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## Regulatory Knowledge Guide for Combination Products

### NIH SEED Innovator Support Team

#### Introduction

The U.S. Food and Drug Administration (FDA) defines **combination products** as “therapeutic and diagnostic products that combine drugs, devices, and/or biological products” and it regulates these products differently than standalone products. There are several FDA guidance documents available to help you ranging from [early development](#) to [post-development](#) considerations.

This guide aims to identify unique considerations for combination product development and introduce innovators to the regulatory process. Note that there are many additional development and regulatory considerations specific to the individual components of combination products; this guide does not include comprehensive information for each individual product type. Depending on the constituent parts in the combination product, the regulatory knowledge guides for small molecule drugs, biologics, and medical devices should also be reviewed and considered.

As an innovator, your critical first step is to determine if a product falls under the combination product category. A combination product is composed of any of the following combinations of regulated constituent parts: drug and device; biological product and device; drug and biological product; or drug, biological product, and device. These constituent parts can be combined into a single entity (e.g., an antibody-drug conjugate product), separate products that are co-packaged (e.g., a drug packaged with a corresponding empty syringe), or packaged separately but cross-labeled to identify the other product required for the full effect of the product, which may require updated labeling on the first-approved component (e.g., a light-activated biological product, cross-labeled for use with an activating light source).

FDA requires combination product constituent parts to be:

- Different product types (a product combining two different drugs would not meet the definition, but a drug and biological product does)
- FDA-regulated medical products (a drug and an FDA-unregulated dietary supplement is not a combination product)
- Labeled as specific for use with the other included components (FDA would not consider a syringe labeled for general use and packaged separately from a drug to be a combination product)

### Combination Products Can Be:

- A drug and device
- A biological product and device
- A drug and biological product
- A drug, biological product, and device

Please use the Word navigation panel to jump to relevant sections for your specific needs. Bolded terms within the text are defined in the Glossary.

If you have questions about the combination product development process, contact the [SEED Innovator Support Team](#) or [FDA](#).



After reading this Regulatory Knowledge Guide, you will have a better understanding of combination product development and the regulatory lifecycle. Specific topics that will be described include:

- How FDA determines which review center will be the lead reviewer of a proposed combination product.
- The special considerations you should be aware of when there are multiple constituent parts and/or a device-led constituent.
- How different types of manufacturing concerns related to combination products need to be addressed.
- The new challenges that the introduction of connected devices that link with apps and Bluetooth create for combination products.

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## 1 Defining the Combination Product

As noted in the introduction, FDA defines a **combination product** as any of the following combinations of regulated components: drug and device; biological product and device; drug and biological product; or drug, biological product, and device. While FDA regulates all combination products, only one of the three review centers within FDA (Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), or Center for Devices and Radiological Health (CDRH)) is determined to be the lead review center for the combination product. FDA assigns a lead regulatory review center based on the product's **primary mode of action** (PMOA), 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.” Both the lead regulatory review center and the regulatory pathway depend on the combination product constituent.

Note that an *in vitro* device that is a companion diagnostic to an associated therapeutic product would not generally be considered a combination product. Please see the *In Vitro* Diagnostic Regulatory Knowledge Guide for more information.

Resources:

FDA: [Definition of Primary Mode of Action of a Combination Product](#)

FDA: [Frequently Asked Questions About Combination Products](#)

### 1.1 Product Designation from FDA

If there is any doubt as to whether FDA considers the new product a combination product, FDA's Office of Combination Products (OCP) offers the **Request for Designation** (RFD) mechanism (also known as an applicant's letter of request).

The following information is required to submit an RFD:

- Basic information required by a Pre-RFD (product description, proposed use or **indications**, description of how the product achieves its intended effects)
- Description of the manufacturing processes
- Supportive data and studies
- Analysis and recommendation of product classification, center assignment, and PMOA
- Description of related products approved in the U.S.

Following receipt of OCP's determination on designation in response to a RFD, you can ask OCP to reconsider if you disagree with the jurisdictional decision. However, if the reconsideration request is based on new information, it must be submitted as a new RFD.

If you do not yet have the detailed information and data required for a RFD and would prefer to inform the development process with non-binding feedback from OCP, you can request an informal **Pre-Request for Designation (Pre-RFD)**.

A Pre-RFD requires:

- Product description
- Proposed use or indications
- Description of how the product achieves its intended effects

If FDA disagrees with your proposed product classification, FDA will notify you and guide the product to the appropriate center or recommend an RFD submission.

A company should decide which regulatory pathway to pursue early on, based on the time and cost goals and patent portfolios. This is a business consideration (i.e., changing the PMOA for a less burdensome path) and can be an important consideration if a different regulatory pathway is determined to be more appropriate. The following resources provide information on principles for premarket review of combination products, coordination within FDA, the interaction between FDA and sponsors regarding combination product regulation, how FDA reviews combination products before they are marketed, and how to determine which type of premarket submissions may be appropriate for your combination product.

Resources:

FDA: [How to Prepare a Pre-Request for Designation \(Pre-RFD\)](#)

FDA: [How to Write a Request for Designation \(RFD\)](#)

FDA: [Principles of Premarket Pathways for Combination Products](#)

## 1.2 Review Center/Division

In addition to providing determination on the combination product's classification, OCP also determines through the RFD processes which FDA center (CBER, CDER, or CDRH) will have primary jurisdiction for product review. The RFD should include a description of all modes of action for the product and a recommendation of a PMOA (supported with reasoning). OCP makes a final determination on the PMOA, and primary center of jurisdiction based on submitted product information, literature, and core information about the scientific characteristics and proposed use of the product.

If the PMOA is unclear, OCP may also use an algorithm to determine the center with primary jurisdiction. This process may be necessary if a product uses two different modes of action, neither being clearly secondary. In this case, OCP aims to assign the product to the center with previous expertise with similar combination products, or expertise in addressing the most pressing safety and efficacy questions raised by the new product.

### 1.3 Regulatory Pathways

Once you have determined that your new product is a combination product, FDA encourages you to confirm the appropriate regulatory pathway prior to going through the investigational or marketing application process. You may request a [pre-Investigational New Drug \(pre-IND\)](#) or [pre-Investigational Device Exemption \(pre-IDE\) meeting](#) with the appropriate center. These meetings are useful to discuss content and any sources of uncertainty before submitting a premarket application. Refer to the Small Molecules, Biological Products, or Therapeutic Devices Regulatory Knowledge Guides for more information on pre-IND or pre-IDE meetings.

For most combination products a single marketing application is used for the entire product, with the application pathway corresponding with the designated lead review center for the product. For instance, in determining the marketing application, the **innovator** would submit a **New Drug Application** (NDA) or an **Abbreviated New Drug Application** (ANDA) for a product with a drug PMOA, a **Biologic License Application** (BLA) for a biologic PMOA, or a **Premarket Approval Application** (PMA), De Novo, or premarket notification ([510\(k\)](#)) for a product with a device PMOA.

Although FDA usually encourages a single application for a combination product, data and information for each constituent part should be included as if they are separate applications. For example, a PMA application for a device-led combination product with a drug constituent part would also include non-clinical pharmacology, toxicology, clinical pharmacology data and chemistry, manufacturing, and chemistry manufacturing and control (CMC) information.

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**While FDA encourages a single application for a combination product, the data and information for each constituent part should be included as if they were separate applications.**

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There may be some circumstances when submitting different marketing applications for the different constituent parts of the combination product is advisable. For example, multiple applications may be necessary if one component is already approved but the new combination product requires a significant update to the existing labeling of the approved component to describe its use in the combination product. Consult with the lead center and OCP before preparing multiple applications.

### 1.4 Intellectual Property Considerations

Development of a combination product with cross-labeled or co-packaged components can create unique intellectual property challenges during the regulatory process. FDA prefers a single marketing application for combination products, which is not an issue for single entity innovators. But for those developing a cross-labeled or co-packaged product with other manufacturers, maintaining intellectual property within the single application is a concern. In these types of cases, FDA allows innovators to submit a letter of authorized cross reference from the other manufacturer. FDA can use the referenced material during review of the marketing application, with two options for cross reference sources:

- Existing investigational (IND or [IDE](#)) or marketing (NDA, BLA, PMA, [510\(k\)](#)) applications: the application could be under co-review for the combination product or already approved for previous purposes or indications.
- Master files (drugs or devices): a voluntary submission to FDA of any information a developer wishes to keep confidential.

Resources:

FDA: [Early Development Considerations for Innovative Combination Products](#):

FDA: [Master Files for Devices](#)

FDA: [Drug Master Files \(DMFs\)](#)

FDA: [Master Files for CBER-Regulated Products](#)

Article: [Combination Products: Regulatory and Patent Issues You Should Consider Now](#)

### 1.5 Approved Constituent Parts

If one of the constituent parts of a combination product is already approved or cleared, reference FDA's prior findings of safety and effectiveness or substantial equivalence in the regulatory submission. However, referencing a previously approved constituent part does not mean that additional studies are not needed. When combining an approved constituent part with another constituent part, FDA requires you to evaluate other scientific and technical issues based on the proposed use. For example, when an approved drug is combined with a new device as a carrier of the drug, the production additives within the device may impact the drug activity, release, and overall product safety and quality.

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**When using a previously approved constituent part, additional studies may be required to show safety and effectiveness of it when used in the combination product.**

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Additional data is particularly needed if the combination product has a new indication for use (IFU), a different target population, a new route of administration, or different local or systemic exposure profiles once the products are combined. For example, a drug that was previously released systemically may be included in a new drug-eluting stent combination product. The drug concentration in the tissue near the stent will likely be much higher than it was with the systemic delivery. Therefore, more study would be needed on the dosage of the drug, in addition to other factors that impact the safety and efficacy of the combination product. Specific considerations for each type of combination product are outlined in Section 2.

Resource:

FDA: [Early Development Considerations for Innovative Combination Products](#)

## 1.6 Constituent Parts with a New Molecular Entity

If the combination product includes a drug/biologic with a **new molecular entity** (NME), the NME component must be studied alone, prior to evaluating the combination product. You should first establish the safety profile of the NME without other constituents, which may include performing genotoxicity, mutagenicity, immunotoxicity, local tolerance, etc. studies before any clinical studies. In addition, compatibility testing of the drug/biologic with the delivery device using *in vitro* and *in vivo* tests will have to be integrated in the early development plan. Doing so helps ensure the PMOA and product **critical quality attribute** (CQA) requirements are met.

## 1.7 Interaction of Product Constituent Parts

For combination products, FDA recommends that developmental studies should consider both the device constituent and the drug/biologic constituent in the context of the proposed combined use. Regardless of whether the combination product consists of devices, drugs/biologics, prior approved/cleared components, or new molecular entities, a key focus in the marketing application should be evaluating how the constituent parts interact with each other (whether the interaction is desired for the function of the product or undesired). Such interactions may impact the stability of the drug/biologic/device component, activity of the drug/biologic component, the dose delivered, product safety, or drug performance. For example, for a drug eluting stent, the mechanical attributes of the polymer coating system that contains the drug substance are important for stent deployment, drug release, biocompatibility, and stability.

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**A key focus in the combination marketing application should be evaluating how the constituent parts interact with each other.**

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FDA recommends combination product developers carefully consider the following when evaluating the interaction of product constituent parts:

- What preclinical and non-clinical testing should be conducted for the product?
- What testing needs to be done to determine interactions of the constituent parts and their effects?
- Are there any prior approval/clearances of any constituent parts?

For some combination products, the constituents may have synergistic effects that should be evaluated (such as synergistic effects in drug-device combination products facilitating multi-target treatment, improved tolerance levels, simplification of dosage regime, and improved symptomatic and pharmacokinetic profiles). For example, a new innovative device used to deliver a drug or biologic to a new area of the body that was previously inaccessible might make it necessary to develop new methods to determine the effect of such localized/targeted delivery, particularly when it results in higher exposure to that target than when the drug is systemically administered.

When combination products include [digital health](#), the computer platforms, connectivity, software, or sensors serve as links to the constituent parts (devices, drugs, and biologics). The FDA continues to evolve its position and expertise on how to regulate digital health tools as part of combination products.

Resources:

NIH SEED: [SaMD & AI/ML Regulatory Workshop](#)

FDA: [What is Digital Health?](#)

FDA: [Guidances with Digital Health Content](#)

## 2 Types of Combination Products

The lead component/PMOA of a combination product dictates both the specific regulatory review center (CDER, CBER, and CDRH) within FDA and the regulatory pathway it will follow. The tables below outline the four types of combination products and the associated review centers and regulatory pathways.

*Table 1. Combination Product: drug + device*

Lead/PMOA	Lead Center	Regulatory Path	Links to Knowledge Guides
Drug	CDER	NDA/ANDA	Small Molecules, <a href="#">Therapeutic Devices</a>
Device	CDRH	PMA/510(k)/De Novo	Small Molecules, Therapeutic Devices

*Table 2. Combination Product: biologic + device*

Lead/PMOA	Lead Center	Regulatory Path	Links to Knowledge Guides
Biologic	CDER/CBER	BLA	Biologics, Therapeutic Devices
Device	CDRH	PMA/510(k)/De Novo	Biologics, Therapeutic Devices

*Table 3. Combination Product: drug + biologic*

Lead/PMOA	Lead Center	Regulatory Path	Links to Knowledge Guides
Drug	CDER	NDA/ANDA	Small Molecules, Biologics
Biologic	CDER/CBER	BLA	Small Molecules, Biologics

*Table 4. Combination Product: drug + device + biologic*

Lead/PMOA	Lead Center	Regulatory Path	Links to Knowledge Guides
Drug	CDER	NDA/ANDA	Small Molecules, Therapeutic Devices, Biologics
Device	CDRH	PMA/510(k)/De Novo	Small Molecules, Therapeutic Devices, Biologics

Biologic	CDER/ CBER	BLA	Small Molecules, Therapeutic Devices, Biologics
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## 2.1 Drug and Device Combination Products

For drug and device combination products, innovators should be aware that if the product does not have a strong patent portfolio or if a timelier approval at a lower cost is the goal, pursuing the medical-device-led pathway might be the best strategy.

### Considerations for Collecting Evidence to Support a Market Application:

Whether or not one of the constituent parts in a drug combination product was previously approved, the development plan may need to include additional studies to establish safety and efficacy data.

These may include:

- *In vivo* pharmacokinetic (PK) studies
- Dose ranging or dose finding studies in humans
- Acute and repeat dose toxicity studies using the new route of administration or method of delivery
- Special safety studies (e.g., hepatotoxicity, QT prolongation, special populations)
- Specific safety monitoring (e.g., local toxicity for a new route of administration)

For previously approved device constituent parts, consider whether the placement area of the device in the body is different from its approved intended use and whether additional study of the device's effect in the new environment is needed. For example, if the device will be placed in neural tissue for drug delivery to the brain for the first time, you may need to study the safety of the device in that environment. For combination products that offer innovative methods to deliver drugs to previously unreachable areas of the body, recognize that accessing these areas may require examining the impact of the localized delivery, often by developing new methods to do so.

There may be many considerations when evaluating potential interactions (desired or undesired) between device and drug constituents. For medical devices it may be appropriate to conduct studies to evaluate the potential for the following:

- Leachables/extractables from the device materials into the drug/biologic substance or final combination product
- Changes in stability of the drug constituent when delivered by the device or when used as a coating on the device
- Impact of drug adhesion/absorption to the device materials on the delivered dose
- Presence of inactive breakdown products or manufacturing residues from device manufacture that may affect safety, or device action that could change the drug performance characteristics at the time of use
- Changes in the stability or activity of a drug constituent when used together with an energy emitting device

### 2.1.a Drug-Led Combination Products

If the drug is the PMOA, then CDER is the lead review center under an NDA or ANDA. The Federal Food, Drug, and Cosmetic Act describes the pathway options.

- A full NDA (under 505(b)(1)) is appropriate when the product contains a new molecular entity.
- A full NDA (under 505(b)(2)) is appropriate when the applicant can use a “scientific bridge” (i.e., show safety of the new product by comparing it to a similar product that has already proved safety and effectiveness).
- An ANDA is appropriate for a drug-led combination product that includes information demonstrating that the non-lead constituent part is compatible with the final formulation of the generic drug constituent part.

Sponsors submit an ANDA for a generic or a 505(b)(2) application for a drug that partly relies on specific data from an already-approved drug. Generics approved via ANDAs are common, but examples of drugs approved under the 505(b)(2) pathway are less well known (e.g., follow-on insulin products).

ANDA and 505(b)(2) applicants have flexibility in the studies, data, and information they may submit. However, ANDA applicants should not submit clinical investigations to establish safety and effectiveness. 505(b)(2) applicants may rely on the FDA’s finding of efficacy and safety for a listed drug if the proposed product shares specific characteristics with the relied-upon listed drug. To justify the reliance on a listed drug, applicants must establish a ‘bridge’ (e.g., comparative bioavailability data) between the proposed product and each listed drug. When the listed drug and the drug proposed in the 505(b)(2) application differ, FDA requires the application include appropriate data to support those differences.

An applicant with ANDA-related questions or requesting a pre-ANDA meeting should contact the Office of Generic Drugs. An applicant with questions about submission of an application through the 505(b)(2) pathway should contact the appropriate review division within CDER’s Office of New Drugs.

Resource:

FDA: [Determining Whether to Submit an ANDA or a 505\(b\)\(2\) Application](#)

### 2.1.b Device-Led Combination Products

If the device is the PMOA, then CDRH is the lead review center, following the Premarket Approval (PMA), De Novo, or 510(k) regulatory pathway.

- High risk class III devices will likely use the PMA pathway. The application must provide sufficient supporting data and information to demonstrate safety and efficacy for both the combination product overall and its constituent parts.
- Moderate risk class II devices with an identified predicate device (that has the same intended use and shares the same technological characteristics of the device constituent parts *and includes the same active drug/biologic ingredients*) will likely use the 510(k) pathway.

- Moderate risk class II devices that are not combined with drug/biologic constituent parts or are combined with different drug/biologic constituent parts will generally not be a suitable predicate for the 510(k) pathway. When a 510(k) pathway is not available, the De Novo pathway for class II devices may be considered. In addition to developing special controls for the novel device constituent parts, a De Novo application should provide evidence to demonstrate the suitability of this pathway versus a PMA based on the drug/biologic constituent parts.

Refer to the Regulatory Knowledge Guide for Therapeutic Devices for additional information.

#### *New Device Constituents*

A combination product using a device constituent that is already cleared will likely only need preclinical study evaluating the new use of the device, e.g., if the device uses a new method of drug delivery or addresses a new indication. For a combination product with a new device constituent (requiring a PMA, De Novo, or 510(k) application), you will need to study safety and efficacy on the device alone, as well as the complete combination product.

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**All device components will require studying the interactions between the device and the drug/biologic component.**

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For both new and already cleared device components, you will need to study any desired or undesired interactions between the device and the drug/biologic component. Specifically, you may need to evaluate the stability of the drug/biologic when delivered with the device, unintended absorption of the drug/biologic to the device component, or manufacturing residues that could affect safety or efficacy of the delivered drug/biologic.

#### *Usability Testing*

Usability, or human factor testing, collects feedback on the form, function, and interface of the device to ensure it is effective and convenient for users. Usability testing results can be incorporated into subsequent product development. The usability test may or may not be on human subjects, but it does focus on feedback from device users. Information for user testing can inform, for example, the instructions for use, screen displays/interfaces, form and function, or packaging. Usability testing is not always required by FDA and can sometimes be implicitly addressed by research and feasibility studies. However, it is good business practice to conduct user testing to indirectly inform and improve regulatory discussions. If needed, human factors evaluation should occur early in development to enable early design modification before performing key safety and efficacy studies for the combination product.

Resources:

FDA: [Applying Human Factors and Usability Engineering to Medical Devices](#)

FDA: [Webinar on Applying Human Factors and Usability Engineering to Medical Devices](#)

FDA: [Principles of Premarket Pathways for Combination Product](#)

## 2.2 Biologic and Device Combination Products

Biologic and device combination products follow many of the same guidelines as drug and device combinations described in Section 2.1. For these types of combinations, products note the following:

- Biologic-device combination products have considerable development, regulatory, and commercialization challenges because of the biologic's unique physicochemical properties and special clinical considerations (e.g., dosing volumes, frequency, co-medications).
- Differences in the development, review, and commercialization of the biologic, device, and the combination demand design controls and risk management processes with extra supporting documentation compared to drug-device combinations.

Biologic-device combination product development and regulatory expectations are evolving rapidly. The evolution is due, in part, because biologics tend to have relatively similar efficacy profiles. So, the biotechnology market is differentiating products with patient-focused, biologic-device combinations that increasingly include digital medicine and connected health technologies.

### 2.2.a Biologic-Led Combination Products

If the biologic is the PMOA, then CBER is the lead review center for the combination product, under one of the two BLA pathways under the Public Health Service Act.

- 351(a) is the original approval pathway for biologics and is the pathway for approval of innovator biologics. It is also known as the traditional pathway for approval of innovator biopharmaceuticals.
- 351(k) is the approval pathway for biosimilars. Under 351(k) the combination product is reviewed as a biosimilar or interchangeable that is highly similar to an FDA licensed reference product.

### 2.2.b Device-Led Combination Products

See Section 2.1.b for specific considerations on device-led combination products.

## 2.3 Drug and Biologic Combination Products

Biologics are increasingly being co-developed in combination with drugs to target multiple, non-redundant mechanisms of action. Rational design of combinations and dual-targeting approaches that consider disease complexities can improve efficacy and safety, increase the duration of clinical benefit, and minimize clinical resistance mechanisms.

Specific development considerations for drug-biologic combinations include:

- Understanding the target biology
- Identifying non-clinical safety risks
- Using dose optimization strategies
- Understanding the regulatory framework

- Identifying pharmacokinetic, immunogenicity, and bioanalytical assay considerations

The disease biology, target dynamics, and pharmacology objectives are essential factors, and non-clinical safety assessment and dose optimization strategies can pose challenges for combinations. Examples of drug-biologic combinations include a monoclonal antibody combined with a therapeutic drug, antibody-drug conjugates, and progenitor cells combined with a drug to promote homing.

When a combination product's PMOA is attributable to a type of biological product assigned to CBER, the product will be given to CBER (e.g., PMOA is attributable to a gene therapy product). Similarly, when a combination product's PMOA is attributable to a type of biological product assigned to CDER, the product will be given to CDER (e.g., PMOA is attributable to a monoclonal antibody). For drug-biologic combination products where CDER regulates both the drug and biological product components, the combination product will be assigned to CDER. For inquiries regarding the most appropriate procedures to follow in determining the lead CDER reviewing division for drug-biologic combination products where CDER regulates both the drug and biological product components of the combination product, FDA recommends that sponsors submit an RFD.

Cell-based products may be regulated as combination products in certain instances and include cellular components (biological) physically or chemically combined with a drug. For the combination product, each constituent part retains its regulatory status (as a biologic or drug). As a result, the differences in regulatory pathways and requirements for each component can impact aspects of the lifecycle of the combination product. These aspects include preclinical testing, clinical investigation, marketing application, manufacturing and quality control, adverse event reporting, labeling and advertising, and post-approval modifications.

While development and approval for drug-led and biologic-led combination products are lengthy and expensive, pursuing them may come with FDA data exclusivities and patent-related protections that make the time and cost worthwhile.

In addition, for a combination product with a drug or biological product constituent that is already approved, it may be possible to tailor the preclinical development program to address safety questions posed by the new route or method of delivery, or the change in indication or population. The goal of these studies would be to evaluate changes that may result in a different extent or distribution of drug constituent exposure. In addition, new dosage (e.g., absolute dose, dosing duration, dosing regimen, or total exposure) will have to be evaluated.

If the combination product includes a drug/biologic with a **new molecular entity** (NME), see Section 1.5.

Resource:

FDA: [Transfer of Therapeutic Products to the Center for Drug Evaluation and Research \(CDER\)](#)

### 2.3.a Drug-Led Combination Products

See Section 2.1.a for specific considerations on drug-led combination products.

### 2.3.b Biologic-Led Combination Products

See Section 2.2.a for specific considerations on biologic-led combination products.

## 2.4 Drug, Device, and Biologic Combination Products

In drug, device, and biologic combinations the same principles for determining the appropriate review center and regulatory pathway apply. Seeking a drug or biological-product lead is more likely a strong choice if the combination product enjoys a robust patent portfolio. If the product does not have a strong patent portfolio or a timelier approval at a lower cost is the goal, pursuing the device-led pathway might be the best strategy.

Effects of the drug/biological product on the device constituent (for example, the material properties of a delivery catheter may be adversely affected by some drug/biologic products but not others) must be evaluated.

When developing combination products that include a drug, device, and a biologic, it is possible that the most important therapeutic action cannot be determined. For example, a combination product containing both a drug and a biologic could have two independent modes of action, and neither is subordinate to the other. To resolve these issues, FDA's regulations at [21 CFR Part 3](#) include rules for determining the center assignment. The algorithm dictates center assignment based on which center regulates combination products raising similar safety and effectiveness questions. If there is no such center, the decision is based on which center has the most expertise to evaluate the most significant safety and effectiveness questions raised by the combination product.

CBER and CDRH often collaborate in the review of combination products that contain a device and biological components. For example, FDA has issued guidance documents that provide current thinking on approaches for evaluating the biological responses to biomaterials and material sourcing issues, as well as physiochemical analyses and preclinical tests that may be appropriate for scaffolding materials. A review of relevant CDRH-recognized consensus standards may also be helpful.

### 2.4.a Drug-Led Combination Products

See Section 2.1.a for specific considerations on drug-led combination products.

### 2.4.b Device-Led Combination Products

See Section 2.1.b for specific considerations on device-led combination products.

### 2.4.c Biologic-Led Combination Products

See Section 2.2.a for specific considerations on biologic-led combination products.

### 3 Manufacturing Combination Products

Manufacturing a combination product may include designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage. In addition to manufacturing the constituent parts, combination products require consideration of how manufacturing may impact the final product as well as how to comply with **current good manufacturing practices** (cGMP). It may also depend on how the products are combined (single entity, co-packaged, or cross-labeled) and if there are multiple manufacturing facilities. All products must comply with relevant cGMP requirements from product development and testing through post-marketing.

Note that cGMP requirements differ depending on what product is manufactured and whether it is for pharmaceutical or diagnostic purposes. Quality systems regulations (QSR) are GMP standards described by the FDA for [manufacturing medical devices](#)—the QSR system represents specific GMP standards. The QSR system is focused on manufacturing systems and the validation of those systems.

#### 3.1 Constituent Parts Manufacturing

A combination product applicant holds the application for a combination product but may not be the manufacturer. A constituent part applicant holds an application for a constituent part of a combination product, which would be relevant if a combination product is cross-labeled and marketed by two different entities. If different entities are involved in developing a combination product, they have different responsibilities based on their role.

There are many considerations when manufacturing a combination product including manufacturing the individual constituent parts and how the constituents will be combined and may interact. In addition, you should consider the stage/phase of testing and development, scaling up, tracking, and evaluating changes in manufacturing. All stages of manufacturing must be compliant with the relevant cGMP requirements.

FDA recommends planning the manufacturing and chemistry manufacturing and controls (CMC) in parallel. These plans are made once preclinical development studies, process and prototype development, analytical testing product attributes, specifications and constituent part interactions, and other characterization methods have been established on both the constituent parts and the combined product. Experienced consultants can help ensure appropriate planning and determine when the combination product is ready for manufacturing. Refer to the Regulatory Knowledge Guide for Small Molecules for more information on cGMP manufacturing. More resources on manufacturing individual constituent products (drug, biological, device) can be found in the product-specific knowledge guides.

Resources:

FDA: [Early Development Considerations for Innovative Combination Products](#)

FDA: [Current Good Manufacturing Practice Requirements for Combination Products](#)

Article: [Product Development and Manufacturing Challenges for Combination Products; American Pharmaceutical Review \(2018\)](#)

### 3.2 Manufacturing Requirements

Manufacturing, scale-up, and quality management are also important considerations during the development of a combination product and impact both premarket development and post market regulation. Innovators should carefully consider the effect of the manufacturing methods on the interaction of the constituent parts. For example:

- The stability of a combination product should be measured as a whole, and also for individual constituents. The stability for the combination product may be different than of the separate constituent parts.
- Terminal sterilization techniques can alter certain drug or biological product critical quality attributes and, therefore, the active dose amount being delivered.
- Maintain manufacturing techniques to ensure aseptic control for the combination product.
- In-process testing, testing specifications, and other characterization methods to assess changes in the constituent parts during “assembly” of the final complete combination product are very important.

Additional bridging studies (*in vitro*, preclinical, or clinical) may be required to demonstrate constituent parts performance comparability.

cGMP requirements for combination products are explained in [21 CFR Part 4](#) and FDA’s [Current Good Manufacturing Practice Requirements for Combination Products](#). The cGMP requirements that apply to a combination product depend on the constituent parts and how the cGMP requirements for each constituent apply to the combination product. For example, for combinations that include biological products and human cells, tissues, and cellular and tissue-based products (HCT/Ps), a manufacturer must comply with the cGMP requirements that apply to the HCT/P or biological products if it were not part of the combination. For HCT/Ps, the current good tissue practice requirements outlined in 21 CFR 1271 would apply. Similarly, the manufacturer should comply with biologic/drug cGMPs and device quality system regulations following 21 CFR part 4. In addition, the combination product applicants retain overall responsibility for the product, including manufacturing, even if the owner is not directly engaged in its manufacture.

Demonstrating compliance with cGMP requirements varies based on how the constituents are combined (single-entity, co-packaged, cross-labeled). For example, for single-entity and co-packaged combination products, a streamlined approach may be used to demonstrate compliance with the drug cGMP (21 CFR parts 210 and 211) and device cGMP (21 CFR part 820) requirements.

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**The cGMP requirements that apply to a combination product depend on the constituent parts.**

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The specific applicable cGMP requirements are influenced by the activities conducted at the manufacturing facility and the type of product being manufactured. CGMPs apply to both the combination product manufacturer and constituent part manufacturers. For example, facilities that manufacture only one constituent part of a co-packaged or single-entity combination product are subject only to cGMP regulations for that part, but once constituent parts have arrived at the same facility the cGMPs for those constituent parts apply. Also of note, specifications developers and contract manufacturers are considered manufacturers and are subject to cGMPs.

Manufacturing changes in the constituent parts should be appropriately documented. Evaluate if the manufacturing changes of the constituent parts impact the safety or effectiveness of the combination product. Demonstrating compliance with cGMP requirements can be done through written procedures and documentation that cGMPs were used and verified. The cGMP compliance approach will need to be documented in premarket submissions. FDA also inspects for compliance with cGMPs, including review of supporting documentation. Experienced consultants can help ensure appropriate requirements are met throughout the process.

Some manufacturing considerations to be aware of include:

- cGMP requirements may vary depending on the stage of development. For example, before Phase 2 trials begin, a drug is exempt from cGMP for Finished Pharmaceuticals in 21 CFR Part 211, although must comply with 210; investigational devices are exempt from part 820, except for design control requirements under 21 CFR 820.30. These exemptions also apply to combination products with a drug or device constituent part.
- The FDA guidance on cGMP requirements for combination products includes information about design controls required for combination products with a device constituent part, including design validation, design transfer, and change control requirements.
- Even if there are already cGMPs in place for the manufacture of an individual constituent product, review of existing cGMPs may be needed once it is combined with another constituent (see FDA guidance Current Good Manufacturing Practice Requirements for combination products example B Drug-coated mesh). For example, design controls may need to be reassessed and revised when an existing drug is combined with an existing device.

### 3.3 Quality System Regulation for Medical Devices

Drug manufacturers planning to market a combination product should be aware of the administrative and technical requirements of the QSR [design control provision](#) for medical devices. Importantly, although design control requirements do not apply to all devices, when applicable, they apply even at the investigational stage. For example, manufacturers of combination products with a device constituent to which design controls apply must create a design history file (DHF), a historical file of a product's development. A DHF contains, among other things, documentation of periodic design reviews and results of verification and validation testing.

Manufacturers can leverage existing product development documentation to satisfy DHF requirements, but drug manufacturers—which may not be familiar with verification or validation testing—may need to carefully consider the testing necessary to ensure their products meet design control requirements.

Resources:

NIH SEED: [Quality Management Systems for Medical Devices](#)

Article: [Practical Considerations in Clinical Strategy to Support the Development of Injectable Drug-Device Combination Products for Biologics](#)

Article: [FDA Describes Streamlined Approach to Good Manufacturing Practice Requirement for Combination Products](#)

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