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# Regulatory Overview of Combination Products

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## Regulatory Overview of Combination Products

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INTRODUCTION

# Introduction to Combination Products

Combination products (CPs)are therapeutic and diagnostic products that combine drugs, devices, and/or biological products.

## The US FDA defines combination products (21 CFR 3.2(e)) as:

- Two or more regulated components, i.e., drug and device, biologic and device, drug and biologic or drug/device/biologic, which are physically, chemically or otherwise combined or mixed and produced as a **single entity;**
- Two or more **separate products packaged together in a single package or as a unit** and comprised of drug and device products, device and biological products, or biological and drug products (co-packaged);
- A drug, device, or biological product **packaged separately** that is intended for use only with an approved **individually specified** drug, device, or biological product where **both are required** to achieve the intended use, indication, or effect (cross-labeled).

Note:

- Combination products are not comprised of only two of the same type of medical product, e.g., drug/drug, device/device, biologic/biologic; a medical product combined only with a non-medical product, e.g., drug/food, drug/cosmetic. See 21 USC 353(g).
- The constituent part is a drug, device, or biological product that is part of a combination product; each retains its regulatory status.

Innovation in drug and biologic therapies along with technological advances in the design and development of delivery devices has resulted in a significant increase in available combination products. In parallel, there is an increasing demand for patients to be able to self-administer their therapies at home. This results in a reduced number of clinic visits, which appeals to both healthcare providers and patients alike. This trend is expected to continue as technological advances merge product types which results in blurring of the historical lines of regulatory separation. Since combination products involve components that would normally be regulated under different types of regulatory authorities, they raise regulatory, policy, and review management challenges. Differences in regulatory pathways for each component can impact the regulatory processes for all aspects of product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control and post-approval modifications.

# Details of United States Regulation of Combination Products

FDA's Office of Combination Products (OCP) makes the determinations of which Center has primary jurisdiction for review of both combination and single-entity (non-combination) products where jurisdiction is unclear or disputed. Thus, they classify products as drugs, devices, biological products or combination products and assign an FDA Center for premarket review and post-market safety oversight. OCP works with industry, CDER, CBER and CDRH and they serve as a resource for industry and FDA review staff. They oversee or assist in coordinating premarket review/approval and ensure consistent and appropriate post-market regulation and guidance. They also develop FDA policy, guidance and regulation.

## Jurisdiction Process and the Primary Mode of Action (PMOA)

The Primary Mode of Action (PMOA) ([503(g)(1)(C)] of the Act) is the single mode of action of a combination product that provides the most important therapeutic action of the combination product and is premised on intended use. The PMOA determines which Center has jurisdiction to be the lead Center to review the application and thus determines the regulatory pathway.

For example, for a drug eluting stent, the PMOA is the stent opening the artery and CDRH is the lead Center, whereas for a drug eluting ophthalmic implant, the PMOA is the ophthalmic drug treating a particular eye disease such as non-infectious uveitis and CDER would be the lead Center. Further, for a vial with a vaccine that is packaged with a delivery device, the PMOA is provided by the vaccine and CBER would be the lead Center. Combination products often have more than one mode of action and if the PMOA can't be determined, the OCP uses an algorithm for determining the Center assignment. The algorithm includes considering which Center regulates combination products with similar types of safety and effectiveness questions or which Center has the most expertise to address such questions.

## Request for Designation

A Request for Designation (RFD), also referred to as an applicant's letter of request (see 21 CFR 3.2(j)), is a written submission to OCP. RFDs generally request a determination of (1) the regulatory identity or classification of a product as a drug, device, biological product, or combination product, and/or (2) either the Agency within FDA that will regulate the product if it is a non-combination product, or which Agency Center will have primary jurisdiction for premarket review and regulation if it is a combination product. A letter of designation, (see 21 CFR 3.2(i)), is FDA's formal response to an RFD and is a binding determination with respect to classification and/or Center assignment that may be changed under conditions specified in Section 563 of the FD&C Act and 21 CFR 3.9 in the regulations. Though a designation letter is generally binding as to classification and/or assignment of a particular product, that determination pertains only to the product described in the designation letter.

FDA recommends submitting an RFD when the classification of a product or the Agency Center to which it should be assigned is unclear or in dispute. Sponsors should submit an RFD as soon as they have sufficient information for FDA to make a decision regarding classification or assignment of a product. The RFD should be submitted before filing any investigational or marketing application for the product. This will avoid a potential stay of the review clock if the classification or assignment of the product under review is determined to be unclear or in dispute during the review process.

OCP will review the submission for completeness within five business days of its receipt of an RFD and determine whether the RFD contains the required information. OCP will then either send the sponsor an acknowledgement letter confirming the filing date of the RFD or notify the sponsor that the RFD was not filed, and identify the information needed to make the RFD complete for filing. For filed RFDs, the acknowledgement letter will also identify the date by which FDA plans to respond to the RFD. If FDA does not issue a designation letter within 60 calendar days of the filing of the RFD, as required by 21 CFR 3.8(b), the sponsor's recommendation for the classification or assignment of the product will become the designated classification or assignment. See FDA Guidance for Industry, How to Write a Request for Designation (RFD), April 20111 for further details on the required RFD content and other important details.

# Combination Product (CP) Development and Regulatory Differences/Challenges

## Requesting Feedback on CPs and Formal Meetings

Application-based mechanisms that are available to drugs, devices and biological products are also available for CPs. However, FDA also provides a new meeting type: Combination Product Agreement Meetings (CPAMs) for which the lead Center is clearly determined. The purpose of the CPAM is to address the standards and requirements for marketing authorization requirements related to post-market modification and other relevant CP issues such as CGMPs. The goal is to get FDA agreement on a sponsor's proposal and more information/data may be needed in a CPAM request to increase the likelihood of FDA agreement. The CPAM package should be provided with the initial CPAM request. However, FDA encourages use of application-based mechanisms since they generally offer the most efficient and effective means to obtain Agency feedback. If there is an active application under review by FDA, application-based mechanisms should be used. CPAM should be submitted only when the sponsor believes they have identified the PMOA, indication for use and design of the CP. The sponsor should provide sufficiently robust information on the merits of the proposal(s) being made to ensure an effective review by all relevant disciplines at FDA. For issues where scientific evidence is limited and/or scientific thinking is evolving, a CPAM is unlikely to be productive. CPAMS are not appropriate to resolve scientific or regulatory issues. The CPAM is submitted to the lead Center, and it should be identified as a CPAM in the cover letter. FDA responds within 21 days, and the meeting is scheduled approximately 75 days after receipt; written agreements are issued at the conclusion. The submission content requirements outlined in Guidance for Industry and FDA Staff, Requesting FDA Feedback on Combination Products, December 20202.

## Differences Between Application-based Meetings:

- CDER/CBER – drug/biologic led CP: Type A (clinical hold, dispute resolution, SPA) Type B (pre-IND, EOP2, pre-NDA/pre-BLA) and Type C (anything other than Type A & B) meetings.
    - Type A – 30 days; Type B – 60 days; Type C – 75 days
- CDRH – device-led CP: Q-Submissions: Pre-Sub (IDE, PMA, 510k, etc.), Submission Issue Request (SIR)
    - Pre-sub meeting – 60 - 75 days; SIR – if received within 60 days of FDA marketing submission letter = 21 days, if > 60 days after FDA marketing submission letter = 70 days as resources permit

### Clinical Development/Studies - CDER/CBER

**21 CFR 312 - Investigational New Drug (IND) - 30 day review**

| Phase 1 | Phase 2 | Phase 3 | Phase 4 |
|---|---|---|---|
| • Safety & dose-ranging pharmacologic, metabolic activity<br>• FIH<br>• Early effectiveness | • Well-controlled to establish probable efficacy, side effects | • Evaluates overall benefit-risk<br>• Expanded well controlled for S&E | • Post-approved studies |

## Clinical Development/ Studies – CDRH:

- 21 CFR 812 - Investigational Device Exemption (IDE) – 30 day review
- Studies:
  - Early feasibility/ Traditional Feasibility/ Pilot – preliminary S&E; not statistically powered & informs pivotal study design
  - Pivotal – statistically powered to collect S&E data to support marketing application
  - Early/Expanded Access – compassionate use, emergency use, continued access
- Number of required studies and size is product-dependent
- No direct mapping to IND phases

**Pre-market Applications**

| FDA Center | Pre-market Application | Regulation | Review Time |
|---|---|---|---|
| CDER | NDA – 3 Types:<br>1. 505(b)(1) – full report of S&E<br>2. 505(b)(2) – full report of S&E but reliance on data from studies not conducted by applicant (e.g., an NDA, pub lit) or leveraging sponsor's previous data<br>3. 505(j) – identical in active ingredient, dosage form, route of administration, use, etc. to a previously approved product (ANDA) | FDCA section 505<br>21 CFR Part 314 | Priority Review = 6 months<br>Standard NDA = 10 months |
| CBER | BLA | Public Health Service Act section 501<br>21 CFR Part 601 | Same as NDA above |

**Exclusivity may apply for drug-led or biologic-led CPs, e.g.:**

- 5 years NCE 505(b)(1) & potentially for 505(b)(2)
- 3 yrs for New Clinical Investigation; 7 yrs for Orphan Drug Exclusivity & 6 mo for Pediatric Exclusivity = 505(b)(1) & 505(b)(2)
- Biologic Exclusivity = 12 yrs

**Pre-market Applications Cont'd**

| FDA Center | Pre-market Application | Regulation | Review Time |
|---|---|---|---|
| CDHR | 1. Pre-market Notification – 510(k): Cleared as substantially equivalent to a predicate device (at least as S&E); mostly class II<br>2. De Novo – risk-based process, provides pathway to classify novel MD as class I or II, no valid predicate<br>3. Premarket Approval (PMA) – class III, Approval: Reasonable assurance of S&E<br>4. Humanitarian Device Exemption (HDE) – marketing application for Humanitarian Use Device. Exempt from effectiveness requirements | 1. FDCA section 510(k)<br>21 CFR 807<br>2. FDCA section 513(f)(2)<br>3. FDCA section 515<br>21 CFR Part 814<br>4. FDCA section 520(m), 21 CFR Part 814 Subpart H | 1. Traditional = 90 days, Special = 30 days, Abbreviated = 90 days<br>2. De Novo decision = 150 days<br>3. 180 days if no panel; 320 days if a panel is required<br>4. 75 days for decision |

## Electronic Submissions and User Fees

CDER and CBER follow the electronic Common Technical Document (eCTD) structure for drugs and biologics whereas CDRH and CBER have the eCopy Program for medical device submissions (reference the Guidance for Industry and FDA Staff, eCopy Program for Medical Device Submissions, April 20203). Also, there is the Electronic Submission Template And Resource (eSTAR) that is an interactive PDF form that guides applicants through the process of preparing a comprehensive medical device submission. As of October 1, 2023, the electronic Submission Template and Resource (eSTAR) must be used for all 510(k) submissions to CDRH and CBER, unless exempted, (reference Guidance for Industry and FDA Staff, Electronic Submission for Medical Device 510(k) Submissions, October 20234). This requirement includes 510(k) combination products and Dual 510(k)/CLIA Waiver IVD submissions. As of the timing of this writing, eSTAR is voluntary for medical device De Novo submissions to CDRH or CBER and 513(g) requests for information to CDRH or CBER. eSTAR is also voluntary for medical device PMA (as of December 6, 2023) and Pre-Submissions (a type of Q-Submission) to CDRH. In August 2024, the FDA issued final guidance on using the eSTAR for submitting De Novo requests for medical devices: Electronic Submission Template for Medical Device De Novo Requests5. This guidance establishes an implementation date of October 1, 2025, for required use of eSTAR for De Novo submissions.

A single marketing application usually is sufficient for combination products and the information on all components must be comprehensive. For example, if the sponsor is submitting an NDA all of the device component details must be included in the relevant CTD sections, as applicable (reference eCTD Technical Conformance Guide, Technical Specifications Document, November 20226). However, FDA does allow multiple applications, for example, an NDA and 510(k), but the sponsor is strongly encouraged to discuss the details with the Agency prior to submissions.

The lead Center determines the type of single marketing application, and the related user fee is paid. If two applications are submitted, then both user fees apply. Fee waivers are available for meeting certain criteria, e.g., Innovative Combination Product Waiver, however, the criteria are challenging, and it is rarely applied.

## Manufacturing and cGMP Compliance

Table 1 below outlines the cGMP regulations for drugs, biologics, human cellular and tissue-based products (HCT/Ps) and medical devices.

| FDA Center | cGMP Regulation |
|---|---|
| CDER | Current Good Manufacturing Practices 21 CFR Parts 210 & 211 |
| CBER: Biologics & Human Cellular and Tissue-based Products (HCT/Ps) | 21 CFR Parts 600-680 21 CFR Part 1271 |
| CDRH | Quality System Regulation (QSR) - CGMPs 21 CFR Part 820 Note: Proposed rule on Feb 23, 2022, to amend the device CGMP requirements to align more closely with ISO 13485. FDA estimates rule to be issued Dec 2023. |

## CGMP Regulation for Combination Products – 21 CFR Part 4

On January 22, 2013, FDA issued the final rule on current good manufacturing practice (CGMP) requirements for combination products (21 CFR Part 4). The final rule did not establish any new requirements; it was intended to clarify which CGMP requirements apply when drugs, devices and biological products are combined to create combination products, and to set forth a streamlined regulatory framework to use to comply with CGMPs.

The constituent parts of a combination product retain their regulatory status (as a drug or device, for example) after they are combined. The final rule clarifies that the CGMP requirements that apply to each of the constituent parts apply to the combination product as a whole. The CGMP requirements for constituent parts of cross-labeled combination products that are entirely manufactured at separate facilities are the same as those that would apply if these constituent parts were not part of a combination product. For example, for a drug/device combination product, only 21 CFR Parts 210 and 211 would apply to the manufacture of the drug constituent part(s) of the cross-

labeled combination product, and only 21 CFR Part 820 would apply to the device constituent part(s)).

For single-entity combination products and co-packaged combination products, 21 CFR Part 4 identifies two options to demonstrate compliance with CGMP requirements. Under the first option, manufacturers demonstrate compliance with all CGMP regulations applicable to each of the constituent parts included in the combination product (quite onerous). Under the second option, manufacturers implement a streamlined approach for combination products that include both a drug and a device by demonstrating compliance with either the drug CGMPs (21 CFR Parts 210 and 211) or the device Quality System (QS) regulation (21 CFR Part 820) as well as demonstrating compliance with the specified provisions from the other of these two sets of CGMP requirements (see Figure 1 below). Also, for a combination product that includes a biological product, the manufacturer must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR Parts 600 through 680. For a combination product that includes any human cells, tissues, or cellular or tissue-based products (HCT/P), the manufacturer must demonstrate compliance with the regulations in 21 CFR Part 1271, including the current good tissue practice (CGTP) requirements and donor eligibility requirements. 21 CFR Part 4.4(c) provides that if a facility manufactures only one type of constituent part (e.g., a drug or device constituent part) of a co-packaged or single-entity combination product, that facility is subject only to the CGMP regulations applicable to that constituent part. 21 CFR Part 4.4(d) provides that when two or more types of constituent parts to be

included in a single-entity or co-packaged combination product have arrived at the same facility, or the manufacture of these constituent parts is occurring at the same facility, that facility must comply with all CGMP requirements described in Part 4 applicable to the manufacturing activities at that facility, and a streamlined approach under 21 CFR Part 4.4(b) may be used to demonstrate compliance with these requirements.

If a facility manufactures an independently marketed device that is subject to Part 820 and a combination product, it cannot manufacture the device under a drug CGMP-based streamlined operating system, even if it is used for the combination product, because this operating system only includes limited, specified provisions from the QS regulation. However, both the device and the combination product may be manufactured under a device QS regulation-based streamlined operating system, with the device that is not part of a combination product then being subject only to Part 820.

Figure 1 below outlines the two options for which manufacturers can comply with the CGMP regulations.

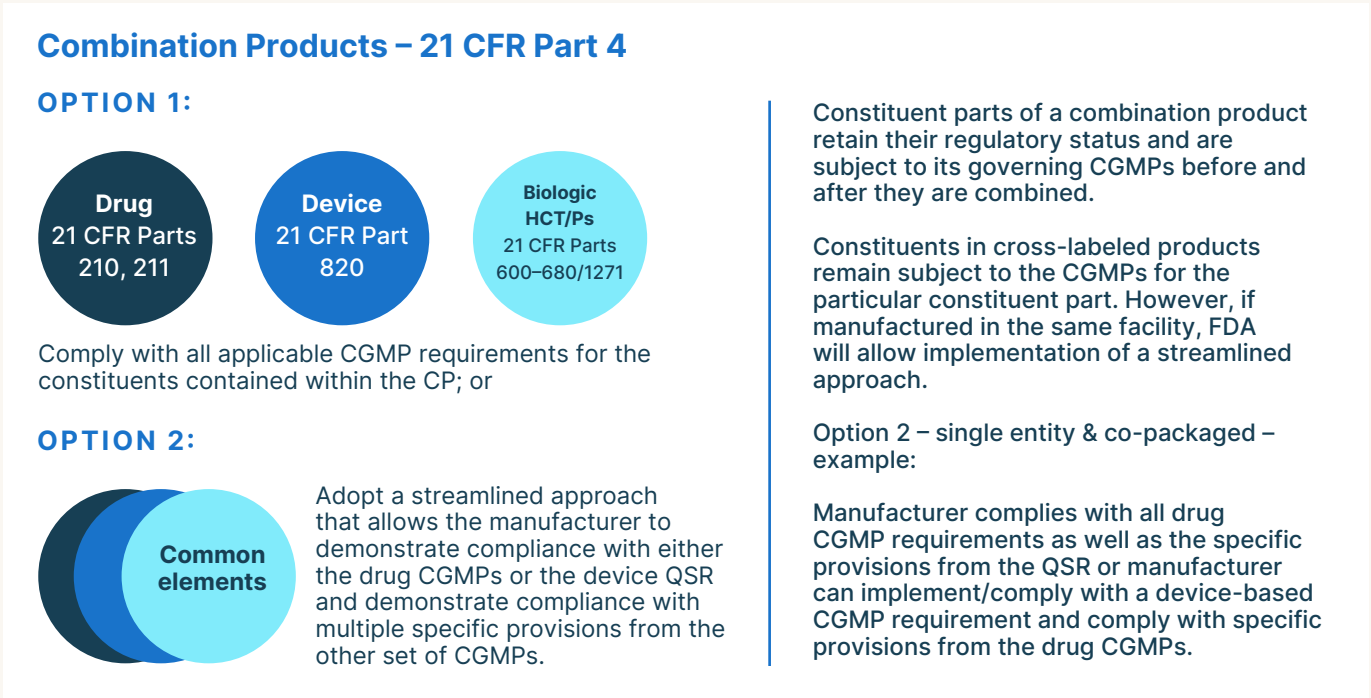



**Figure 1: Options to Comply with CP CGMPs**

The Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products, January 20177 elaborates on the FDA's expectations for implementation of the provisions.

- Note: a CP that contains a biologic or an HCT/P must comply with the requirements that would apply if either were not part of a CP
- A biologic regulated under 351 of PHS Act is also by definition either a drug or device.
    - Therefore, in addition to the applicable parts in Parts 600-680, a biologic is always subject to the drug CGMPs or the device QS regulations, regardless of whether it is a constituent part of a CP.

## Development Considerations of CPs: Integrating Quality by Design with Design Controls

Quality by Design and Design Controls are systematic approaches used during drug development and medical device design and development, respectively. While each has unique elements, there are a number of common principles between them and their ultimate objectives are comparable: using risk-based practices and scientific evidence throughout the product and process development and life cycle, resulting in a safe and effective product that remains fit for purpose for the life of the product. For example, both QbD and Design Controls begin with identifying patient/user needs, then defining product design requirements (i.e., specifications, design outputs), and include product testing/validation (i.e., characterization/ performance testing, clinical study, as applicable), process development/validation, risk analysis and risk management and life cycle management. Table 2 outlines the elements for QbD and Design Controls and how they correlate.

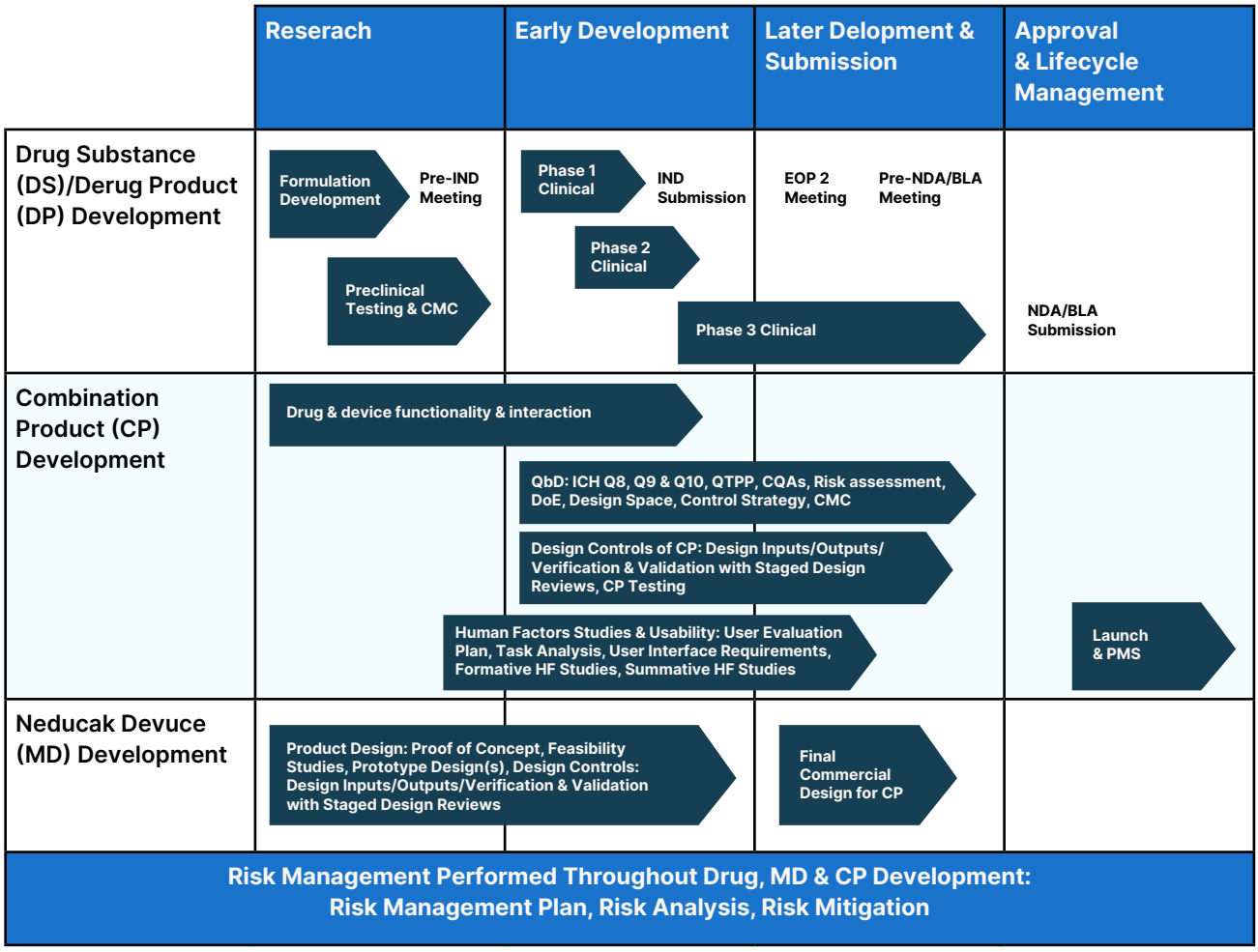
**Table 2 Correlation of QbD and Design Controls**

| Drug Development – QbD | Device Development – Design Controls |
|---|---|
| Quality System Framework: ICH Q10 Pharmaceutical QS, 21 CFR 211 (Drugs), 21 CFR 600 (Biologics) | 21 CFR 820 QSR and ISO 13485<br>Combination Product (CP) cGMPs: 21 CFR Part 4 (Streamline Approach) |
| Development Process: ICH Q8 Pharmaceutical Development | 21 CFR 820.30 Design Controls and ISO 13485 (7.3) Design and Development |
| Risk Evaluation: ICH Q9(R1) Quality Risk Management | ISO 14971 Risk Management – Devices |
| Master Project Plan | Design and Development Plan |
| Target Product Profile (TPP), Technical Requirements, Quality Target Product Profile (QTPP), CQA | User Needs, Essential Performance Requirements, Design Input 21 CFR 820.30(c), ISO 13485 (7.3.3) Design and Development Inputs, Human Factors: IEC 62366-1 Usability Engineering |
| Specifications, Drawings, MBR | Design Outputs 21 CFR 820.30(d), ISO 13485 (7.3.4) Design and Development Output |
| CMC stage gate reviews | Design Reviews: 21 CFR 820.30(e), ISO 13485 (7.3.5) Design and Development Review |
| Characterization/Suitability | Design Verification: 21 CFR 820.30(f), ISO 13485 (7.3.6) Design and Development Verification |
| Clinical Studies | Design Validation: 21 CFR 820.30(g), ISO 13485 (7.3.7) Design and Development Validation |
| Tech Transfer | Design Transfer: 21 CFR 820.30(h), ISO 13485 (7.3.8) Design and Development Transfer |
| Master Batch Records | Device Master Record: 21 CFR 820.181 |
| Change Control | Design Change Control: 21 CFR 820.30(i), ISO 13485 (7.3.9) Design and Development Changes |
| Product Dossier: Product Development Reports, Drug Development Project Files | Design History File: 21 CFR 820.30(j), ISO 13485 (7.3.10) Design and Development Files |

Robust combination product development requires that the interactions between the drug and device constituents be considered throughout development and lifecycle management to understand how they each function and how the function of the final combination product may be impacted. The development phases of the drug and device constituents must occur in parallel and be integrated to include touch points at key phases. For example, challenges will arise if the device constituent development does not correspond with the development of the overall combination product such as when the device constituent design is not representative of the planned commercial product. Therefore, it is important that the design iterations of the device constituent keep pace with the overall CP development process. A related consideration is the timing of when the formative and summative human factors studies are conducted. The formative HF studies learnings help to inform the device design over the development process and the summative HF studies is the final user/device interface testing and is part of the

design validation testing. Figure 2 below outlines the development process for a drug-device combination product and includes phases of each of the drug and device constituents and illustrates the integration of QbD and Design Controls.

**Figure 2 – Integration of QbD and Design Controls in Drug-Device CP Development**



## Post-approval Requirements

Post-approval changes to CPs generally follow the requirements of the lead Review Center. The CP Safety Reporting requirements are outlined in 21 CFR Part 4 Subpart B and the FDA Guidance for Industry and FDA Staff Post marketing Safety Reporting for Combination Products, July 20198, provides further details.

## CDER –High Level Summary of Post Market Requirements

- Changes to your NDA or ANDA: e.g., manufacturing process/manufacturing sites, specifications, container closure, labeling, etc.
    - Major changes – Prior Approval Supplement (PAS)
    - Moderate changes – Changes Being Effected (CBE), CBE-30 or CBE
    - Minor changes – Annual reports
- Annual reports
- Adverse Event reporting as per 21 CFR Part 314

## CDRH –High Level Summary of Post Market Requirements

- Changes to a legally marketed device
    - New PMA – significant changes to design/ performance rendering a new device
    - PMA supplements (multiple guidance to address each type)
        - Panel-Track supplement – changes to indications for use (patient population, different conditions of use)
        - 180-day supplement – significant design changes, new features, new principle of operation, hardware & software (SW) changes, etc.
        - Real-time supplement (90 days) – interactive, minor changes to design, SW, sterilization, labeling, etc.
        - Special PMA supplement – CBE – enhances safety, new warning, improved IFU
        - 30 Day Notice/135 Day supplement – minor improvements to manufacturing process, add supplier for critical material
- 510(k) – Traditional (90 day) - significant change to safety and efficacy (S&E), indications for use, etc.
    - Special 510(k) (30 day) – if design controls determine no performance data is needed, or if needed, well-established methods used to evaluate the change, including change to indications of use (previously prohibited),
- PMA Annual Reports (not applicable to 510(k))
- Adverse Event Reporting – 21 CFR Part 803

## Bridging for Drug-Device CPs and Biologic-Device CPs

FDA Draft Guidance for Industry Bridging for Drug-Device and Biologic-Device Combination Products, December 20199 provides the approach to bridging in NDAs or BLAs for drug-device and biologic-device single-entity or co-packaged CPs. Bridging is the process of establishing scientific relevance of information developed

in an earlier phase or another development program and leverage it to streamline CP development and support the marketing application. The sponsor should consider applying this to regulatory strategies to help streamline the development of the CP, for example using the 505(b)(2) regulatory pathway. Also, when post-approval changes are planned to the CP, such as changing from a pre-filled syringe to an autoinjector, the sponsor needs to plan for bridging studies to ensure the performance of the constituent parts and the overall CP itself are appropriately evaluated.

The draft Guidance outlines an analytical framework that includes a five-step approach:

**Step 1 – identify individual and aggregate differences.**

**Step 2 – identify existing S&E information and how it supports approval.**

**Step 3 – determine how and why existing information can be leveraged.**

**Step 4 – identify other supportive information (e.g., Summary Basis of Approvals, Labeling)**

**Step 5 – determine remaining information gaps.**

The draft Guidance recommends after completing the five steps the applicant meet with lead Center Review Division with consulting reviewers to discuss any information or clinical gaps that need to be addressed to support a marketing application for the new CP. Bridging is likely to be acceptable for well-characterized drug or well-understood device but may not be possible with some CPs due to complexity of the constituent parts, e.g., biologics that are likely affected by minor changes or for complex delivery systems. The draft guidance does provide case studies going through the five-step process.

# Summary of EU Requirements for CPs

The requirements for CPs in the EU differ significantly as compared to the US. The EU regulations do not use the term "combination product" but instead uses "drug-device combination", (DDC). The Primary Intended Action (i.e., PMOA) determines how the product is regulated.

Combination products can be regulated under the Medicinal Product Directive (Directive 2001/83/EC) as a medicinal product or the Medical Device Regulation (2017/745; MDR) as a medical device. Agencies involved in assessments include the European Medicines Agency (EMA), National Competent Authorities (NCA) & Notified bodies (NB) which is an organization designated by the European Commission (EC) to assess conformity of medical devices. If there is any uncertainty as to the classification of the CP, it is recommended that applicants seek opinion from a qualified Competent Authority (CA) and/or a properly designated NB.

**There are two main categories identified in the MDR:**

- Integral DDCs: Article 1(8)-a medical device that forms a single integral product with a medicinal substance intended for use in combination and is not reusable. a. Where the action of the medicinal substance is ancillary, the product is regulated as a medical device and must be CE marked and a scientific opinion must be provided from a medicines regulatory authority before a NB can issue a certificate for the CP. b. Where the action of the medicinal substance is principal, the CP is regulated as a medicinal product. Then the general safety and performance requirements (GSPR) of the MDR apply to the device.

- In Article 1(9): Devices intended to administer a medicinal product, where they form a single internal product intended exclusively for use in the given combination and which is not reusable. (Note: Typically, these devices have measuring, metering or delivery functions)

- The CP is regulated as a medicinal product and the relevant GSPRs of the MDR apply to the device.

- Non-integral DDCs: Article 2(11): The medicinal product and device are not integrated during the course of manufacturing but are combined for administration and co-packaged. The other type is the medicinal product and device are not integrated during manufacturing, are supplied separate but are combined for administration, labelled for use together in the Summary of Product Characteristics and Package Leaflet of the medicinal product.

- For co-packaged (non-integral) DDCs the medicinal product and medical device are each regulated individually under their respective regulations.

Manufacturers of DDCs will have to meet MDR Article 117 which applies to the device part and requires NB involvement for EU marketing authorization of a medicinal product (except for Class I non-sterile, non-measuring devices). Article 117 amends Annex I of the Medicinal Product Directive (MPD) 2001/83/EC (see point 12 in Section 3.2) and applies to single integrated, non-reusable products for which the drug constituent is the PMOA. In that case, the marketing authorization dossier must include the relevant general safety and performance requirements (GSPRs) of the device set out in Annex I to Regulation (EU) 2017/745 (MDR).

The DDC marketing authorization dossier must include, where available, the results of the assessment of conformity for the device part (i.e., the declaration of conformity (drawn up by the manufacturer or authorized representative)) or the relevant EU certificate issued by a NB which allows for CE marking of the device.

If the dossier does not include the results of the assessment of conformity, and an EU certificate from a NB would be required if the device was used separately, then the applicant will be required to provide an opinion

from a NB on the conformity of the device part with relevant requirements of Annex I to Regulation (EU) 2017/745 (i.e., the NB confirms compliance to the GSPRs and issues a report) as part of the Marketing Authorization Application.

If the device component does have a CE Mark, then the declaration of conformity/EU certificate issued by the NB will be available. However, it must be determined if it was assessed under MDD or MDR.

If assessed under the previous MDD, note the deadline of when it must comply with MDR (certificates issued under the old MDD will become void at different dates, depending on the class of the device (but not a blanket extension: e.g., additional requirements if certificates expire prior to March 20, 2023 and still not applicable to simple class I devices, no NB required):

- Dec 31, 2028 - Class I* (sterile, measuring, reusable surgical devices)/IIa/IIb (non-implantable or well established technologies (WET))
- Dec 31, 2027 – Class IIb (implantable non-WET)/III
- May 26, 2026 – Class III (custom-made implantable)

*Class I non-sterile, non-measuring devices must be in compliance with the MDR now. The extension does not apply to these devices.

**However, in order to take advantage of the extended timelines, a formal application for conformity assessment of the legacy device or its replacement MUST have been submitted to the NB by May 26, 2024 and a written agreement to conformity assessment signed by sponsor and the NB by September 2, 2024.**

If these deadlines are not met, the validity of the MDD certificates will not be extended and the legacy product must undergo the full assessment under MDR by the NB and the MDR CE certificate issued in order to be legally placed (and kept) on the market. Any legacy medical devices remaining on the market whose MDD certificates have expired must be taken off the market.

Note: Article 117 does not apply in the case of combined advanced therapy medicinal products as defined under Article 2(1)(d) of Regulation (EC) No 1394/2007 i.e., gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products.

# Conclusion

The innovative development of combination products is destined to continue, in part because the technological developments in the design and development of delivery devices keeps advancing and this has resulted in the ability of patients to self-administer their therapies conveniently at home, thus reducing required clinical visits. The merging of product types often pose regulatory challenges for both industry and regulatory authorities alike. Furthermore, the global regulatory landscape for combination products continues to be varied in policy amongst regulatory authorities and thus challenging in preparing effective global regulatory and commercial strategies. Future initiatives and collaboration amongst global regulatory authorities to harmonize policies and requirements are needed to help facilitate bringing innovative and technologically advanced CPs to global markets faster.

## REFERENCES

1. Guidance for Industry, How to Write a Request for Designation (RFD), April 2011.
2. Guidance for Industry and FDA Staff, Requesting FDA Feedback on Combination Products, December 2020.
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