SUBJECT: Inspections of CDER-led or CDRH-led Combination Products	IMPLEMENTATION DATE: June 4, 2020
DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Use Appropriate Product Code	Use Product/Assignment Code(s) for the Base Compliance Program (see PART III.1.A)

FIELD REPORTING REQUIREMENTS:

EIRs (Establishment Inspection Report) and FDA-483: A single EIR and, when applicable, FDA-483 should be used to document all observations made during an inspection at a *combination product manufacturer*[1] (See PART III.2– Reporting). Follow the Office of Regulatory Affairs (ORA) policies associated with the *lead center*, for example, regarding whether to annotate the 483 and practices for inspections (see also Reference 12, Chapter 5).

Reporting Requirements: Document the inspection in accordance with the field reporting requirements of the *base compliance program* for the combination product and with specific expectations identified in this Compliance Program:

1. For pre-approval inspections of CDER-led combination products approved under an Abbreviated New Drug Application (ANDA) or a New Drug Application (NDA), document in accordance with the field reporting requirements of Compliance Program 7346.832. For pre-licensing inspections of CDER-led combination products approved under a Biologics License Application (BLA), document in accordance with the field reporting requirements of Compliance Program 7356.002M.
2. For pre-approval inspections of CDRH-led combination products (Premarket Approval (PMA)), document in accordance with the field reporting requirements of Compliance Program 7383.001.
3. For surveillance inspections of CDER-led NDA/ANDA combination products, document in accordance with the field reporting requirements of Compliance Program 7356.002. For surveillance inspections of CDER-led BLA combination products, document in accordance with the field reporting requirements of Compliance Program 7356.002M.
4. For surveillance inspections of CDRH-led combination products, document in accordance with the field reporting requirements of Compliance Program 7382.845.
5. See PART III.2 – Reporting, for additional, specific reporting expectations.

Coordination with the Lead Center: If a compliance action is contemplated following a combination product inspection, ORA should coordinate with the *lead center* before such an action is taken. The *lead center* should be contacted regardless of which Current Good Manufacturing Practice (CGMP) regulations are cited (e.g., for a CDRH-led product, inspections resulting solely in drug-CGMP (21 CFR Part 211) and, if applicable, 21 CFR Part 600 observations, the compliance action should still be coordinated through CDRH).

[1] See Attachment C for discussion of "lead center" and other italicized terms used throughout this compliance program.

Investigators are encouraged to request pre-inspectional meetings through the *lead center* to support alignment regarding instructions or approach. Communication between the *lead center* and ORA should be conducted consistent with existing processes for ORA and that center.

Use of Profile Codes for CDER-led Combination Products: Inspections of CDER-led *combination product manufacturers* as described in this program should include at least one drug profile code and one device profile code (e.g., for an inspection of a facility manufacturing a sterile-filled prefilled syringe, use profile codes SVS-Sterile-filled small volume parenteral drugs and IDD-injectable delivery device (syringes, auto injectors/pens)). See also Reference 12, Exhibit 5-14.

NOTE: CBER-led combination products are not covered by this Compliance Program. For CBER-led combination products, refer to the CBER Compliance Programs, found at https://www.fda.gov/vaccines-blood-biologics/enforcement-actions-cber/compliance-programs-cber

Contents

PART I – BACKGROUND

In January 2013, FDA published a Final Rule on Current Good Manufacturing Practice (CGMP)[2] requirements for combination products (21 CFR Part 4, Subpart A). Before issuance of the final rule, CGMP regulations were in place to establish requirements for drugs, devices, biological products, and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). However, there were no regulations to clarify and explain the application of these CGMP requirements to combination products. The final rule was followed by an accompanying final guidance document *Current Good Manufacturing Practice Requirements for Combination Products* (Reference 9).

1. Combination Products

Definition of a Combination Product. A combination product is a product comprised of two or more different types of medical products (i.e., drug and device, drug and biological product, device and biological product, or all three together) (see 21 CFR 3.2(e)). A *constituent part* of a combination product is a drug, device, or biological product that is part of a combination product. This Compliance Program focuses on two types of combination products:[3]

- *Single-entity combination product*: The *constituent parts* are physically or chemically combined (e.g., a prefilled syringe or drug-eluting stent). See 21 CFR 3.2(e)(1).
- *Co-packaged combination product:* The *constituent parts* are packaged together (e.g., a surgical or first-aid kit containing devices and drugs, a delivery device packaged with a container of drug product). See 21 CFR 3.2(e)(2).

Examples of combination products include (see also list of examples):

- Prefilled syringes, transdermal systems, autoinjectors containing or packaged with drugs or biologics
- Drug-eluting stents
- Implants coated/impregnated with an antimicrobial drug
- Filled intravenous (IV) bags
- Antibody-drug conjugates

A combination product is assigned to an Agency center that will have primary jurisdiction (i.e., the *lead center*) for that combination product's review and regulation. Assignment of a combination product to a *lead center* is based on which *constituent part* provides the primary mode of action of the combination product (21 U.S.C. 351(g)). Generally, the application type, if any, for a combination product is aligned with the *lead center* (e.g., CDRH-led products would be approved or cleared under PMAs/510(k)/De Novo, whereas CDER-led combination products would be approved under ANDA/NDA/BLA). Generally, when needed, the lead center serves as the primary point of contact for the field related to an inspection of a *combination product*

[2] See 78 FR 4307.

[3] There is a third type of combination product, *cross-labeled*, where the constituent parts are distributed separately (e.g., as might be the case for a light-activated drug product and a separately distributed laser, drug-activating device) (21 CFR 3.2(e)(3), (4)). Manufacturers of *constituent parts* of *cross-labeled combination products* need only comply with the requirements otherwise applicable to that type of product (e.g., 21 CFR Parts 210 and 211 for a drug *constituent part* or 21 CFR Part 820 for a device *constituent part*). See also footnote 8 regarding expectations when *constituent parts* of a *cross-labeled combination product* are manufactured at the same facility.

manufacturer. The lead center will engage other FDA organizational components, as appropriate (see also Part VII – CENTER RESPONSIBILITIES).

2. Combination Product CGMPs

For *single-entity combination products* and *co-packaged combination products*, 21 CFR Part 4, Subpart A identifies two ways to demonstrate compliance with CGMP requirements for the combination product:

1. Compliance with all Applicable CGMPs. Demonstrate compliance with all CGMP regulations applicable to each of the *constituent parts* included in the combination product,

   OR

2. Streamlined Approach. Implement a *streamlined approach* for combination products that include both a drug and a device or a biological product and a device by demonstrating compliance with (i) either the drug CGMPs (21 CFR Parts 210 and 211) or the device Quality System (QS) regulation (21 CFR Part 820) (*base CGMPs*) and (ii) also with specified provisions (*called-out provisions*) from the other of these two sets of CGMP requirements. See below regarding additional requirements that apply to combination products that include a biological product *constituent part*.

   Specifically, the *streamlined approach* allows *combination product manufacturers* to meet the requirements of both the drug CGMPs and device QS regulation by designing and implementing a *CGMP operating system* that demonstrates compliance with either of the following:

   - The drug CGMPs and the following *called-out provisions* from the device QS regulation in accordance with 21 CFR 4.4(b)(1) (drug CGMP-based *streamlined approach*):
     - 21 CFR 820.20 - Management responsibility
     - 21 CFR 820.30 - Design controls (if applicable)
     - 21 CFR 820.50 - Purchasing controls
     - 21 CFR 820.100 - Corrective and preventive action
     - 21 CFR 820.170 - Installation (if applicable)
     - 21 CFR 820.200 - Servicing (if applicable)

   OR

   - The device QS regulation and the following *called-out provisions* from the drug CGMPs in accordance with 21 CFR 4.4(b)(2) (device QS regulation-based *streamlined approach*):
     - 21 CFR 211.84 - Testing and approval or rejection of components, drug product containers, and closures
     - 21 CFR 211.103 - Calculation of yield
     - 21 CFR 211.132 - Tamper-evident packaging requirements for over-the-counter (OTC) human drug products
     - 21 CFR 211.137 - Expiration dating
     - 21 CFR 211.165 - Testing and release for distribution
     - 21 CFR 211.166 - Stability testing

- 21 CFR 211.167 - Special testing requirements
- 21 CFR 211.170 - Reserve samples

Regardless of whether a streamlined approach is used, in addition, for a combination product that includes a biological product, the manufacturer must demonstrate compliance with all applicable CGMP requirements for biological products (including standards) that are found within 21 CFR Parts 600 through 680 (21 CFR 4.3(c)). For a combination product that includes any HCT/P, the manufacturer must demonstrate compliance with all applicable regulations in 21 CFR Part 1271.

PART II - IMPLEMENTATION

1. Scope

This compliance program focuses on inspections of *combination product manufacturers* (see definition in Attachment C) of CDER or CDRH-led[4] *single-entity* and *co-packaged finished combination products* that include both drug and device or biological product and device *constituent parts*, with limited reference to inspectional considerations for combination products that include a biological product or a human cell, tissue, or cellular or tissue-based product (HCT/P) *constituent part*. This compliance program should be used for pre-approval, post-approval, surveillance, for cause, and other risk-based inspections.[5] This compliance program does not cover inspection of combination products for which CBER is the *lead center*.[6]

This combination product compliance program should NOT be used for:

1. Facilities that manufacture[7] only one type of *constituent part* of a combination product (e.g., only the drug, device, or biological product). Such facilities should be inspected according to the existing *commodity-specific compliance program* for that product (see Attachment C and also footnote 3 regarding *cross-labeled combination products*). For example, if a facility manufactures only a drug *constituent part* that is then sent to a separate facility to be filled into a syringe, the facility manufacturing the drug constituent part to ship to the filling facility would be inspected according to the appropriate drug compliance program; whereas this combination product compliance program would be used to inspect the facility that fills the syringe with the drug *constituent part* to produce the *single-entity combination product*.[8]

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[4] The use of the term "CDRH-led" or "CDER-led" refers to which center is the *lead center* for the combination product.

[5] Third-party audit, appraisal or inspection programs (e.g., the Medical Device Single Audit Program (MDSAP)) may impact implementation of this compliance program. Contact the *lead center* if you have questions.

[6] For CBER-regulated products, refer to the CBER Compliance Programs, found at https://www.fda.gov/vaccines-blood-biologics/enforcement-actions-cber/compliance-programs-cber. CBER will consult with the other center(s), as appropriate, to evaluate inspectional observations for combination products. See SMG 4101 Inter-Center Consult Request Process.

[7] Note that "manufacturing" includes activities related to the design of the combination product (21 CFR 4.2). Any facility participating in design control, including recordkeeping, for the combination product is a *combination product manufacturer*. See Section III.C of Reference 9 and Attachment C of this Compliance Program.

[8] As discussed in the combination product CGMP guidance (Reference 9), for *cross-labeled combination products* manufactured at the same facility, the Agency does not intend to object to the use of a streamlined CGMP operating system for the manufacture of the combination product rather than distinct systems for the manufacture of each constituent part that is occurring at that facility. Contact the *lead center* if such a situation is encountered during an inspection. See also footnote 3.

2. Facilities that manufacture only "components[9]." 21 CFR Part 4 does not alter the CGMP regulatory requirements for component manufacturers. Facilities that manufacture only device components are not subject to the QS regulation (21 CFR 820.1(a)) and, similarly, manufacturers of active pharmaceutical ingredients, other components (e.g., excipients), or container/closures[10] of a drug product are not subject to 21 CFR Part 211 (though such manufacturers are subject to statutory CGMP requirements under Section 501 of the FD&C Act (21 U.S.C. 351). *However, a facility that assembles components into a combination product is subject to combination product CGMPs and is within the scope of this compliance program.*

2. Objective

The objective of this compliance program is to provide a framework for conducting inspections of *single-entity* and *co-packaged combination product* manufacturing facilities. This compliance program relies on relevant inspectional processes for CGMPs from the compliance programs specific to drugs, devices, and biological products, and addresses combination product-specific considerations.

A. Approach

Generally, the inspectional and administrative practices of the *lead center* and *base compliance program* will be the foundation of a combination product inspection. However, the approach outlined in this compliance program also relies extensively on other *commodity-specific compliance programs* associated with the *constituent parts* of a combination product (see PART III – INSPECTIONAL), to guide the conduct of combination product inspections.

Because most *combination product manufacturers* use a *streamlined approach*, this compliance program focuses on inspections of compliance with the *base CGMPs* plus the *called-out provisions* specified in 21 CFR Part 4.

B. Inspectional Planning

For surveillance inspections, the Office of Medical Device and Radiological Health Operations (OMDRHO), Office of Biological Products Operations (OBPO), and Office of Pharmaceutical Quality Operations (OPQO), within the Office of Regulatory Affairs (ORA), will compare workplan assignments for combination products and will utilize a risk-based evaluation of the product and the complexity of the manufacturing to determine each program's role.

For pre-approval inspections other than for BLAs, the ORA program aligned with the *lead center* will be the lead on the inspection. For example, for preapproval inspections of CDER-led NDA

[9] Under the drug CGMPs, "component" is defined as "any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product." (21 CFR 210.3). Under the device QS regulation, the term "component" is defined as "any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device." (21 CFR 820.3(c)).

[10] If the container/closure is provided as a finished device, the facility that manufactured that device *would* be subject to 21 CFR Part 820 requirements.

products, OPQO will be the lead on the inspection. For pre-licensing inspections for CDER-led BLAs, CDER will be the lead for the inspection.

Investigators are encouraged to request pre-inspectional meetings through the lead center to align instructions or approach. These meetings can be requested via the inspectional assignment contact, where available, or using the contacts in PART VI.3 – Program Contacts.[11]

If not already available, investigators should request the following information from the *lead center* before the inspection and/or, when the inspection is pre-announced, from the firm. The application holder for a combination product has and maintains overall responsibility for the combination product CGMPs and should be able to describe how all applicable CGMPs are being met for the combination product at each facility involved in the manufacturing of the combination product. If the information below cannot be obtained prior to the inspection, the information should be addressed early in the inspection.

- CGMP Operating System Approach. Determine the *CGMP operating system* chosen by the *combination product manufacturer*. Most *combination product manufacturers* choose to follow a *streamlined approach* that aligns with the *lead center*/application type (e.g., combination products approved under a PMA usually follow the QS regulation-based *streamlined approach* complying with all 21 CFR Part 820 requirements and the specified *called-out provisions* from the drug CGMPs). However, regardless of application type, a *combination product manufacturer* can choose to follow either of the *streamlined approaches* or full compliance.
- Relationship Between Entities. Request information about the facilities involved in the manufacturing (including design activities, see also footnote 7) for the combination product and about the scope of CGMP responsibilities of the facility to be inspected. CGMP activities for a combination product may occur at multiple facilities. For example, if another site is responsible for design controls for the combination product, (e.g., a specification developer contracting with the *combination product manufacturer* with documented responsibility for design), it may be more efficient or necessary to perform an additional inspection at that other site. Additional information or clarification about responsibilities determined during an inspection should be communicated back to the *lead center*.
- Availability of Documentation. For pre-announced inspections, confirm that documentation needed for review during the inspection will be available or accessible at the site being inspected. Documentation should include materials to enable review of compliance with called out provisions, including where to find content on considerations relating to called out provisions within related, broader elements of the facility's *CGMP operating system* (See e.g., Attachment A, discussion of augmenting 21 CFR 820.80 acceptance activities to address 21 CFR 211.84 requirements).

[11] If during preparation for an inspection or during an inspection an investigator believes a product may be a combination product that has not been identified as such, the investigator may contact the Office of Combination Products (combination@fda.hhs.gov) for assistance.

C. Personnel

Combination product inspections with coverage of both CGMP systems as described in this compliance program may be conducted with dual-program staffing (e.g., both a drug and a device investigator) or by an investigator with training and experience in combination product CGMPs. Regardless of the staffing for a combination product inspection, the inspection will be conducted consistent with the approach described in this compliance program.

3. Program Management Instructions.

Inspections for CDER-led and CDRH-led combination products should be conducted as indicated in this compliance program using content from the *commodity-specific compliance programs* (e.g., drug, biological product, and device) as described. This compliance program describes inspection considerations specific to facilities involved in the manufacturing of combination products. For example, PART III - INSPECTIONAL describes full and abbreviated inspection options for *combination product manufacturers* that are different from the options for drug-only or device-only facility inspections.

Where appropriate, the *lead center* will communicate any specific products for coverage or focus for the inspection via the established mechanisms for communicating such information.

Any interactions between the field and the centers regarding a combination product inspection should include the *lead center*. The *lead center* will engage expertise from other agency components, including other center(s), as needed, including to support review of inspectional findings (see Part VII – CENTER RESPONSIBILITIES).

PART III - INSPECTIONAL

1. Operations

A. Inspections

Combination Product CGMP Coverage During Inspections. As discussed below, coverage of CGMPs during a combination product inspection depends upon the inspection type, *base CGMPs*, scope of manufacturing activities at the facility, inspectional instructions provided by the *lead center*, and the application type for the product being inspected. Investigators are encouraged to request pre-inspectional meetings through the *lead center* and ORA supervisory staff to discuss inspectional coverage, center instructions, or the approach described in this compliance program. Communicate with the *lead center* via the contact provided in the inspection request, if available, or using the contacts in PART VI.3 – Program Contacts.

Some facilities participate in a limited part of combination product CGMP activities (e.g., a facility that manages only the design activities for the combination product, or a facility that only sterilizes a combination product). Inspectional coverage should be of those CGMP activities occurring at the facility. If there are questions regarding which facility is responsible for particular CGMP requirements, contact the *lead center* for assistance.

Approach for Combination Product CGMP Inspections. The inspectional approach described below involves (i) conduct of an inspection under the *commodity-specific compliance program* relevant to the *base CGMPs* and type of inspection (i.e., inspection under the *base compliance*

program) plus (ii) coverage of the relevant *called-out provisions* of 21 CFR Part 4 (see PART II.2 - Objective above).

Base CGMPs. Use of inspectional elements from the *base program* should include evaluation of CGMP considerations for the combination product as a whole. For example, during coverage of the production system at a facility that uses a drug CGMP-based *streamlined approach*, the investigator should evaluate production and process controls as directed in the associated drug compliance program. This evaluation should include evaluation of production and process controls for each *constituent part* and the combination product. Any observations related to these types of controls would be deficiencies in the 21 CFR Part 211 requirements (e.g., 21 CFR 211, Subpart F). Conversely, for a facility that uses a device QS-based *streamlined approach*, the investigator should evaluate production and process controls for the *constituent parts* and the combination product as directed in the associated device compliance program. Any observations related to these types of controls would be deficiencies in the 21 CFR Part 820 requirements (e.g., 21 CFR 820.70, 820.72, 820.75).

Called-out Provisions. Regarding *called-out provisions* (covered as described in Table 1 or Table 2 below), any observations related to these provisions would be deficiencies against the associated 21 CFR Part 820 or 21 CFR Part 211 requirements. Additional information on combination product inspectional considerations for *called-out provisions* is contained in Attachment A and Attachment B.

Other Inspectional Considerations for Combination Products: When conducting inspections of a *combination product manufacturer*, consider:

- The terminology (for example the definitions used in different quality system or regulatory documents) used by *combination product manufacturers* may vary (e.g., because they otherwise manufacture drugs or devices). Terminology differences should not be the basis of 483-observations as long as the *combination product manufacturer* can explain how their practices meet the requirements of the CGMP regulations applicable to the facility.
- FDA has signaled some flexibility in the CGMP approach for combination products in areas including testing and release for distribution (21 CFR 211.165), stability testing (21 CFR 211.166), special testing requirements (21 CFR 211.167), reserve samples (21 CFR 211.170), and design controls (21 CFR 820.30). See Reference 9. If a *combination product manufacturer* is using such approaches, appropriate evidence and an explanation of the rationale to support the approach should be accessible for review during facility inspections.

NOTE: If during an inspection an investigator identifies potential problems related to registration and listing, the investigator should contact the lead center for assistance. The investigator should contact ORA supervisory staff if there are any questions about combination product District Use Codes (DUCs) for a facility.

(1) Pre-Approval Inspections

Pre-announcement will typically apply to pre-approval inspections for ANDA/NDA/PMA combination products, consistent with the ORA inspectional process for the *lead center* (see also Reference 12). Pre-licensing inspections for CDER-led BLAs are also typically preannounced.

For combination product pre-approval inspections, the focus of the inspection should be on the combination product for which marketing approval is sought. Follow any inspectional guidance provided by the center(s), which will specify the coverage to be conducted during the pre-approval inspection. When coverage of both the *base CGMPs* and *called-out provisions* is specified, the *base compliance program* should be used to conduct the inspection, with additional inspectional coverage of the *called-out provisions* as specified in Table 1. Process validation coverage, including what process validation activities are expected to be complete at the time of the pre-approval inspection, will be communicated from the *lead center*. If there are questions on expectations for process validation, contact the *lead center* for assistance.

Generally, *combination product manufacturers* use a *streamlined approach* with *base CGMPs* that align with the application type for which pre-approval is sought (e.g., a drug CGMP-based *streamlined approach* for an NDA or ANDA, or a device QS regulation-based *streamlined approach* for a PMA). Although this is the most common situation, it is also acceptable for a *combination product manufacturer* to choose to operate under the other *streamlined approach* (e.g., a manufacturer for a PMA combination product could choose to operate under a drug CGMP-based streamlined approach). In these situations, the *lead center* will provide additional information or instruction in pre-inspectional meetings as necessary, and the coverage may differ from Table 1. If there are questions regarding coverage, the investigator should consult with ORA supervisory staff and the *lead center*, as appropriate.

NOTE: If a facility indicates that their combination product CGMP operating system is compliant with 21 CFR Part 820 and 21 CFR Part 211 in their entirety, conduct the inspection consistent with the approach for the combination product's application type as shown in Table 1. For example, if the pre-approval inspection is for a PMA, follow the inspection approach outlined for a PMA.

Table 1. General Approach to Pre-Approval Inspection Coverage for Combination Product Manufacturing Facilities

Application Type for Pre-Approval Inspection	**Base CGMPs**	**Base Compliance Program**	**Additional Coverage of Called-out Provisions**
NDA/BLA[12]/ ANDA	Drug CGMP (21 CFR Part 211)	7346.832[13] (NDA/ANDA) 7356.002M 7356.002A (BLA)	Cover the following requirements in accordance with Attachment B: Management Controls (21 CFR 820.20) Design Controls (21 CFR 820.30) Purchasing Controls (21 CFR 820.50) CAPA (21 CFR 820.100) Installation (21 CFR 820.170) and/or Servicing (21 CFR 820.200), if appropriate[14] *NOTE: If the combination product includes a CBER-regulated biological product or an HCT/P,[15] follow the relevant inspectional instructions and compliance programs (see Compliance Program 7345.848 and Compliance Program 7341.002) or contact ORA supervisory staff and the lead center for assistance.*

[12] CDER-led combination products that include a biological product *constituent part* are subject to both the drug CGMPs in 21 CFR Part 210 and 211 and the applicable CGMP requirements for biological products (including standards) found in 21 CFR Parts 600 through 680. As such, a manufacturer using a drug CGMP-based streamlined approach for such a combination product is subject to all of the requirements in 21 CFR Parts 210, 211, and 600 through 680 (as well as the *called-out provisions* of 21 CFR Part 820 if the combination product includes a device *constituent part*). See also PART I.2 – Combination Products CGMPs.

[13] Compliance Program 7346.832 is the general pre-approval inspection program for drugs. Other compliance programs, such as Compliance Program 7356.002A for Sterile Drugs should also be used, as applicable.

[14] Coverage of installation (21 CFR 820.170) and servicing (21 CFR 820.200) requirements and tamper-evident packaging requirements (21 CFR 211.132) should be included only for those products for which the requirements apply (i.e., combination products that require installation and servicing or OTC combination products, respectively).

[15] Biological products and biologic-led combination products are assigned to either CBER or CDER, depending on the type of biological product (see https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-research-cber/transfer-therapeutic-products-center-drug-evaluation-and-research-cder).

Application Type for Pre-Approval Inspection	Base CGMPs	Base Compliance Program	Additional Coverage of Called-out Provisions
PMA	Device QS (21 CFR Part 820)	7383.001	Cover the following requirements in accordance with Attachment A: Testing and approval or rejection of components, drug product containers, and closures (21 CFR 211.84) Calculation of yield (21 CFR 211.103) Tamper-evident packaging requirements for over-the-counter (OTC) human drug products (21 CFR 211.132)[14] Expiration dating (21 CFR 211.137) Testing and release for distribution (21 CFR 211.165) Stability testing (21 CFR 211.166) Special testing requirements (21 CFR 211.167) Reserve samples (21 CFR 211.170) *NOTE: If the combination product includes a biological product or an HCT/P,[15] follow the relevant inspectional instructions and compliance programs (for CDER-led biological products see Compliance Program 7356.002M, for CBER-led HCT/Ps see Compliance Program 7341.002 and for CBER-led biological products see Compliance Program 7345.848) or contact ORA supervisory staff and the lead center for assistance.*

(2) Surveillance Inspections

Pre-announcement will apply to surveillance inspections, as appropriate, consistent with the process for the *base compliance program*. For surveillance inspections where combination product coverage is conducted, investigators should prioritize combination products recently approved, cleared, or significantly changed (in terms of design) or those that include complex technology or manufacturing considerations. This applies unless there are indicators that there are safety and effectiveness concerns with other products. In all cases, coverage should include review of complaint trends to identify any potentially significant defects for inspectional scrutiny.

Abbreviated Inspections. Abbreviated inspections are generally used when the facility has a record of satisfactory CGMP compliance with no significant product defect incidents (including

significant Field Alert Reports (FARs), biological product deviation reports (BPDRs), medical device reports (MDRs), safety alerts, or recalls). See also Compliance Program 7356.002 and Compliance Program 7382.845.

Abbreviated inspections should typically *not* be used if:

- The facility has a history of non-compliance, recent product quality problems, complaint-handling issues, or significant defect issues, recalls, quality related consumer complaints, failure to meet specifications, potency failures, impurity failures and/or newly discovered impurities
- There have been significant changes in management or organization procedures (e.g., a change in ownership)
- New technologies or equipment requiring new expertise have been implemented since the previous inspection

An abbreviated inspection for a *combination product manufacturer* may be conducted in one of two ways, depending on whether the facility has previously been inspected against the *called-out provisions*:

1) *Abbreviated Base Plus Full Call-outs* (Abbreviated coverage of ONLY the *base CGMPs* plus FULL coverage of all the *called-out provisions*): The Abbreviated Base Plus All Call-outs option is appropriate when the facility has a record of satisfactory CGMP compliance and no significant product quality issues but has never been inspected against the *called-out provisions*. The abbreviated coverage applies only to the *base CGMPs* and the abbreviated coverage is consistent with the underlying compliance program for the *base CGMPs*. See Table 2.

2) *Abbreviated Base and Abbreviated Call-outs* (Abbreviated coverage of the *base CGMPs* AND abbreviated coverage of the *called-out provisions*): The Abbreviated Base and Abbreviated Call-outs option is appropriate when the facility has a record of satisfactory CGMP compliance, has been inspected against the *called-out provisions*, and has had no significant product quality issues. The abbreviated coverage applies to the *base CGMPs* and the *called-out provisions*. See Table 2.

During an abbreviated inspection, verification of overall quality system activities may warrant additional coverage in other systems. For example, for CDRH-led combination products, when the facility manufactures a sterile drug *constituent part* and/or combination product, coverage of related critical production and process control elements should be considered (see also Compliance Program 7356.002A).

An Abbreviated Inspection may change to a Comprehensive (Full) Inspection upon findings of objectionable conditions (see PART V – REGULATORY/ADMINISTRATIVE STRATEGY) with ORA division concurrence.

Comprehensive (Full)[16] inspections. Comprehensive (Full) inspections will be performed as resources permit, based on a risk-based determination**:**

- For the first inspection of a *combination product manufacturer* (e.g., an initial inspection)

[16] The terms "Comprehensive" and "Full" for purposes of this compliance program are equivalent. Because the underlying compliance programs for devices and drugs, respectively, use these terms, they are both included for completeness.

- For the initial coverage of called-out provisions after introduction of combination product manufacturing operations to a facility that previously manufactured only a drug, device, or biological product.
- When directed by the assignment
- For CDRH-led combination product foreign inspections
- When an inspection, started as an abbreviated inspection, reveals postmarket information or objectionable conditions (see PART V – REGULATORY/ADMINISTRATIVE STRATEGY) that cannot be adequately assessed in abbreviated inspectional coverage

Conduct abbreviated and full inspections consistent with the row of Table 2 for the *base CGMPs* in use at the facility.

NOTE: If a facility indicates that the combination product CGMP operating system is compliant with 21 CFR Part 820 and 21 CFR Part 211 in their entirety, conduct the inspection described in Table 2 for the base CGMPs that align with the application type(s) of the combination product(s) being covered during the inspection. For example, if the inspectional coverage is of NDA approved combination products, follow the inspection approach outlined for "Drug CGMP-Based." If the inspectional coverage if for PMA approved or 510(k) cleared combination products, follow the inspectional approach outlined for "Device QS-Based."

Table 2. General Approach to Surveillance Inspectional Coverage for Combination Product Manufacturing Facilities

Base CGMPs	Base Compliance Program	Additional Coverage of Called-out Provisions
Drug CGMP-Based (21 CFR 211)	7356.002[17] (NDA/ANDA) 7356.002M[18] 7356.002A (BLAs)	**For Comprehensive (full) AND for Abbreviated Base Plus Full Call-outs inspections, cover in accordance with Attachment B:** • Management Controls (21 CFR 820.20) • Design Controls (21 CFR 820.30), if applicable • Purchasing Controls (21 FR 820.50) • CAPA (21 CFR 820.100) • Installation (21 CFR 820.170) or Servicing (21 CFR 820.200), if applicable[14] **For Abbreviated Base and Abbreviated Call Outs inspections, cover in accordance with Attachment B:** • Design Controls (21 CFR 820.30), if applicable • CAPA (21 CFR 820.100) • Purchasing Controls (21 CFR 820.50) *NOTE: If the combination product includes a CBER-regulated biological product or an HCT/P[15], follow the relevant inspectional instructions and compliance programs (see Compliance Program 7345.848 and Compliance Program 7341.002) or contact ORA supervisory staff and the lead center for assistance.*

[17] Compliance Program 7356.002 is the general inspection program for drugs. Other compliance programs, such as Compliance Program 7356.002A for Sterile Drugs should also be used, as applicable.
[18] Compliance Program 7356.002M for inspections of licensed therapeutic biological products does not distinguish between full and abbreviated coverage. For surveillance inspections for combination products that contain a therapeutic biological product either full or abbreviated coverage of the call-outs may be used based on the inspectional history and other factors as discussed in the "Abbreviated Inspections" section above.

Base CGMPs	Base Compliance Program	Additional Coverage of Called-out Provisions
Device QS-Based (21 CFR Part 820)	7382.845[19]	**For Comprehensive (full) AND for Abbreviated Base Plus Full Call-outs inspections, cover in accordance with Attachment A:** Materials System: • Testing and approval or rejection of components, drug product containers, and closures (21 CFR 211.84) Laboratory Controls System: • Testing and release for distribution (21 CFR 211.165) • Stability testing (21 CFR 211.166) • Special testing requirements (21 CFR 211.167), if applicable • Reserve samples (21 CFR 211.170) Production System • Calculation of yield (21 CFR 211.103) Packaging and Labeling System • Tamper-evident packaging requirements for over-the-counter (OTC) human drug products (21 CFR 211.132), if applicable[14] • Expiration Dating (21 CFR 211.137) **For Abbreviated Base and Abbreviated Call Outs inspections, cover in accordance with Attachment A:** Laboratory Controls System: • Testing and release for distribution (21 CFR 211.165) • Stability testing (21 CFR 211.166) • Special testing requirements (21 CFR 211.167), if applicable • Reserve samples (21 CFR 211.170) *NOTE: If the combination product includes a biological product or an HCT/P, follow the relevant inspectional instructions and compliance programs (for CDER-led biological products see Compliance Program 7356.002M, for CBER-led HCT/Ps see Compliance Program 7341.002, and for CBER-led biological products see Compliance Program 7345.848) or contact ORA supervisory staff and the lead center for assistance.*[15]

[19] See also Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practices Regulations.

(3) For Cause and Risk-Based Inspections

These inspections are carried out in response to information that raises questions or concerns about a combination product or a facility that manufactures a combination product. These inspections are usually initiated at the request of the *lead center* for the combination product. The inspectional assignment provided by the *lead center* will outline coverage. These assignments are typically conducted to address specific issues (e.g., adequate implementation of corrective actions to address observations from previous inspections, or in response to specific events such as adverse events, complaints, FARs, BPDRs, or recalls).

For Cause inspections may require additional center expertise, especially for more complex products or when investigating apparent defects that could pose a significant health hazard. These inspections may not require coverage of all *constituent parts* and/or CGMP requirements that apply to the combination product. When such inspections are related to *called-out provisions* from 21 CFR Part 4, refer to Attachments A and Attachment B as resources for combination product inspectional considerations.

(4) Post-approval / Postmarket Inspections

Post-approval/Postmarket [20] inspections may be conducted for combination products to confirm continued compliance, including monitoring changes in the manufacturing processes that occur after product approval.

For both CDER-led and CDRH-led combination product post-approval/postmarket inspections, inspectional coverage should include assessment of the combination product and not just a *constituent part*, as appropriate. For example, if process validation for the specific combination product is covered during the inspection, process validation for any device, drug, or combination product manufacturing processes occurring at the facility should be assessed. If necessary, based on significant findings during a post-approval/postmarket inspection for a specific combination product, the scope of the inspection may be expanded.

For CDER-led combination products, post-approval inspections will be conducted consistent with *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations*, an agreement established between CDER and ORA in 2017. Post-approval inspections largely focus on the process validation lifecycle, change management, changes submitted to the application, and the execution of supporting activities per application commitments and CGMP requirements. Coverage of combination product CGMP requirements will be described in the related inspectional assignment.

For CDRH-led combination products, PMA postmarket inspections will be conducted consistent with Compliance Program 7383.001and coverage of combination product CGMP requirements aligns with Table 1 above.

(5) Special Situations – Combination Product "Convenience Kit" Manufacturers

Some facilities may assemble combination product "convenience kits."[21] These are kits that include only *constituent parts* that 1) are already legally marketed independently, and

[20] The terms "Post-approval" and "Postmarket" are used consistent with the terminology in the underlying compliance programs for drugs and devices, respectively.

[21] The term "convenience kits" is used in other documents for other types of kits. The definition of convenience kits in this Compliance Program is specific to combination product convenience kits (see also Reference 9, Section VI.1).

2) packaged in the kit consistent with how they are independently marketed (i.e., cannot include a change to the intended use of any of the *constituent parts*). Combination product convenience kit manufacturers only need to demonstrate compliance with applicable CGMP requirements with respect to the assembly, packaging, labeling, sterilization, and further processing of the kit itself, including purchasing controls.

If an investigator has questions about whether a combination product is a convenience kit and what CGMP requirements apply, they should contact the *lead center* or Office of Combination Products (OCP) for assistance (see PART VI.3 - Program Contacts). During review of Corrective and Preventive Action (CAPA) and complaints for a purported convenience kit, if there are 1) indicators of safety issues or 2) other concerns that suggest a change in intended use for any *constituent part(s)* as compared to the use(s) for which the *constituent part(s)* is legally marketed independently, the investigator should collect supporting documents, including any instructions for use, inserts, other product labeling, and evidence of interstate commerce for the combination product and *constituent parts*. Document the content of the kit and contact the *lead center* for assistance.

(6) Special Situations – Device Constituent Part Exempt from the device QS-regulations

FDA has exempted some devices from all or certain provisions of the device QS regulations (including Design Controls). This is not a consideration relevant to most types of devices that may be used as *constituent parts* of combination products. However, if such an exemption applies to a device type, it is also considered to apply to device *constituent parts* and, thereby, to the combination products of which they are a part in cases where the device *constituent part* in the combination product is of that same type (i.e., it does not have a new intended use and does not otherwise raise different device performance-related safety and/or effectiveness questions). If the exemptions for a device *constituent part* of a drug-device combination product cover all of the 21 CFR Part 820 provisions included in 21 CFR 4.4(b)(1), then the Agency will consider the *combination product manufacturer* CGMP compliant so long as the *CGMP operating system* is compliant with 21 CFR Part 211 (no demonstration of compliance with 21 CFR Part 820 will be necessary). See also Reference 9.

Many devices commonly used in combination products such as syringes, autoinjectors, and metered dose inhalers are NOT exempt. Examples of device types that may be exempt include medicine cups and oral dosing devices such as droppers and oral syringes. If a *combination product manufacturer* claims that the device *constituent part* and/or their combination product is exempt from 21 CFR 820 requirements, any investigator with concerns should contact the *lead center*.

2. Reporting

A single EIR and, when applicable, FDA 483 should be used to document all observations made at a *combination product manufacturer*.

Compliance with *base compliance program* reporting requirements. Documentation of the inspection should be in accordance with the reporting requirements of the *base compliance program* for the combination product (see FIELD REPORTING REQUIREMENTS on the cover page of this Compliance Program).

Additional reporting requirements. In addition to complying with the *base compliance program* reporting requirements, the EIR should include information on:

- The *CGMP operating system* in use at the facility for the combination product (e.g., Drug CGMP-based *streamlined approach*, Device QS-based *streamlined approach*, or full compliance with all drug CGMPs and device QS regulation requirements).
- A description of the manufacturing activities (including design activities, if applicable) occurring at the facility inspected. Also describe the relationship between the facility being inspected and other facilities that supply *constituent parts* or components thereof and/or perform combination product manufacturing activities (see footnote 7). For example, if the inspected facility is the contract manufacturer for the combination product, but a separate facility maintains the Design History File (DHF) and handles complaints, this should be documented in the EIR.
- Collect the evidence and samples necessary to support each observation including, where necessary, both specific examples and related procedures. For example, if an observation is made against the CAPA system, collect a copy of the overall CAPA procedure for the facility in addition to collecting evidence regarding the example(s) of failure to establish and/or maintain a CAPA system.

Citations. If a *combination product manufacturer* is operating under a *streamlined approach*, citations should ONLY be to provisions of the *base CGMPs* and to the relevant *called-out provisions* from the other CGMP system (e.g., for a drug-CGMP *streamlined approach*, citations should be limited to 21 CFR Part 211 and the *called-out provisions* from 21 CFR Part 820. Citations should not be made to other provisions of 21 CFR Part 820 that are not called-out).

Note: Observations on the FDA 483 should be limited to those related to the adequacy of, and adherence to, the procedures and/or controls established by the firm. Do not place observations on the FDA 483 that concern the adequacy, safety, or efficacy of a particular design. Any such concerns should be noted in the EIR and flagged for review by the lead center. See also Compliance Program 7382.845 "Special Instructions Concerning Design Controls."

PART IV – ANALYTICAL

Refer to PART IV of the applicable compliance programs for discussion of sampling and analytical testing:

- Compliance Program 7346.832 for pre-approval inspections for CDER-led combination products
- Compliance Program 7356.002 for surveillance inspections of CDER-led combination products
- Compliance Program 7382.845 for surveillance inspections of CDRH-led combination products
- Compliance Program 7383.001 for pre-approval and postmarket inspections for CDRH-led combination products

If there are questions on sampling or analytical testing, contact the *lead center* for assistance.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

The risks and intended use of the combination product and the potential adverse effect of the CGMP deviations on the finished combination product must be considered when determining the appropriate action needed.

Official Action Indicated-OAI. The field (ORA division (OMPTO, OPQO or OMDRHO)) submits a recommendation for regulatory action (OAI) to the *lead center* when a judgment is made that the *combination product manufacturer* is not operating in a state of control and management is unwilling or unable to make adequate corrective actions in an appropriate timeframe. See also PART V.2 and PART V.4 below.

Voluntary Action Indicated-VAI. If the nature of the CGMP deviations poses minimal risks when considered in relation to the risks and intended use of the product and there is not a history of repeat observation(s), the recommendation should normally be voluntary corrections by the firm (VAI). When voluntary action to address observation(s) identified during a previous inspection is not accomplished or when the deviations observed pose a serious risk to the consumer, then regulatory and/or administrative action should be recommended.

The procedures for developing recommendations and determining the need for regulatory action following an inspection are conducted consistent with the established process within and between ORA and the *lead center*. The *lead center* process should be used regardless of the types of observations (e.g., for a CDER-led product, even if the recommendation for regulatory action is based on 21 CFR Part 820 observations, the recommendation should be managed consistent with the CDER process). See also PART VII-CENTER RESPONSIBILITIES.

1. Pre-approval Inspections for Combination Products

FDA expects that a *combination product manufacturer* is compliant with the requirements in 21 CFR Part 4 at the time of a pre-approval inspection. After a pre-approval inspection for a *combination product manufacturer*, the inspection team makes an initial recommendation to the *lead center* through the Establishment Inspection Report (EIR) endorsement to approve or withhold the application approval based on the outcome of the establishment inspection.

Significant observations from either the *base CGMPs*[22] or *called-out provisions* (see PART V.4 below) should be equally considered when making a recommendation to approve or withhold. The *lead center* classifies the inspection after consideration of recommendations from the consulted center, as applicable (see PART V.3 below and also PART VII – CENTER RESPONSIBILITIES).

[22] As discussed in PART III.1.A – Inspections, inspectional elements from the *base compliance program* should include evaluation of CGMP considerations for the combination product as a whole. As such, significant observations from the *base CGMPs* may involve any type of constituent part or the combination product as a whole, as appropriate. For example, under a drug-CGMP based *streamlined approach*, significant deficiencies related to production and process controls for a device constituent part, drug constituent part, or the combination product as a whole would be cited under the *base CGMPs* (21 CFR Part 211).

2. Surveillance Inspections and Risk-Based Inspections for Combination Products

Inspection findings that demonstrate significant CGMP deficiencies or repetition of deficiencies identified in previous inspections, in relation to either the *base CGMPs*[22] or *called-out provisions* (see PART V.4 below), are bases for an inspection being recommended as OAI.

3. Inspections for Pre-approval in Conjunction with Another Type of Inspection

Combination product pre-approval inspections may be conducted in conjunction with another type of inspection that involves commercially-marketed product(s) (e.g., a pre-approval inspection conducted in conjunction with a surveillance inspection). Separate recommendations and associated actions may occur in these cases, as appropriate. For example, if significant findings result in a withhold decision for the pre-approval inspection and the findings extend beyond the pre-approval combination product, regulatory and/or administrative actions (such as issuance of a Warning Letter) may also be taken after coordinating with the *lead center*.

4. Significant Findings from the Called-out Provisions of 21 CFR Part 4

For combination product inspections, significant findings relating to the *called-out provisions* (in addition to the *base CGMPs*) should be considered when determining the division recommendation as explained below.

General Considerations. Regardless of the *CGMP operating system* for a combination product facility, non-correction of significant findings from previous inspections or repeat findings of the same or similar type as those observed on previous inspections (repeat observations) are significant findings.

Drug CGMP-Based Streamlined Approach. For a facility using a drug CGMP-based *streamlined approach*, in addition to the significant findings identified in the *base compliance program*, the following are examples of significant findings from the *called-out provisions* of the device QS regulation that could warrant an ORA division recommendation[23] to withhold approval or OAI (the following is not intended to be an exhaustive list):

1. Existence of combination products that do not meet the manufacturer's specifications and/or the applicable CGMP requirements in the 21 CFR Part 4 regulation and were not adequately addressed by the CAPA process.

2. Failure to adequately define, document, or implement Quality System Regulation requirements that apply to combination product facilities under 21 CFR Part 4, Subpart A. Consistent with Compliance Program 7382.845, examples include, where required:
    a. No procedure(s) that address corrective and preventive action (21 CFR 820.100)
    b. No procedure(s) on how quality data will be analyzed and used (21 CFR 820.100(a)(1))
    c. Where design controls are required, no design controls procedure(s) for the combination product (21 CFR 820.30)

[23] Note that for CDER-led pre-license BLA inspections, CDER is the lead for the inspection and the inspection team submits this initial recommendation.

d. Where design controls are required, no design change control procedure(s) (21 CFR 820.30(i))

e. No purchasing control procedure(s) (21 CFR 820.50)

Device QS Regulation-Based Streamlined Approach. For a facility using a device QS Regulation-based *streamlined approach*, in addition to significant findings identified in the *base compliance program*, the following are examples of significant findings from the *called-out provisions* from the drug CGMPs that could warrant an ORA division recommendation to withhold approval or OAI (the following is not intended to be an exhaustive list):

1. Significant data integrity problems, including misrepresented data or other conditions as related to the *called-out provisions* of 21 CFR Part 211. Issues related to data integrity should typically be cited under the related 21 CFR Part 211 *called-out provision* with associated discussion in the EIR narrative.
2. Incomplete or unsuccessful analytical method validation or verification for testing methods used to comply with *called-out provisions* of 21 CFR Part 211 for the drug *constituent part* and/or the combination product (e.g., testing methods used for stability (21 CFR 211.166), sterility/final release testing (21 CFR 211.165, 21 CFR 211.167), testing of reserve samples (21 CFR 211.170)).
3. Pattern of failure to follow approved analytical procedures and/or testing methods used for *called-out provisions* of 21 CFR Part 211 for the drug *constituent part* and/or the combination product (e.g., identity testing (21 CFR 211.84), testing methods used for stability (21 CFR 211.166), sterility/final release testing (21 CFR 211.165, 21 CFR 211.167), testing of reserve samples (21 CFR 211.170)).
4. Significant stability concerns (21 CFR 211.166) that raise questions about the drug *constituent part* such as:
    a. Stability study failures under recommended storage conditions
    b. Pattern of failure to follow stability programs
    c. Pattern of failure to evaluate stability failures
5. Pattern of failure to conduct testing (21 CFR 211.84 - identity testing for components, 21 CFR 211.165 - testing and release for distribution), including with regard to device *constituent parts* that also serve as a container/closure or part thereof.
6. An expiration date that is not supported by stability studies (21 CFR 211.137).

Particular attention should also be paid to the relationships between requirements, and to broader implications of deficiencies in one element for other elements or the operating process. For *combination product manufacturer* inspections, related deficiencies under different elements of the CGMP and/or Quality System *subsystems*[24] could warrant an ORA division recommendation to withhold approval or for OAI (see PART V of Compliance Program 7382.845 and Compliance Program 7383.001). In particular, deficiencies in requirements related to control of supplied products and in investigation of product problems can indicate a significant problem. For instance:

[24] *Subsystems* refers to the 21 CFR Part 211 (drug CGMP) subsystems as described in Reference 10 and the 21 CFR Part 820 (device Quality System) subsystems as described in Reference 9. See also Attachment C.

- For a facility operating under a drug CGMP-based *streamlined approach*, deficiencies in both purchasing controls (21 CFR 820.50) and testing and release for distribution (21 CFR 211.165) can indicate a significant finding is warranted. Similarly, a mixture of CAPA deficiencies (21 CFR 820.100) and complaint file (21 CFR 211.198) deficiencies can indicate a significant finding related to the firm's control over nonconforming product.
- For a facility operating under a device QS-based *streamlined approach*, deficiencies in both purchasing controls (21 CFR 820.50) and control of components, containers, and closures (21 CFR 211.84) can indicate a significant finding.

PART VI REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. References

1. Chapters II, III, V, and VII of Federal Food, Drug, and Cosmetic Act, as amended
2. Code of Federal Regulations, Title 21, Parts 4, 210, 211, and 820 as revised
3. Compliance Program 7346.832 - Pre-Approval Inspections [Drugs]
4. Compliance Program 7356.002 - Drug Manufacturing Inspections
5. Compliance Program 7356.002A - Sterile Drug Process Inspections
6. Compliance Program 7356.002M - Inspections of Licensed Biological Therapeutic Drug Products
7. Compliance Program 7382.845 - Inspection of Medical Device Manufacturers
8. Compliance Program 7383.001 - Medical Device Premarket Approval and Postmarket Inspections
9. Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*
10. Guidance for Industry - *Quality Systems Approach to Pharmaceutical CGMP Regulations*
11. *Guide to Inspections of Quality Systems, Quality System Inspection Technique*
12. Investigation Operations Manual – Chapter 5

2. Attachments

- Attachment A - Combination product inspectional considerations for the Called-out provisions of 21 CFR Part 211 (see 21 CFR 4.4(b)(2))
- Attachment B - Combination product inspectional considerations for the Called-out provisions of 21 CFR Part 820 (see 21 CFR 4.4(b)(1))
- Attachment C – Definitions and Acronyms

3. Program Contacts

Office of Regulatory Affairs
Questions regarding inspectional requirements and/or technical assistance:

- OMDRHO: ORADeviceinspectionPOC@fda.hhs.gov
- OPQO: ORAHQDrugInspectionPOC@fda.hhs.gov

Center for Drug Evaluation and Research
For questions related to CDER-led combination products:

- Pre-approval inspections: CDERPAIProgram@fda.hhs.gov
- Surveillance Inspections: CDERSurveillance@fda.hhs.gov
- For Cause Inspections: CDEROMQCompliance@fda.hhs.gov or CDERSurveillance@fda.hhs.gov (depending on the issuing office for the For Cause Inspection)
- If the product includes a CDER biologic, include: CDERBIOTECHINSPECT@fda.hhs.gov

Center for Devices and Radiological Health
For questions related to CDRH-led combination products:
CDRHProductJurisdiction@fda.hhs.gov

Center for Biologics Evaluation and Research
For questions on CDER/CDRH-led products that include a CBER biologic:
CBERInspections@fda.hhs.gov

Office of Combination Products
For questions related to the status of a product as a combination product or cross-cutting combination product policy questions: combination@fda.hhs.gov

PART VII - CENTER RESPONSIBILITIES

When ORA contacts the *lead center* during a combination product inspection as provided in this program, the *lead center* will facilitate interaction between product reviewers in that and secondary center(s) for the product.[25] When center review before an inspection identifies manufacturing concerns or issues that need to be addressed by the *combination product manufacturer*, that information will be highlighted in the inspection request. In some cases, expert(s) from the centers may accompany the ORA investigators during an inspection.

For CDER-led combination products, following a combination product inspection, findings will be reviewed consistent with the existing process for center review.[26] For CDRH-led combination products, a combination product inspection with findings[27] should be reviewed by CDRH. In either case, the *lead center* will engage other center(s) and OCP, as applicable, to ensure application of relevant expertise, appropriate consideration of cross-cutting implications of any action that may be taken, and consistency of Agency actions to address similar issues.

[25] The *lead center* will consult with the other center, as needed, to evaluate inspectional observations. See SMG 4101 Inter-Center Consult Request Process.
[26] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm576307.htm.
[27] CDRH review of NAI inspections for PMAs and Foreign Surveillance Inspections will occur as consistent with existing practices.

ATTACHMENT A – Combination Product Inspectional Considerations for Called-out Provisions of 21 CFR Part 211

This attachment provides additional information regarding the *called-out provisions* of the drug-CGMPs (21 CFR Part 211) for *combination product manufacturers* who utilize the device QS regulation (21 CFR Part 820) as their *base CGMPs*.

In addition to covering the device QS requirements according to the applicable *base compliance program*, evaluate the *combination product manufacturer's* compliance with the *called-out provisions* of 21 CFR Part 211 as described below.

21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures

Combination Product Considerations for 21 CFR 211.84:

For purposes of 21 CFR 211.84, *component* could include active pharmaceutical ingredients, excipients, and water or process gases that contact the drug *constituent part* (see 21 CFR 210.3(a)(3)). A container closure is the sum of packaging components that together contain and protect the drug *constituent part*. This includes primary packaging components that contact the drug *constituent part* and will also include secondary packaging components if intended to provide additional protection to the drug *constituent part*.

Combination product manufacturers do not need to comply with 21 CFR 211.84 for device *constituent parts* or materials used in the manufacture of a device *constituent part* **unless** the device *constituent part* is also the drug container or closure or a part thereof. For example, syringe components that are prefilled with the drug *constituent part* would be subject to 21 CFR 211.84, whereas materials used solely for manufacture of a device constituent part that is not part of the drug container or closure (e.g., a co-packaged syringe with a drug vial) would not be subject to 21 CFR 211.84.

21 CFR 211.84 may be related to other supplier controls activities (see also discussion of 21 CFR 820.50, Purchasing Controls, in Attachment B).

Inspectional Approach to 21 CFR 211.84 for a Facility Operating under a Device QS-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 211.84. For pre-approval inspections, refer to Compliance Program 7346.832: 1) Objective 1(b), related to the sampling, testing, and evaluation of drug *constituent part* components, containers, and closures, 2) Objective 2 elements related to the analytical methods for tests of drug *constituent part* components, containers, and closures described in the application, and 3) Objective 3 elements related to the authenticity and veracity of any incoming material testing results. For surveillance inspections, refer to Compliance Program 7356.002 "Materials System" elements related to the drug *constituent part* components, containers, and closures.

It is appropriate for facilities operating under a device QS-based *streamlined approach* to comply with 21 CFR 211.84 requirements by augmenting acceptance activities under 21 CFR 820.80 to incorporate 21 CFR 211.84 compliant measures.

For any active pharmaceutical ingredient and/or drug product intended for further processing into

the drug *constituent part* that is supplied to the *combination product manufacturer*, coverage of 21 CFR 211.84 should include confirming that at least one test is conducted to verify the identity of incoming material. If the facility relies on the supplier's report of analysis, the facility should have established the reliability of the supplier's analysis through appropriate validation of the supplier's test results at appropriate intervals and conduct additional testing (e.g., at least one specific identity test on components and at least visual identification for containers/closures, as appropriate. See 21 CFR 211.84(d)).

Reference/Resources:

- Compliance Program 7346.832 - Pre-Approval Inspections.
- Compliance Program 7356.002 - Drug Manufacturing Inspections.
- Section IV.B.1, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*
- Guidance for Industry - *Quality Systems Approach to Pharmaceutical CGMP Regulations*

21 CFR 211.103 Calculation of Yield

Combination Product Considerations:

Yield calculation requirements apply to the drug *constituent parts* of combination products. For *single-entity combination products*, calculation of yield must be performed on every batch of the combination product. For *co-packaged combination products*, calculation of yield must be performed on every batch of the drug *constituent part(s)*.

Although data on the number of device *constituent parts* and components used and lost during the manufacture of a combination product may be necessary to ensure appropriate control of the manufacturing process in accordance with 21 CFR 820.70, yield calculation in accordance with 21 CFR 211.103 is not required for device *constituent parts*. However, problems with the device *constituent part* during combination product manufacturing may affect drug yield. For example, prefilled syringes that are rejected because of nonconformity of the syringe needle may result in corresponding loss of drug. Any loss would be captured as part of the yield calculations for the drug *constituent part*. Investigation into the cause of that loss should identify the manufacturing problem that led to these device nonconformities.

Inspectional Approach to 21 CFR 211.103 for a Facility Operating Under a device QS-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 211.103. Calculation of yield should be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, and holding for the drug *constituent part(s)* and for the combination product as a whole. Accordingly, calculation of yield should be determined at each phase at which drug component, in-process material, or product loss may occur, including during the formulation of the drug, during incorporation of the drug into the combination product (e.g., filling or coating), and, where applicable, during the packaging process.

Reference/Resources

- Compliance Program 7346.832 - Pre-Approval Inspections
- Compliance Program 7356.002 - Drug Manufacturing Inspections
- Section IV.B.2, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*

21 CFR 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products

Combination Product Considerations for 21 CFR 211.132:

If a combination product is accessible to the public while it is for sale (i.e., non-prescription), it should have tamper-evident packaging. If this packaging is breached or missing, the consumer should be able to determine that tampering occurred. For *single-entity combination products*, the requirement for tamper-evident packaging applies to the combination product. For *co-packaged combination products*, the requirement for tamper-evident packaging applies to the drug *constituent part(s)*, but this requirement can be met if the entire combination product, including the drug *constituent part*, has tamper-evident packaging.

Certain combination products may be exempt from over-the-counter (OTC) tamper-evident packaging requirements, see 21 CFR 211.132(b)(1) (e.g., dentifrice products such as toothpaste co-packaged with a toothbrush or dermatological products such as a dermatological drug pre-filled into a delivery device, see 21 CFR 211.132(b)(1)). Certain combination products may be exempt from bearing a statement of tamper-evident features on the package, see 21 CFR 211.132(c)(1) (e.g., propellant-based aerosols and saline nasal sprays).

Inspectional Approach to 21 CFR 211.132 for a Facility Operating Under a device QS-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 211.132. Note that 21 CFR 211.132 is only applicable to OTC products and is, therefore, not applicable to many types of CDRH-led combination products. If an investigator has questions on whether this requirement applies, contact the *lead center* for assistance.

Reference/Resources

- Compliance Program 7346.832 - Pre-Approval Inspections
- Compliance Program 7356.002 - Drug Manufacturing Inspections
- Section IV.B.3, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*

21 CFR 211.137 Expiration dating

Combination Product Considerations for 21 CFR 211.137:

21 CFR 211.137 helps ensure that drug constituent parts of combination products meet applicable standards of identity, strength, quality, and purity at the time of use, by requiring that the product labeling bear an expiration date. Shelf-life[28] expectations for device constituent parts generally arise from design considerations (see 21 CFR 820.30). Generally, when *constituent parts* of a *co-packaged combination product* can be used independently, expiration dating, when required, should be listed separately for each *constituent part*. If a single expiration date is listed for a *co-packaged combination product*, this date should be the earliest expiration date/shortest shelf-life for any *constituent part*. In some cases, the drug *constituent part* might not have an expiration date because current regulations exempt it from this requirement (e.g., homeopathic drug products and investigational use products see 21 CFR 211.137(e) – (h)).

The expiration date for a combination product may be shorter than the expiration date or shelf-life for its *constituent part(s)* if marketed independently. Reasons for a shorter expiration date could include interactions between the *constituent parts* when combined, the effects of additional manufacturing steps, or one *constituent part* having a shorter expiration date than the other(s).

Inspectional Approach to 21 CFR 211.137 for a Facility Operating under a Device QS-based Streamlined Approach:

For pre-approval inspections, refer to Objective 2 elements of Compliance Program 7346.832 related to ensuring that the batches placed on stability for purposes of establishing expiration date are representative of the proposed marketed product (see also discussion of stability in 21 CFR 211.166 section below). For surveillance inspections, refer to "Packaging and Labeling System" elements of Compliance Program 7356.002 related to labeling the product with an expiration date.

Any observations related to the shelf-life/expiration dating for only the device *constituent part* should not be cited under 21 CFR 211.137. Such device *constituent part* considerations should be evaluated and, when appropriate, cited under 21 CFR 820.30 and related provisions (see also Attachment B for discussion of 21 CFR 820.30).

Reference/Resources:

- Compliance Program 7346.832 - Pre-Approval Inspections.
- Compliance Program 7356.002 - Drug Manufacturing Inspections.
- Section IV.B.4, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*
- Guidance for Industry - *Quality Systems Approach to Pharmaceutical CGMP Regulations*

[28] Expiration dating is the more commonly used term for drug constituent parts, whereas shelf life is more commonly used for device constituent parts.

21 CFR 211.165 Testing and release for distribution

Combination Product Considerations for 21 CFR 211.165:

Testing must be conducted to confirm whether drug *constituent parts* meet final specifications prior to releasing for distribution. For *single-entity combination products*, laboratory testing must be performed on every batch of the combination product. For *co-packaged combination products*, laboratory testing must be performed on every batch of the drug *constituent part(s)*.

For *single-entity combination products*, instead of using units from a finished combination product batch, manufacturers may wish to use samples that are not finished combination products but are representative of the finished combination product with respect to the characteristics and attributes relevant to testing the drug *constituent part* (see Section IV.B.5, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*).

Inspectional Approach to 21 CFR 211.165 for a Facility Operating under a Device QS-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 211.165. For pre-approval inspections, refer to Compliance Program 7346.832: 1) Objective 1(a) elements related to out-of-specification (OOS) results during final product testing;[29] 2) Objective 1(b) elements related to sampling, testing and evaluating finished products, 3) Objective 2 elements related to analytical methods validation for testing of the finished combination product, and 4) Objective 3 elements related to the authenticity and veracity of analytical results. For Surveillance Inspections, refer to Compliance Program 7356.002 "Materials System" elements related to testing and release of products for distribution.

If a *combination product manufacturer* uses product samples that are not finished combination products, appropriate evidence and an explanation of the rationale to support the approach should be accessible at the manufacturing facility for review during the inspection. If samples are being used for testing and release and there does not appear to be adequate data or justification for the approach, contact the *lead center* for assistance.

Reference/Resources:

- Compliance Program 7346.832 - Pre-Approval Inspections.
- Compliance Program 7356.002 - Drug Manufacturing Inspections.
- Section IV.B.3 and IV.B.5, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*
- Guidance for Industry - *Quality Systems Approach to Pharmaceutical CGMP Regulations*

[29] Quality data from OOS investigations and any related corrective actions should be addressed through the *combination product manufacturer's* quality system (see also 21 CFR 820.100 Corrective and Preventive Action (CAPA) below)

21 CFR 211.166 Stability testing

Combination Product Considerations for 21 CFR 211.166:

For both *single-entity* and *co-packaged combination products*, stability testing must be performed on the drug *constituent part* as incorporated into the finished combination product.

For *co-packaged combination products*, if the drug product is purchased from another manufacturer for inclusion in the combination product, the *combination product manufacturer* is still responsible for ensuring the stability of the drug *constituent part* as marketed in the *co-packaged combination product* through appropriate mechanisms, such as by implementing purchasing controls to ensure the adequacy of the drug product manufacturer's stability testing or by conducting additional stability testing (see 21 CFR 820.50). Documentation of such oversight should be included in the CGMP records.

Combination product manufacturers may be able to use bracketing and matrixing approaches or use stability data for a previously marketed product when a new combination product is a modification of that already marketed product and the modification does not impact the stability of the drug *constituent part* (see Section IV.B.6, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*). Appropriate evidence and an explanation of the rationale to support the approach should be accessible at the manufacturing facility for review during the inspection.

Inspectional Approach to 21 CFR 211.166 for a Facility Operating under a Device QS-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 211.166. For pre-approval inspections, refer to Compliance Program 7346.832: 1) Objective 1(a) elements related to out-of-specification (OOS) results during stability testing;[30] 2) Objective 1(b) elements related to sampling, testing, release, 3) Objective 2 elements related to assurance that the batches placed on stability for purposes of establishing expiration date will be representative of the marketed product (see also discussion of expiration date in 21 CFR 211.137 section above), and 4) Objective 3 elements related to assurance that the analytical results obtained are accurate. For surveillance inspections, refer to Compliance Program 7356.002 "Laboratory Control System" elements related to the stability program.

If the manufacturer is using stability data from a previously marketed product or bracketing or matrixing approaches, and there does not appear to be adequate data or justification for the approach, contact the *lead center* for assistance.

Reference/Resources:

- Compliance Program 7346.832 - Pre-Approval Inspections
- Compliance Program 7356.002 - Drug Manufacturing Inspections
- Compliance Program 7356.002B - Drug Repackagers/Relabelers
- Section IV.B.6, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*

[30] Quality data from OOS investigations and any related corrective actions should be addressed through the *combination product manufacturer's* quality system (see also 21 CFR 820.100 Corrective and Preventive Action (CAPA) below).

- Guidance for Industry - *Quality Systems Approach to Pharmaceutical CGMP Regulations*

21 CFR 211.167 Special testing requirements

Combination Product Considerations:

Special testing requirements to perform laboratory testing on each batch apply only if a combination product or the drug *constituent part* thereof is: purported to be sterile and/or pyrogen free,[31] includes an ophthalmic ointment or is a controlled-release product.

Parametric release in lieu of these special testing requirements may be acceptable for some terminally sterilized combination products and is common for some types of CDRH-led combination products. Use of parametric release requires FDA approval for combination products approved in an NDA, BLA, ANDA, or PMA. For some combination products (e.g., 510(k) cleared products), it may be permissible for manufacturers to adopt parametric release postmarket for a few well-established sterilization modalities (e.g., Ethylene Oxide Sterilization, Gamma Irradiation Sterilization) and control such changes under their Quality System without FDA review. If an investigator has concerns about whether a change to sterilization procedures should have been reviewed by FDA, contact the *lead center* for assistance.

It may be acceptable for the combination product manufacturer to define "batch" based on the drug *constituent part* rather than the finished combination product for purposes of special testing requirements for pyrogens and endotoxins. For example, it may be acceptable to define a batch as a subcomponent of the combination product that incorporates the drug *constituent part* (see Section IV.B.7, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*). Appropriate evidence and an explanation of the rationale to support the approach should be accessible at the manufacturing facility for review during the inspection.

Inspectional Approach to 21 CFR 211.167 for a Facility Operating under a Device QS-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 211.167. For products requiring sterility and endotoxin testing prior to batch release, refer to Compliance Program 7356.002A, Section 3.10 "Laboratory Controls System." For manufacturers using parametric release for sterility and endotoxins see Quality System Inspection Technique (QSIT) Product and Process Controls *Subsystem* and *Sterilization Process Controls*. If the manufacturer is using a parametric release approach, and there does not appear to be adequate data or justification for the approach, contact the *lead center* for assistance.

Generally, for terminally-sterilized CDRH-led combination products that are labeled as sterile, the sterility assurance level (SAL) is expected to be 10^{-6} (see Guidance *Submission and Review of Sterility Information in Premarket Notification (510(k) Submissions for Devices Labeled as Sterile* below). If a CDRH-led combination product or *constituent part* thereof labeled as sterile has another SAL value, you may contact the *lead center* for assistance, as needed.

If the combination product contains a sterile biological product *constituent part*, the *combination product manufacturer* must also comply with the requirements of 21 CFR 610.12 (Reference Compliance Program 7345.848, "Laboratory Controls System" "Availability for Distribution and Testing for Release for Distribution," Compliance Program 7356.002M "Aseptic/controlled

[31] Note that the appropriate terminology on the label of products may vary based on the combination product (for example, use of "non-pyrogenic," "meets pyrogen limit specifications" or "pyrogen free"). If an investigator has questions related to the labeling of a combination product, contact the *lead center* for assistance.

processes," and Compliance Program 7356.002A). Note that although 21 CFR 610.12 is specifically referenced as related to sterile product requirements, if a combination product contains a biological product all other requirements in 21 CFR 600 through 680 also apply (see PART I.2 – Combination Product CGMPs)

If the manufacturer is defining batch based on the drug *constituent part*, and there does not appear to be adequate data or justification for the approach, contact the *lead center* for assistance, as needed.

Reference/Resources

- Compliance Program 7345.848 – Inspection of Biological Drug Products (CBER)
- Compliance Program 7356.002A - Sterile Drug Process Inspections
- Compliance Program 7356.002M - Inspections of Licensed Biological Therapeutic Drug Products
- Guide to Inspections of Quality Systems, Quality System Inspection Technique
- Compliance Policy Guide Sec. 490.200 - Parametric Release of Parenteral Drug Products Terminally Sterilized by Moist Heat
- Section IV.B.7, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*
- Guidance for Industry - *Quality Systems Approach to Pharmaceutical CGMP Regulations*
- FDA Guidance for Industry - *Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions: Annex 14 Bacterial Endotoxins Test General Chapter*
- FDA Guidance for Industry - *Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes*
- FDA Guidance for Industry - *Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice*
- Guidance for Industry and Food and Drug Administration Staff - *Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile*

21 CFR 211.170 Reserve samples

Combination Product Considerations:

Single-entity and *co-packaged combination product manufacturers* must keep reserve samples of each lot of the active ingredient, if any, that they receive, in whatever form it arrives at their facility (e.g., as bulk active pharmaceutical ingredient or incorporated into an in-process material) as well as reserve samples for the combination product.

For *co-packaged combination products*, the requirement to keep reserve samples for the combination product can be met by maintaining samples of the drug *constituent part* in its immediate container-closure system without retaining samples of the device *constituent part* from the same package. For *single-entity combination products*, the combination product reserve sample is generally the finished combination product, including the device *constituent part* or components thereof that come into contact with the drug *constituent part* as packaged for distribution. This may involve retaining the entire combination product (e.g., prefilled syringe) or a separable portion (e.g., a cartridge).

It may be acceptable for *combination product manufacturers* to retain reserve samples that are representative of, but not identical to, a finished drug *constituent part* or combination product, or to maintain validated surrogates for some testing while retaining complete samples of the combination product for other tests (see below). It may also be acceptable to retain samples that are representative lots of a larger batch (e.g., representative samples of each size from within a broadly defined batch that includes multiple sizes of the same family of coated combination products such as drug eluting stents or drug coated catheters). (See Section IV.B.8, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*). Appropriate evidence and an explanation of the rationale to support the approach should be accessible at the manufacturing facility for review during the inspection.

The *combination product manufacturer* must maintain twice the quantity of active ingredient and combination product reserve samples necessary to perform required tests, except for sterility and pyrogen testing (see 21 CFR 211.167 Special testing requirements above for additional information regarding sterility and endotoxin testing). The quantity of product kept as reserve samples should be aligned with the batch definitions in any related premarket submission for the combination product. A sample of the device *constituent part(s)* may also need to be kept if, for example, the device *constituent part* is needed to perform any required tests.

Inspectional Approach to 21 CFR 211.170 for a Facility Operating Under a device QS-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 211.170. For pre-approval inspections, refer to Compliance Program 7346.832 Objective 2 to assess whether the reserve sampling practices at the facility are consistent with what was specified in the premarket application and/or follow any instructions provided from the *lead center* regarding acceptable reserve sample approach. For surveillance inspections, refer to Compliance Program 7356.002 "Laboratory Control System" elements related to the stability program.

If a *combination product manufacturer* is keeping reserve samples that are representative but not identical to the marketed product or using samples from a representative lot (see above), and there does not appear to be adequate data or justification for the approach contact the *lead center* for assistance.

Reference/Resources

- Compliance Program 7346.832 - Pre-Approval Inspections
- Compliance Program 7356.002 - Drug Manufacturing Inspections. Refer to "Laboratory Control System" elements related to the stability program
- Section IV.B.8, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*
- Guidance for Industry - *Quality Systems Approach to Pharmaceutical CGMP Regulations*

ATTACHMENT B – Combination product inspectional considerations for Called-out provisions of 21 CFR Part 820

This attachment provides additional information regarding the *called-out provisions* for the *streamlined approach* under 21 CFR 4.4(b) and information on the inspectional approach for these provisions for *combination product manufacturer*s who use the drug CGMP-based *streamlined approach*.

In addition to covering the drug requirements according to the applicable *base compliance program*, evaluate the *combination product manufacturer's* compliance with the *called-out provisions* of 21 CFR Part 820 as described below.

NOTE: ***If the combination product is exempt from the device QS regulations, this attachment does not apply.*** *See PART III.1.A.(6) - Special Situations – Device Constituent Part Exempt from the device QS-regulations. If a manufacturer claims that the device used in their combination product is exempt from 21 CFR 820 requirements and the investigator has concerns, contact the lead center.*

NOTE: Installation (21 CFR 820.170) and Servicing (21 CFR 820.200) are called-out provisions but are not described below. These requirements are not typically a focus of inspections and do not apply to most CDER-led combination products. If an investigator has questions on these requirements for a particular combination product or inspection, contact the lead center for assistance.

21 CFR 820.20 Management responsibility

Combination Product Considerations:

Although companies that traditionally manufacture drug products are subject to statutory CGMP provisions related to management responsibility and quality management systems,[32] there are specific requirements in 21 CFR 820.20 that are not explicitly addressed in drug CGMP requirements (e.g., conducting management reviews to assess the suitability and effectiveness of the quality system at defined intervals). Manufacturers of a combination product that includes a device *constituent part* must satisfy all elements of 21 CFR 820.20.

Inspectional Approach to 21 CFR 820.20 for a Facility Operating Under a drug CGMP-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 820.20. Refer to QSIT section on Management Responsibility.

Reference/Resources

- Guide to Inspections of Quality Systems, Quality System Inspection Technique (QSIT). Refer to QSIT section on Management Responsibility.
- Compliance Program 7382.845 - Inspection of Medical Device Manufacturers

[32] See Section 501(a)(2)(B) of the FD&C Act [21 USC 351(a)(2)(B)].

- Compliance Program 7383.001 - Medical Device PMA Preapproval and PMA Postmarket Inspections
- Section IV.A.1, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*

21 CFR 820.30 Design controls

Combination Product Considerations:

Design controls requirements apply to the combination product as a whole, including design considerations for each *constituent part* specific to its use in the combination products However, it is appropriate for a *combination product manufacturer* to leverage design and development information for any *constituent part* as part of the overall design controls for the combination product. For example, design control activities for a combination product composed of a device to be used with an already developed drug product, can leverage the drug properties as inputs for design control activities that would focus on ensuring that the device appropriately delivers the drug and that the drug quality is not adversely affected by its contact with the device.

Note that in some cases, design activities may occur at a separate facility from other manufacturing activities for the combination product (see also "Special Instructions Concerning Design Controls" in Compliance Program 7383.001 and Compliance Program 7382.845). These facilities (often termed "specification developers") may maintain the Design History File (DHF) for the combination product. The combination product DHF may include cross-references to relevant information rather than be a direct repository for all the information it needs to include. Regardless of where DHF information is maintained, the *combination product manufacturer* should be able to access necessary DHF information during the inspection to demonstrate compliance with design control requirements. However, if another site is responsible for design controls for the combination product, (e.g., a specification developer, see also PART II.2.B), it may be more efficient or necessary to perform an additional inspection at that other site.

Inspectional Approach to 21 CFR 820.30 for a Facility Operating Under a drug CGMP-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 820.30. Refer to the QSIT section on Design Controls, which discusses comprehensive coverage of design controls. Evaluation of design controls should start with the DHF for the combination product.

In cases where the *combination product manufacturer* is purchasing the device *constituent part* (or its components to be assembled) from another entity (e.g., buying syringe components to be combined and filled with the drug product), the combination product DHF may reference design information from the supplier to support design of the device *constituent part*. However, the DHF should demonstrate how the *constituent part's* specifications are appropriate for its use in the combination product, addressing any interaction of the *constituent parts* when combined. Similarly, if the *combination product manufacturer* designed the entire product, previously developed *constituent part* information can also be referenced in the DHF (e.g., using development information on a previously approved drug product that is now being developed in a pre-filled delivery device configuration).

Pharmaceutical development practices such as *Quality by Design*[33] can be used and built upon to demonstrate compliance with 21 CFR 820.30. However, the *combination product manufacturer* should be able to communicate to the investigator how their design practices and terminology align with design controls requirements. The manufacturer should also communicate how the procedures in place align with all the requirements of 21 CFR 820.30. For example, the

[33] See the Guidance for Industry on Q8(R2) Pharmaceutical Development.

manufacturer should have procedures that describe the process for design verification and design validation and should be able to explain the design verification and validation activities that were conducted for the combination product.[34]

Reference/Resources

- Guide to Inspections of Quality Systems, Quality System Inspection Technique (QSIT). Refer to QSIT section on Design Controls.
- Compliance Program 7382.845 - Inspection of Medical Device Manufacturers
- Compliance Program 7383.001 - Medical Device PMA Preapproval and PMA Postmarket Inspections
- Section IV.A.2, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*
- Design Control Guidance for Medical Device Manufacturers
- Guidance for Industry - *Q8(R2) Pharmaceutical Development*
- Guidance for Industry - *Q9 Quality Risk Management*
- ISO 14971 – Medical devices – Application of risk management to medical devices

[34] *Design validation* provides objective evidence that product specifications conform with user needs and intended uses. Design validation activities may include, for example, clinical evaluations or simulated use testing. *Design verification* provides objective evidence that design outputs (e.g., diagrams, drawings, specifications and procedures) meet design inputs (e.g., the physical and performance requirements). Design verification activities may include, for example, tests, inspections, analyses, measurements, or demonstrations. See also Section IV.A.2, *FDA Guidance for Industry and FDA Staff Current good Manufacturing Practice Requirements for Combination Products*.

21 CFR 820.50 Purchasing controls

Combination Product Considerations:

Purchasing controls are required for products received at the facility for use in the manufacture of the combination product, for all suppliers of these products, and for suppliers of services obtained (such as terminal sterilization conducted by an outside entity). Purchasing controls are also related to acceptance activities performed to ensure that the supplied products and services meet requirements. (Under a drug CGMP-based *streamlined approach*, acceptance activities are evaluated under relevant 21 CFR Part 211 provisions including 21 CFR 211.82 and 21 CFR 211.84.)

Inspectional Approach to 21 CFR 820.50 for a Facility Operating Under a drug CGMP-based Streamlined Approach:

Evaluate the *combination product manufacturer's* compliance with 21 CFR 820.50. Evaluate the following purchasing controls elements:

- Purchasing control and related incoming acceptance procedures.
- Purchasing data to evaluate the facility's approach to accepting suppliers and communicating specifications for purchased products and services.
- Actions taken in response to findings from supplier assessments.
- Relationship(s) and agreements between the *combination product manufacturer* and other entities (e.g., the combination product sponsor (if not the manufacturer), *constituent part* manufacturers, component suppliers). Determine how changes made by one of these entities is communicated to the *combination product manufacturer* and, if applicable, to other entities.
- How received products are tested, when needed, and controlled to ensure that specifications are met.

Evaluation of purchasing controls should include suppliers of *constituent parts* and/or components of *constituent parts* (note that components can include not only device components but also drug components, as well as containers and closures, that are subject to the requirements of 21 CFR 211.84 – see Attachment A discussion of 21 CFR 211.84). For example, if conducting an evaluation of purchasing controls for a CDER-led combination product for which device *constituent parts* (or their components) are purchased from a supplier, evaluate purchasing controls over that supplier.

NOTE: Although constituent part suppliers may themselves be subject to premarket review and to CGMP requirements, purchasing controls for these suppliers should still be a focus of evaluation. For example, if supplied biological products or HCT/Ps are used in the combination product, suppliers of the biological product and/or HCT/P should be evaluated during coverage of purchasing controls even though the suppliers may themselves be subject to premarket review and be subject to CGMP requirements applicable to biological products (see 21 CFR Parts 210, 211, 600 through 680) and/or current good tissue practice and donor eligibility requirements for HCT/Ps (21 CFR Part 1271). As discussed in PART I.2, the combination product manufacturer must also demonstrate compliance with applicable CGMP requirements under 21 CFR Parts 600 through 680 and/or 21 CFR Part 1271.

Reference/Resources:

- Compliance Program 7382.845 - Inspection of Medical Device Manufacturers
- Compliance Program 7383.001 - Medical Device PMA Preapproval and PMA Postmarket Inspections
- Section IV.A.3, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*
- GHTF Final Document - Quality Management System – Medical Devices – Guidance on the Control of Products and Services Obtained from Suppliers
- FDA Guidance - *Contract Manufacturing Arrangements for Drugs: Quality Agreements*

21 CFR 820.100 Corrective and preventive action

Combination Product Considerations:

Although there is flexibility in coordinating CAPA across facilities, a *combination product manufacturer* must ensure that applicable 21 CFR 820.100 requirements are met for their facility.[35] The manufacturer should have appropriate mechanisms in place to ensure that issues are identified and action(s) needed to correct and prevent recurrence are taken. The *combination product* manufacturer should take appropriate measures, which may include CAPAs, with regard to all relevant manufacturing activities, including coordinating with other manufacturers, as needed, to correct problems with the combination product and to prevent or mitigate them going forward. The CAPA process should consider the impact of corrective and preventive actions on the *constituent parts* and for the combination product as a whole.

Inspectional Approach to 21 CFR 820.100 for a Facility Operating Under a drug CGMP-based Streamlined Approach:

Evaluate the *combination product manufacturer's* responsibility for and compliance with 21 CFR 820.100. Refer to the QSIT section on Corrective and Preventive Action (but see also NOTE below). Confirm that the CAPA process ensures a comprehensive review of activities is undertaken to determine the cause of existing or potential problems, which could include manufacturing problems, deviations (including issues with product yield), or nonconformities for a *constituent part* or the combination product as a whole.

The *combination product manufacturer's* CAPA process should consider implications of corrective and preventive actions for each *constituent part* and for the combination product as a whole. For example, review the CAPA documentation for implications of how changes may impact *constituent parts* and the product as a whole, including adequate testing/evaluation of the change. Effectiveness checks may need to consider the product as a whole even if the corrective action is to a single *constituent part*.

NOTE: QSIT contains information in the CAPA section on coverage of Medical Device Reporting (MDR), Corrections and Removals, and Medical Device Tracking. Compliance with these requirements should NOT be evaluated in an inspection for a CDER-led combination product unless such coverage is specifically requested in the inspectional assignment. If you have questions, contact the lead center.

Reference/Resources:

- Guide to Inspections of Quality Systems, Quality System Inspection Technique (QSIT). Refer to Refer to QSIT section on CAPA.
- Compliance Program 7382.845 - Inspection of Medical Device Manufacturers
- Compliance Program 7383.001 - Medical Device PMA Preapproval and PMA Postmarket Inspections
- Section IV.A.4, FDA Guidance for Industry and FDA Staff - *Current Good Manufacturing Practice Requirements for Combination Products*

[35] Relevant requirements in the drug CGMPs include 21 CFR 211.192 and 21 CFR 211.180(e). Quality data from OOS investigations and any related corrective actions should be addressed through the *combination product manufacturer's* quality system.

ATTACHMENT C – Definitions and Acronyms

Definitions:

Base Compliance Program: The commodity-specific (e.g., drug, device, or biological product) compliance program that aligns with the *base CGMPs* and the type of inspection being performed at combination product manufacturing facility. For example, for an NDA preapproval inspection of a combination product facility operating under a drug CGMP-based *streamlined approach*, the base compliance program would be the compliance program for pre-approval inspection of NDAs (Compliance Program 7346.832).

Base CGMPs: For combination product manufacturers using a *streamlined approach*, the base CGMPs are the drug or device CGMPs that the manufacturer will follow in their entirety. The base CGMPs can be either the drug CGMPs (21 CFR Parts 210 and 211) or the Quality System Regulation (21 CFR Part 820).[36]

Called-out Provisions: Provisions from 21 CFR Part 4 that are specified for manufacturers of combination products using a *streamlined approach*. The called-out provisions are those provisions that the manufacturer is required to comply with from the non-base CGMPs. See PART I.2 for the specific called-out provisions.

Commodity-specific Compliance Program: Compliance programs developed for the inspection of drugs, devices, or biological products.

Constituent Part: A drug, device, or biological product that is part of a combination product.

Cross-labeled Combination Product: A combination product for which the constituent parts are distributed separately (as may be the case for a light-activated drug product and a separately distributed laser drug-activation device). See 21 CFR 3.2(e)(3), (4).

Co-packaged Combination Product: The *constituent parts* are packaged together (e.g., a surgical or first-aid kit containing devices and drugs, a delivery device packaged with a container of drug product). See 21 CFR 3.2(e)(2).

Current Good Manufacturing Practice (CGMP) Operating System: The operating system within an establishment that is designed and implemented to address and meet the current good manufacturing practice requirements for a combination product. (21 CFR 4.2).

Lead Center: The Agency medical product center (e.g., CBER, CDER, or CDRH) that has primary jurisdiction for a specific combination product's review and regulation.

Combination Product Manufacturer: A combination product manufacturer is an entity (facility) engaged in activities for a combination product that are considered within the scope of manufacturing for drugs, devices, biological products, and HCT/Ps. Such manufacturing activities include, but are not limited to, designing, fabricating, assembling, filling, processing, sterilizing, testing, labeling, packaging, repackaging, holding, and storage, including a contract manufacturing facility (see also 21 CFR 4.2 and Reference 9).

[36] Note that for combination products that include a biological product, the manufacturer must demonstrate compliance with applicable CGMP requirements for biological products that are found within the standards in parts 600 through 680 (21 CFR Parts 600 through 680). For a combination product that includes any HCT/P, the manufacturer must demonstrate compliance with applicable regulations in part 1271 (21 CFR Part 1271).

Single-entity Combination Product: A combination product the constituent parts of which are physically or chemically combined (e.g., a prefilled syringe or drug-eluting stent). See 21 CFR 3.2(e)(1).

Streamlined Approach: Demonstrating compliance with either the drug CGMPs (21 CFR Parts 210 and 211) or the device Quality System (QS) regulation (21 CFR Part 820) (base CGMPs) and also demonstrating compliance with specified provisions identified in 21 CFR Part 4 (*called-out provisions*) from the other of these two sets of CGMP requirements (see PART I.2). Using 21 CFR Parts 210 and 211 as the *base CGMPs* with the specified *called-out provisions* of 21 CFR Part 820 is a "drug CGMP-based streamlined approach." Using 21 CFR Part 820 as the *base CGMPs* with the specified *called-out provisions* of 21 CFR Part 211 is a "device QS regulation-based streamlined approach."

Subsystem: The elements which together comprise the CGMP Operating System for the *base CGMPs*. For 21 CFR Part 211, these subsystems include Quality System, Production System, Facilities and Equipment System, Laboratory Controls System, Materials System, and Packaging and Labeling System (see Reference 10). For 21 CFR Part 820, these subsystems include Management Controls, Design Controls, Corrective and Preventive Action, and Production and Process Controls (see Reference 11).

Acronyms:

ANDA: Abbreviated New Drug Application

API: Active Pharmaceutical Ingredient

BLA: Biologic License Applications

BPDR: Biological Product Deviation Report

CAPA: Corrective Actions and Preventive Actions or Corrective and Preventive Actions

CGMP: Current Good Manufacturing Practice

DHF: Design History File

EIR: Establishment Inspection Report

FAR: Field Alert Report

HCT/P: Human Cells, Tissues, and Cellular and Tissue-Based Products

MDR: Medical Device Report

NDA: New Drug Application

OAI: Official Action Indicated

OOS: Out-of-Specification

OTC: Over-the-Counter

PMA: Premarket Approval

QS: Quality System

QSIT: Quality System Inspection Technique