FDA. This algorithm is predicated on evaluating the primary mode of action (PMOA) that is employed to accomplish the intended use of the product. In this section, drug delivery products are used as examples for ease of understanding.

There are more complicated examples all the time, and as complexity rises, more care must be taken. Preventing costly and time-consuming errors necessitates early collaboration meetings and the use of the FDA's processes for classification and determination. Prior to utilizing the algorithm, The rule was refined and published in 2005; interested parties should review the content of the publication in the US Federal Register [Federal Register: August 25, 2005 (Volume 70, Number 164)]. This document, also referred to as the PMOA Rule, addresses the challenges and subtleties associated with developing the rule as well as the FDA's authority to exercise discretion when it comes to public health. The following are the guidelines and definitions:

Modes of action: "A product's mode of action is how it accomplishes a therapeutic effect."

Primary mode of action: A combination product's primary mode of action is its one active ingredient that delivers the majority of its therapeutic benefits. The mode of action that is anticipated to have the biggest impact on the combination product's overall therapeutic effects is the most significant therapeutic action.

Techniques of Action. "Mode of action" is defined by the PMOA Final Rule as the mechanism by which a product accomplishes its intended therapeutic effect or action. According to this definition, a product's "therapeutic" action or effect is any effect that the manufacturer intends to diagnose, treat, mitigate, or prevent disease, or to alter the body's structure or any of its functions. Products may function as drugs, biological products, or devices [3]. Combination products usually have more than one mode of action because they consist of multiple types of regulated articles (drugs, devices, or biological products), and each constituent part adds a mode of action for the drug, device, or biological product. As per subsection 351(i) of the Public Health Service Act, a component part of a combination product has a biological product mode of action if it functions through 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 human disease or condition· If a constituent part of a combination product satisfies the requirements outlined in section 201(h)(1)±(3) of the ACT, does not have a mode of action specific to biological products, and does not accomplish its main goals by acting chemically within or on the bodies of humans or other animals, it has a device mode of action.

ALGORITHM

It might not always be easy to identify which combination product's mode of action is most crucial for its intended therapeutic effect. When a combination product has two entirely distinct modes of action, none of which is dependent upon the other, determining the PMOA of the product becomes even more difficult. In order to assign such products as consistently, predictably, and transparently as possible, the FDA published an assignment algorithm in the PMOA Final Rule (21 CFR 3.4(b)). When this occurs, the FDA will designate the combination product to the division within the agency that oversees other combination products that raise comparable concerns about the combination product's overall safety and efficacy. We would assign the combination product to the agency component with the most expertise in relation to the most significant safety and effectiveness questions raised by the combination product when there are no other combination products that raise similar concerns about safety and effectiveness with regard to the combination product as a whole (for example, it is the first of its kind, or variations in its intended use, design, formulation, etc. raise different concerns about safety and effectiveness). The assignment algorithm should be utilized if you are unable to identify the combination product's primary therapeutic effect. Firstly, you should think about whether the FDA regulates other combination products that raise comparable concerns about the combination product's overall efficacy and safety [4]. Or, to put it another way, think about whether an FDA Center has firsthand experience with a product that is comparable to yours. You should list any additional combination products you would like the FDA to take into account when assigning your product. You should address the second algorithmic criterion if you do not think that your product as a whole is comparable to others that the FDA has reviewed or is currently reviewing. It's advised to proceed to the second algorithmic step even if you think your product is similar to another.

REGULATION OF DRUG – DEVICE COMBINATION PRODUCTS IN USA

To prevent thrombus, antithrombotic medication coatings have been applied to a variety of catheters, including central venous catheters, which are combination devices. Furthermore, a product's designation as a combination drug or combination device does not imply that it will undergo the strictest clinical trials and approval procedures. These are more precedent-based and risk-based decisions. These topics will be covered in more detail in Section 19.4. In conclusion, it may be possible for product developers to determine the probability that a given product is essentially a drug, device, or biologic. A formal request for designation should only be taken into consideration in cases where there is a significant doubt or when the designation is unclear. In conclusion, product developers might be able to determine the probability that the product in question is essentially a drug, device, or biologic. A formal request for designation should only be taken into consideration in cases where there is a significant doubt or when the designation is unclear. The product's designation is just one stage in a multi-step process. The combination device

designation, for instance, does not offer a clear route for regulatory approval or clearance to market in the case of a medical device. Devices make up the great majority of combination products, and many of them are 510(k) cleared—that is, approved for marketing based on the performance of a predicate device[4]. In addition to addressing these two filing-related justifications, the request for classification response will provide some insight into the FDA's considerations regarding the device's risk profile. Similar to those outlined in the section on requests for designation, there are rules associated with filing a request for classification. The FDA's CDRH website under "device advice" has information about the user fee that applies to this request. A minimum set of information needed to submit a 513(g) classification request is as follows: · trade name, proprietary name; · classification code/common name; · Code of Federal Regulations (CFR) number; · code; · common name; · classification; · establishment registration; · owner/operator number; · registration number; · manufacturing facility; · equivalent devices; · intended use statement; · standards, special controls; · device description; · usage; · components; · device labeling.
A 513(g) request will normally receive a response within 60 days of being filed. Classification letters are legally binding, but if the applicant believes that new information could affect the classification assigned, they may use it as justification for a new classification request.

DRUG DESIGNATIONS

When a combination product has a lead assigned to the CDER, the clinical trials related to the product's study must receive approval from an investigational new drug (IND) study. The application for product approval will be submitted as a new drug application (NDA). It would take volumes to describe the intricacies of the IND and NDA procedures, which are outside the purview of this chapter. However, the FDA CDER website has a wealth of information for people who are unfamiliar with the IND/NDA procedures. Applicants who are confident that CDER will be the primary review agency for their combination products should acquaint themselves with the pertinent guidelines, regulations, and guidelines pertaining to preclinical research, clinical research, and the regulatory process involved in receiving approval. Even if the services of an experienced consultant are used, this should still be done[5]. Every product will be sent to the branch CDER determines to be the most appropriate for submission review. This may be challenging to evaluate due to the variations in the components of a combination product, as mentioned in the FDA's assessment of the combination product discussion (Section 19.13). Regardless, all correspondence for the combination product in the designated branch will go through the lead reviewer after the assignment is made. For instance, the CDER's oncology products branch would probably be in charge of a chemotherapy drug product that is administered through the use of a biologically derived carrier, such as an alginate. The processes of creating and launching a new medication are costly and time-consuming. Prospective applicants for drug-biologic combination products must take into account early collaboration meetings with the FDA, which include representatives from the CDER and the CDRH. This will ensure that they are aware of which agency regulations will apply to their product and identify any areas where guidelines and rules conflict [6]. The final approval procedures for a biologics license application (BLA) and an IND are different in both scenarios, even though the drug and biologic processes go through the same IND during clinical research. The FDA will arrange early meetings for collaboration with all companies concerning a new drug application and the prerequisites for preclinical and clinical testing. Regarding early collaboration meetings, each center has its own set of regulations, and these regulations are always changing as combination products are introduced. Examining the policies of the specific agency that will oversee the review procedure is the best course of action [7]. You can find web resources at the end of this chapter. Unless specifically requested under freedom of information laws, the FDA will maintain all pre-IND information as confidential. In the event that this happens, there will be a chance for both the FDA and the applicant to remove any proprietary or confidential information. Readers who create pharmaceuticals or other medical products should keep in mind that your company will always have greater product knowledge than the FDA. Effective communication between the FDA and the developers, or the early sharing of this information in the development procedure, which will greatly improve product development chronology. Pre-IND meetings are not legally binding on the FDA or the applicant, but the most common reason for denials is miscommunication. Meetings can take place in person or, at the applicant's option, over the phone.

DEVICE DESIGNATIONS

When combination products are referred to as combination devices, they are typically assigned to the review branch with the greatest experience in the relevant technology or are formally assigned to it. For instance, the Cardiovascular Devices Branch is responsible for drug-eluting stent devices. As previously mentioned, in order to ensure that the regulations are fully understood, it is crucial to investigate the device classification using the FDA database as early in the development process as feasible. The FDA has a large number of guidance documents, many of which are branch-specific. Being aware of the classification in advance will help you get in touch with the FDA employee who is most likely in charge of the review

procedure. As previously mentioned, it's critical to ascertain whether a predicate combination device that is comparable to the one under consideration has previously passed the CDRH. This would be a PMA application or a clearance through the 510(k) procedure. If a previous 510(k) for a comparable product has been approved, the FDA may be contacted quickly and informally at the outset. Additionally, it's possible that the FDA has created special guidelines for this kind of device that will help to clarify its views on what should be included in a premarket notification (510(k) filing) or an investigational drug exemption (IDE) to help with understanding FDA expectations, comprehensive guidance documents are available even for many PMA combination devices, like drug eluting stents. There is no need for early collaboration meetings with the FDA if there is clear evidence that the combination device will fall under the 510(k) premarket notification scheme (e.g., a central venous catheter coated with an anti-thrombotic coating), with the possible exception of meetings pertaining to any specific intended use statements that would necessitate clinical study[8]. When the evidence is ambiguous, it is appropriate to have an early collaboration meeting. Should there be any unanswered questions or significant disagreements from the early collaboration meeting, the more formal processes of RFDs and classification requests should be taken into consideration. The FDA will typically rely a great deal on prior decisions. Historical rulings are frequently consulted for guidance.

PRODUCT APPROVAL PROCEDURE

Product developers can request market authorization from the lead center by submitting the necessary market application to the lead center once the lead center has been assigned. Product submissions should be made under NDA if the lead center is CDER; product assignments to CBER should be made under BLA; similarly, applications filed under 510k or PMA based on device classification should be made under CDRH. For instance, the Gem 21S dental bone graft with growth factor is a combination product that contains both drug and device components. This product's main objective is to treat periodontal abnormalities. The drug component's secondary action is to encourage the formation of new bone. The product is governed by the CDRH as a Device since its main mode of action is derived from the Device component, and a PMA application would be used to review it. An additional instance yielding a distinct result is the transdermal patch. The patches main function is to treat ADHD; they are only a means of delivering the medication.

Drug and Device Development and Approval Process

Determining whether a device belongs in class I, II, or III and developing the necessary data—such as biocomparability, pre-clinical, and clinical data—are the first steps in obtaining approvals for devices. Different procedures are used depending on the classification of the devices: Pre-Market Notification for Class II devices, IDE, and Pre-Market Approval (PMA) for Class III devices. These authorized devices must have the correct labeling, registration, and listing. Additionally, as part of the approval process, the manufacturing site will be subject to GMP inspections by the FDA using a quality system. Drug development is, in general, a far more time-consuming and costly process that involves a wide range of phases, including pre-clinical, clinical, and research and development. Phase 1, Phase 2, and Phase 3 human clinical studies are further subdivided with varying objectives, lengths of study, and scales of study. These phases are intended to assess the product's efficacy as well as its initial safety and dosage. Candidate selection, synthesis, and purification are the first steps in the process. The animal testing phase comes next and could take up to 18 months. The second phase of human clinical research takes two to five years, spanning from phase 1 studies in healthy subjects to phases 2 and 3 in patient populations[9]. Lastly, it usually takes between six and ten months for the NDA/BLA to be submitted and reviewed for marketing approval. The FDA's ongoing regulatory oversights following marketing approval include post-approval modifications submission, adverse event reporting, and post-marketing surveillance.

CLINICAL CONSIDERATINS

Stakeholders in the industry should think about creating combination products that could challenge current methods for moving from a unique concept to a cutting-edge product that is sold. It might be necessary to create new processes for manufacturing, assessing preclinical safety in specific body regions, and designing clinical trials to prove efficacy and safety. A device and a medication or biological product are found in many combination products. In this combination, the Device component may fulfill the primary purpose, while the other product fulfills an auxiliary function. In other situations, the Device might have a secondary function of delivering the drug or biologic. Compatibility testing is necessary for each of the products, regardless of the situation. Elution testing will be assessed for use in timed-release applications[10].

DEVICE CONSTITUENT PART

Preclinical testing for device constituents that have already received approval for another use would primarily concentrate on the device constituent's novel application as a component of the combination product. For long-term drug delivery in the brain, new biocompatibility studies might be required if a

combination product includes an indwelling intravenous drug delivery catheter. This would help to confirm that the device materials are safe to be placed in neural tissues[10].

POTENTIAL SKILLS FOR EVALUATION

- Materials from the device that can be extracted or leached into the drug, biological material, or finished combination product.
- alterations in the drug constituent's stability when applied to the device or when the device is coated.
- Drug adhesion/absorption to the materials of the device, which may alter the dose that is delivered.
- The existence of manufacturing residues or inactive breakdown products from the device's manufacture that could compromise safety, or actions taken by the device that could alter the drug's performance characteristics during use.
- When combined with an energy-emitting device, a drug's constituents may become less stable or active.
- Drug and biological products can have a negative impact on the material properties of a delivery catheter.

STERILITY REQUIREMENTS

If a device is meant for sterile use or to be used for sterilizing other products, sterility is essential. Determining the test method and validation point will require consideration of sterilization techniques such as steam, ethylene oxide, gamma radiation, and so forth. The sterility assurance level (SAL) should be determined by the testing. Medical device manufacturers are required to verify all procedures, including sterilization, before releasing a device that is advertised as sterile. When a product is labeled as sterile, it is considered to be a stability characteristic and needs to be tested for shelf life. Stability testing should be included in the design validation of such devices. In order to ensure that the device remains sterile until it is used, sterility testing should consider the mechanical performance of the device, the integrity of the packaging, the shipping and transportation methods, and any other environmental factors [10].

STABILITY REQUIREMENTS

Stability testing is done to give proof of how a substance's or product's quality changes over time when exposed to different environmental conditions like light, humidity, and temperature. Through these tests, the manufacturer can determine or alter suggested storage conditions, intervals for retests, and shelf life or dating periods. Testing the shelf life of products that deteriorate over time is crucial. The duration of shelf life may also depend on the particular body fluids that the device may come into contact with, particularly for long-term implantable devices[10]. As such, the shelf life should be sufficiently supported and validated by real-time testing.

INVESTIGATIONS INTO DEVICE COMPATIBILITY CARRIED OUT DURING PREMARKET APPROVAL OF COMBINED PRODUCTS

The regulatory requirements for a single component of a combination product may be unfamiliar to the manufacturers because different laws and regulations have different approval processes. In particular, it can be challenging to conduct sufficient stability testing of drug/device combinations to meet these requirements.

In order to ensure the stability of these combinations, it is crucial to carry out stability studies correctly, from the initial phases of drug testing to the post-marketing research to ensure its effectiveness. Stability testing for drug components in combination products typically adheres to ICH guidelines (e.g., ICH Q1A). By contrast, there are significant differences in the requirements for Device stability testing. For instance, current ICH guidelines for drugs and biologics do not cover aging studies of a device. However, in order to evaluate the stability of a combination product, tests must account for both the drug and the device components, and the following concerns must be taken into account when developing the product:

- Requirements for stability data and shelf-life estimation.
- Conditions for shipping and storage.
- Investigations on the aging of devices containing drug components.
- The stability of a drug's carrier components, if any.
- Harmony between medication and equipment parts.
- Extractables and leachables while being stored.
- The impact of the production process on the stability of the product.
- Sterilization procedure and stability of the product.
- Stability during use, encompassing mechanical stress.
- Manufacturing adjustments and stability testing.
- Set aside samples for examination of stability.

When creating a stability program for a drug-device combination, there are also a few special items that need to be taken into consideration. First, in order to gather enough data to support the final product approval, the final stability protocol for a drug-device combination must be developed early due to a shorter development cycle. Second, unlike traditional drug products, combination products like drug-eluting stents are usually produced in small lots; as a result, in order to minimize the amount of samples required for stability testing, matrixing and bracketing designs are required. Ultimately, the following factors determine stability indicating tests: (1) drug component release rate in vivo and in vitro; (2) stability of important inactive ingredients (like coating polymer integrity); (3) drug-device interactions; (4) product effects of sterilization; and (5) monitoring of fatigue, corrosion, and durability of the device part [11]. But in order to approve a PMA for a product like a drug-eluting coronary stent, stability data from the finished product—which includes the device's final design and formulation—must be gathered and submitted in the marketing package. This data must be produced at the commercial production site and scale. The stability data must be used to determine the products' expiration dates. Additionally, stability data obtained during high stress or during use might be required for final product approval [11]. An expiration dating backed by stability data is a must for a drug-device combination product, unlike the approval of devices, for which it is typically not. The tests designed to indicate stability should encompass the distinct features of both the drug and device components in a combined product and evaluate the impact of their interactions on stability. Moreover, it is a good idea to use skip-lot and bracketing/ matrixing techniques to lower the sample size needed for stability testing [11].

CONCLUSION

In order to alleviate challenges that arise in the product jurisdiction of combination products, wherein one product is under the purview of either of the three centers—CDER, CDRH, or CBER—US regulations for combination products were developed. Although the primary mode of action of the product determines the lead agency center, the FDA has limited discretion in this regard. Combination products open up additional possibilities for creativity and flexibility. It is necessary to have a clear understanding of the product's primary mode of action in order to facilitate the creation, development, production, and approval of combination products.

AUTHOR CONTRIBUTIONS

KOMMALAPATI SWATHI IS the main contributor of the manuscript, writing and editing, and collecting data editing, and submission/correspondence of the above review article. The project was conducted under the supervision of: Koushik Yetukuri, Associate Professor.

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