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Guidance for Industry and FDA:

Application of cGMP Regulations to Combination Products: Frequently Asked Questions

PROPOSED GUIDANCE
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U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of Combination Products

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I. Purpose

This document provides guidance to industry and FDA staff on the applicability of current good manufacturing practice ("cGMP") provisions to combination products as defined under 21 CFR 3.2(e). Such provisions apply to the manufacture of combination products to ensure that (1) the product is not adulterated; (2) the product possesses adequate strength, quality, identity, and purity; and (3) the product complies with performance standards as appropriate for the marketed combination product. This guidance does not address technical manufacturing methods.

We have received several questions about the application of cGMP regulations to combination products. We have responded to many questions on a case-by-case basis, and we are currently developing a Proposed Rule for cGMPs applicable to combination products. However, we realize that the industry needs broader statements on the application of cGMP regulations to combination products in order to plan effectively for current and future compliance, and that a Final Rule on which industry can rely necessarily will require a significant amount of time to create.

This guidance document addresses the questions that industry has asked most frequently with regard to the application of cGMPs to combination products generally. After we address those frequently asked questions, this guidance document also provides some case studies that illustrate how cGMP regulations apply in certain situations. The appendices to this guidance also set forth algorithms that a manufacturer can use to help determine what cGMP regulations apply to its facilities.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

II. Definitions

Q.1. What are "current good manufacturing practices"?

A. For purposes of this guidance document, the term *current good manufacturing practice* or *cGMP* refers to the current good manufacturing practice regulations for drugs and most biological products under 21 CFR Parts 210 and 211, for certain biological products under 21 CFR Parts 600-680, and the quality system regulations for devices under 21 CFR Part 820.

Q.2. What does it mean to "manufacture"?

A. For purposes of this document, the term *manufacture* refers to the methods to be used in, and the facilities and controls to be used for, the manufacture, processing, packing, or holding of a drug or biological product (21 CFR 210.1(a)), and those used for the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use (21 CFR 820.1(a)), and the steps in propagation or manufacture and preparation of biological products (21 CFR 600.3(u)).

Q.3. What is a "manufacturer"?

A. For purposes of this guidance document, the term *manufacturer* refers to any person who would be required to comply with cGMP regulatory requirements for drugs, biological products, devices, or combination products. A manufacturer of a finished product has a responsibility to ensure the overall quality of the product. As part of this obligation, a manufacturer should ensure that the cGMP compliance of "third party service providers" is adequate (see Question 4).

Q.4. What is a "third party service provider"?

A. For purposes of this guidance document, a *third party service provider* or a *service provider* is an entity that performs certain functions, including manufacturing functions, on behalf of a manufacturer.

Q.5. What is a "facility"?

A. For purposes of this guidance document, a *facility* is the physical location at which a combination product, or a constituent part of a combination product, is made.

Q.6. What is a "constituent part" of a combination product?

A. For the purposes of this guidance document, a *constituent part* of a combination product is an article in a combination product that can be distinguished by its regulatory identity as a drug, device, or biological product, as defined in section 201 of the Federal Food, Drug, and

Cosmetic Act (the Act) or 351(i) of the Public Health Service Act. For example, a device coated or impregnated with a drug has two constituent parts, the device and the drug. For simplicity, the concepts in this guidance are described in the context of a combination product composed of two constituent parts. These concepts are also relevant for combination products with more than two constituent parts.

Q.7. What are "single entity" and "kit" combination products?

A. A "single entity" combination product is a "product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity" (21 CFR 3.2(e)(1)).

A "kit" combination product is "two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products" (21 CFR 3.2(e)(2)).

Q.8. What are "virtual" combination products?

A. Virtual combination products include the following types of combination products:

A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose. (21 CFR 3.2(e)(3)).

Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect. (21 CFR 3.2(e)(4)).

III. Questions Specific to Single Entity and Kit Combination Products

a. Determining Which Regulations Apply

Q.9. What determines which cGMP regulations apply to a combination product?

A. First, and most basic, each constituent part of a combination product is subject to its governing cGMP regulations before the constituent parts are combined, merged, or joined. After the constituent parts are combined, merged, or joined, the cGMP regulations under which the manufacturer currently operates are the regulations that principally govern the combination product. However, the manufacturer should also assess whether its existing quality system is adequate to ensure the quality of the product. In determining whether a current system is adequate, manufacturers should evaluate various factors, for example, whether the manufacturer already has systems in place that address a particular requirement of another set of cGMP regulations. The questions below and Appendices A – D provide more detail on a suggested approach for manufacturers of single entity and kit combination products.

Q.10. Does FDA have an algorithm that a manufacturer can use to determine which cGMPs apply?

A. Yes. We have developed four algorithms that set forth a process manufacturers may use to determine what cGMP regulations apply when constituent parts of a combination product are combined, merged, or joined in a single entity or kit combination product.

Q.11. Can compliance with cGMPs be achieved "by using the current good manufacturing practice system already operating at a manufacturing facility"?

A. Not necessarily. Although a manufacturer's current cGMP system will principally be used to control a combination product's quality, the manufacturer will often need to incorporate elements from other cGMP regulations to ensure the product's quality. This is particularly true for single entity combination products, and for certain kit combination products as well. See the discussion below and the algorithms in Appendices A – D for a suggested analysis in determining whether an existing quality system is adequate.

Additionally, certain facilities may not have a cGMP system in place (e.g., facilities of a start-up company or new facilities of an established manufacturer). When a facility does not have a cGMP system in place, the facility should implement the cGMP regulations that correspond to the primary mode of action ("PMOA") of the combination product that will be manufactured at the facility. For example, if the PMOA is that of a drug, then the facility should implement Parts 210 and 211. Please note that the algorithms in Appendices A – D assume that the facility in question is already operating under a quality system. Facilities that do not have an existing system should use the Appendix that corresponds to the PMOA of the combination product in question (and thus the cGMP that the manufacturer will implement). In the example discussed in this question, the facility is implementing Parts 210 and 211, therefore Appendix A or

Appendix B could be used to assess the facility's cGMP compliance, depending upon whether the combination product manufactured at the facility is a single entity or a kit combination product.

Q.12. What cGMP regulations apply to a third party service provider that a finished product manufacturer engages to perform manufacturing functions?

A. The cGMP regulations that apply to a third party service provider are those that would otherwise apply under relevant law. For example, if a third party service provider manufacturers only a device constituent part of a combination product, then only Part 820 would apply. If, however, a service provider joins two constituent parts to create a single entity or kit combination product, then provisions of more than one set of cGMP regulations may apply, as discussed elsewhere in this guidance.

Additionally, the manufacturer of the finished combination product has a responsibility to ensure the overall quality of the product. As part of this obligation, the manufacturer should ensure that the cGMP compliance of third party service providers that perform manufacturing functions is adequate. Manufacturers that use third party service providers may use the algorithms set forth in this guidance document to evaluate the cGMP obligations for third party service providers, or the manufacturer can delegate that responsibility to the third party service provider. The manufacturer (or third party service provider, as relevant) should use the algorithm that corresponds to the cGMP system under which the third party service provider operates (or, if the service provider does not have an existing cGMP system, the algorithm that corresponds to the PMOA of the combination product; see Question 4). The manufacturer (or third party service provider, as relevant) should answer the questions in the algorithm in terms of the service provider's facility in which the combination product is manufactured. Case Studies 1 and 3 illustrate how the algorithms apply to third party service providers.

Q.13. Could a single entity or kit trigger more than one cGMP regulatory scheme before they are combined, merged, or joined?

A. Manufacturers will not be required to implement provisions of more than one cGMP system before joining or merging constituent parts of a product. Though not a regulatory requirement, before constituent parts are combined, merged, or joined, some manufacturers may opt to take certain steps in order to achieve compliance when the constituent parts are joined. For example, if a manufacturer knows that a given constituent is destined to be joined into a particular combination product, a manufacturer might consider whether it should lay the groundwork for compliance with regulatory requirements that will come into force later.

Q.14. Is there a list of cGMP decisions for approved combination products?

A. Yes, FDA has posted a list of redacted cGMP decisions on its website.

b. Implementation

i. Hybrid cGMP Systems

Q.15. What is a "hybrid cGMP system"?

A. A hybrid cGMP system is a cGMP system that embodies provisions of cGMP regulations other than the regulations under which a facility is currently operating.

Q.16. If a manufacturer needs to implement a hybrid cGMP system at a facility, does that mean the facility must implement all of the provisions of another cGMP system?

A. No. Implementing a hybrid cGMP system is a matter of degree. If a hybrid cGMP system is required, a facility should implement the relevant controls to the degree needed to ensure the product's quality. The extent to which controls need to be implemented will depend on factors such as the product's risk and the existing controls the facility has in place.

Q.17. How does a manufacturer know if it needs a hybrid cGMP system at a given facility?

A. At a high level, a facility's quality system needs to be adequate to ensure the quality of the products that are manufactured at that facility. If only a constituent part is made at the facility, and the facility's quality system corresponds to that type of constituent part (e.g., a device constituent part and Part 820), then the facility's existing system should be adequate.

Determining whether an existing cGMP system is adequate is more challenging when a facility joins, merges, or combines two or more constituent parts into a single entity or kit combination product. As stated previously, the facility's existing cGMP system will be the overarching cGMP system in this situation. That said, a manufacturer should also assess whether the existing system at a facility is adequate to ensure the quality of the finished combination product. Quite often a facility that manufactures single entity or kit combination products will need to implement provisions of cGMP regulations other than those that are already implemented at the facility in order to have an adequate system.

Furthermore, due to the differences among cGMP regulations and the differences in the types of combination products, the specific analysis undertaken by a manufacturer is different depending upon the facility's existing cGMP system and what type of combination product is being manufactured. Each set of cGMP regulations contains key elements based

upon the unique characteristics of the types of products the regulations were designed to address. Table 1, below, sets forth these unique elements:

Table 1: cGMP Regulations that are Different Across cGMP Systems

Devices	Drugs and Most Biological Products	Certain Other Biological Products
Design controls (820.30) Purchasing controls (820.50) CAPA (820.100)	Containers and closures (211.84) Calculation of yield (211.103) Aseptic control assurance for constituent parts unable to withstand terminal sterilization (211.113(b) and 211.42) OTC drug constituent parts (211.132) Expiration dating (211.137) Testing and release for distribution (211.165) Stability testing (211.166) Special testing requirements (211.167) Reserve samples (211.170)	Additional requirements as they apply under 21 CFR Parts 600-680

Due to these differences, as well as the differences in single entity and kit combination products, we have developed four approaches, which the questions below and Appendices A – D, describe. (Remember that, as noted above, the algorithms assume that the facility in question is already operating under a quality system. Facilities that do not have an existing cGMP system should use the Appendix that corresponds to the PMOA of the combination product in question.)

For simplicity's sake, we refer to the entity using the algorithms as the "analyzer", because the relevant entity may be a manufacturer or a third party service provider (see Question 12).

Appendix A: Facility Operating Under ***Parts 210/211*** Adding a ***Device*** Constituent Part to a ***Single Entity*** Combination Product

The analyzer should go through this algorithm once for each of the relevant controls: design controls, purchasing controls, and corrective and preventative action ("CAPA") (i.e., go through the analysis three times – one for each provision).

The analyzer should first consider whether the facility either develops specifications or is changing the intended use for the device constituent part. If the answer to either of these questions is yes, the analyzer should ensure that a standard risk analysis for the device constituent part is

performed, as well as an analysis that evaluates the impact of possible design changes to the device. The relevant design changes to be considered include all possible changes. For example, if the device supplier is contractually permitted to make changes, then the analyzer should consider the ramifications of those hypothetical changes. If the design changes would pose a significant safety-related risk or would change the effectiveness of the combination product, the analyzer should consider whether quality system controls could adequately control the risk. If such controls could not control the risk, then the device must be redesigned. If quality system controls can control the risk, then the facility should implement the relevant control (design controls, purchasing controls or CAPA) as needed to adequately ensure product quality. If changes in the device would neither pose a significant safety related risk nor change the effectiveness of the product, then the facility does not need to implement design controls or purchasing controls; however, the facility should implement CAPA or should integrate CAPA requirements with its existing system to the degree needed to ensure product quality.

If the drug facility neither originates specifications nor changes the device's intended use, the algorithm next asks whether the device is a container for the drug. A standard risk analysis should be performed to ensure that the device is either a proper container or a proper constituent part of the finished product. As long as the device is a proper container or constituent part, the algorithm next asks whether the device supplier(s) complies with the relevant controls for the device. If supplier does not comply with these controls, the drug facility should implement the relevant control to the degree needed to ensure product quality. However, if the device supplier does comply with relevant controls, the facility is not required to implement design controls or purchasing controls; however, the facility should implement CAPA or should integrate CAPA requirements with its existing system to the degree needed to ensure product quality.

Appendix B: Facility Operating Under ***Parts 210/211*** Adding a ***Device*** Constituent Part to a ***Kit*** Combination Product

This algorithm analyzes all of the unique controls in Part 820 (design controls, purchasing controls, and CAPA) in one unified analysis (i.e., go through the analysis only once).

The first step in the analysis instructs the analyzer to consider whether the device constituent part is exempt from design controls, purchasing controls, and CAPA. If it is not exempt, the analyzer should evaluate whether the facility has systems that already address the relevant control. The algorithm includes specific questions for design controls, purchasing controls, and CAPA. If the facility does not have existing systems to address any of these provisions, the facility should implement the control

to the degree necessary to ensure product quality (and consider the next requirement). After this, the analyzer should consider whether the device supplier(s) comply with the controls that are at issue for the device constituent part. If the device supplier is not in compliance with the relevant controls, the facility should implement the control to the degree necessary to ensure product quality. If, however, the device supplier is in compliance, the analysis is complete.

Appendix C: Facility Operating Under ***Part 820*** Adding a ***Drug or Biologic*** Constituent Part to a ***Single Entity*** (and Certain Kit) Combination Product

Similar to Appendix B, this algorithm addresses the unique controls in Parts 210/211 that are not also in the QSR in one unified analysis, so the analyzer should go through the analysis only once. Under this algorithm, if a facility's existing system does not address the relevant provisions after the facility receives a drug constituent part, the algorithm instructs the facility to implement the control to the degree necessary to ensure product quality (and consider the next requirement). After this, the algorithm then asks whether the drug supplier(s) complies with the controls for the drug constituent part. If the drug supplier(s) is not in compliance with the relevant controls, the facility should implement the control to the degree necessary to ensure product quality. If, however, the drug supplier(s) is in compliance, the analysis is complete.

Appendix D: Facility Operating Under ***Part 820*** Adding a ***Drug or Biologic*** Constituent Part to a ***Kit*** Combination Product

This algorithm applies to certain kit combination products. However, as the first two questions of the algorithm demonstrate, if: (1) the facility sterilizes the finished kit or all of the kit's constituent parts; or (2) the facility changes or modifies the kit's constituent parts; or (3) the kit's configuration itself changes or modifies any of the kit's constituent parts, then Appendix C should be used to analyze the facility's cGMP obligations. The scope of the analysis in (2) and (3) should include an assessment of changes in the intended use of the constituent parts. This analysis is needed in order to determine whether the facility is changing the drug or biological product constituent part directly, or whether changes in the device constituent part may have the potential to change the drug or biological constituent part. If such changes may occur, the facility needs to assess whether controls under Parts 210/211 may be needed to ensure the quality of the drug or biological.

If, however, the answer to the above questions is "no", then the kit is being re-packaged, and the facility is not required to implement provisions of Parts 210/211.

ii. Merged and Separate cGMP Systems

Q.18. FDA has said that manufacturers that make single entity or kit combination products should generally not need to maintain two separate manufacturing systems to ensure compliance with both sets of regulations during and after joining constituent parts. How do you reconcile this with requiring a hybrid cGMP system for many combination products?

A. As described above, a single product may be subject to regulations from more than one set of cGMP regulations when its constituent parts are combined, merged, or joined. When this happens, appropriate regulation of the product may require incorporation of certain elements from cGMP regulations in addition to the cGMP regulations already implemented at the facility that manufactures the product. We do not believe that this will require two separate manufacturing systems or quality systems, and instead will entail incorporation of certain provisions of cGMP regulations that are absent from other cGMP regulations to the extent needed to ensure product quality. (See above at Table 1). From a purely regulatory perspective, relevant cGMP requirements correlate to the physical development and manufacture of a product. Given that when a product becomes a combination product may be unclear, some manufacturers may find establishing and implementing cGMP regulations based upon the intended use of the finished product to be helpful. However, this is not a regulatory requirement.

Q.19. Will a facility ever need to implement parallel cGMP systems?

A. A facility should not need parallel cGMP systems unless the facility makes different types of constituent parts. A constituent part is subject to its governing cGMP regulations before it is combined, merged, or joined with another constituent part to form a single entity or kit combination product; therefore, different types of constituent parts (e.g., a drug and a device) may be subject to different cGMP regulations before they are combined, merged, or joined. (See also Question 6).

Take, for example, a facility that operates under Parts 210 and 211 that acquires a manufacturing line for device constituent parts. The facility should manufacture the devices under a quality system that is compliant with Part 820.

Q.20. When more than one set of cGMP regulations apply, which regulations have precedence when the approaches overlap (e.g., CAPA systems or design control/product development systems)?

A. We do not intend for a manufacturer to implement overlapping or duplicative regulatory requirements. A facility that manufactures a kit or single entity combination product should use the existing cGMP system at

the facility. (Or, if the facility does not have an existing cGMP system, the facility should implement the cGMP system that corresponds to the PMOA of the finished combination product.) If additional controls need to be implemented pursuant to the approaches discussed elsewhere in this guidance document, such additional controls may be limited to those unique elements of another cGMP regulatory scheme (see above at Table 1 and Appendices A – D).

IV. Questions Specific to Virtual Combination Products

Q.21. Does the application of cGMP regulations to virtual combination products differ from other combination products? How?

A. The application of cGMP regulations to virtual combination products differs because virtual combination products are not joined, merged, or combined together. They remain distinct constituent parts throughout their lifecycle. A constituent part of a combination product is subject to its governing cGMP regulations; therefore, each constituent part of a virtual combination product is subject to only to the cGMP regulations that correspond to that part.

However, one type of a virtual combination product requires the cooperation of two manufacturers to ensure the safety and effectiveness of the products. These are the products that require the labeling of an approved product to be changed and thus the cooperation of the approved product's manufacturer (21 CFR 3.2(e)(3)). The cooperation between the manufacturers goes beyond labeling, though, and encompasses cooperation with respect to ensuring the product's quality. Such cooperation between the manufacturers should include working together to communicate on current and future design and modification issues.

Q.22. Would a manufacturer of a constituent part of a virtual combination product ever be subject to more than one cGMP regulatory scheme?

A. Potentially yes. If a facility manufactures different types of constituent parts, that facility may need to implement parallel cGMP systems. See Question 19.

V. Specific Questions about Differences in cGMP Requirements

Q.23. The QSR requires a quality plan for a device (21 C.F.R. 820.20). For a drug-device or biologic-device combination product, is a quality plan and/or a quality manual that encompasses the entire product – i.e., all constituent parts – required?

A. 21 C.F.R. 820.20(d) provides that "Each manufacturer shall establish a quality plan which defines the quality practices, resources, and activities

relevant to devices that are designed and manufactured. The manufacturer shall establish how the requirements for quality will be met." This regulation thus applies to devices that a manufacturer designs and manufactures. If a manufacturer is operating under Part 820, the manufacturer's quality plan should address the quality practices, resources, and activities as are relevant to that device as a constituent of a combination product. For example, how will the quality of the device be ensured when it is merged, packaged, or labeled for use with another product? If, however, a manufacturer is operating under Parts 210/211, then compliance with 21 C.F.R. 820.20 would not be required.

Q.24. How do design controls play a role in drug-device or biologic-device combination products?

A. Design controls apply to all devices, except for class I devices that are exempt. However, even if a device constituent part of a combination product is exempt, the finished combination product may no longer be exempt from design controls, if the intended use of device constituent has been changed. Note that this principle is not always true for device constituents of a kit -- devices can be constituent parts of a combination product kit without changing their intended use.

For facilities operating under Part 820 that make finished combination products, design controls will apply to the combination product unless the finished product is a kit (or a virtual) and the device constituent part is exempt from design controls. Therefore, if a facility operates under Parts 210/211, it should consider whether it manufactures a kit and whether the device constituent part is exempt from design controls. If both answers are yes, then the facility is not required to comply with design controls. (See Appendix B.) For a facility that operates under Parts 210/211 and that manufactures a single entity combination product, the analysis is a bit more complex. Ultimately, if the facility does not develop design specifications, does not change the intended use of the device constituent part, ensures that the device is a proper container/constituent part, and ensures that device suppliers comply with design controls, then the facility should not be required to implement design controls.

VI. Communication with FDA

Q.25. What is FDA's mechanism for determining which cGMP regulations apply during manufacture of combination products?

A. It is the manufacturer's obligation to evaluate and determine what regulations apply to its products in the first instance. FDA may make its own determinations about applicable regulations, for example, during inspections and when reviewing marketing applications. Therefore, we strongly encourage manufacturers to communicate with FDA about

decisions relating to cGMP compliance, particularly if a manufacturer is developing systems for the first time. While FDA makes determinations about applicable regulations when reviewing a marketing submission or inspecting a facility, manufacturers' previous discussions with the agency play a critical role in our determinations about what regulations apply. This section of the guidance describes in detail how manufacturers can effectively communicate with FDA on these issues.

Q.26. How can manufacturers can get more information on how cGMP regulations apply to combination products?

A. Under 21 C.F.R. § 10.85, you may submit a request for an advisory opinion to the Division of Dockets Management. In general, the regulations require the agency to respond within 180 days of receipt of such a request.

In making a request, a manufacturer should include a statement of the issues involved and specific questions on which the manufacturer requests an opinion. The manufacturer should also include a full statement of all facts and legal points that are relevant to the request. (See § 10.85(b)). After the agency receives a request, we will review the information submitted and notify the requestor if we need clarification or require additional information.

In considering a request for an advisory opinion, the agency will make every effort to ensure that relevant parties, including the manufacturer and various agency personnel, are included in discussions. Some of the methods that we will use to ensure that this occurs are:

- Conferences
- Meetings
- Discussions
- Correspondence
- Various types of hearings
- *Federal Register* notices requesting information and views

(See 21 C.F.R. § 10.20(h)).

To ensure inclusion in all relevant discussions, a manufacturer may ask FDA to engage in the above avenues of communication (as appropriate under relevant regulations) to discuss the manufacturer's request. In addition, the agency encourages manufacturers to suggest certain agency personnel that should be included within a discussion or should otherwise have input into a request.

The agency will respond to a request in writing. The response represents the formal position of the agency on the issues involved. Except in unusual situations where an immediate and significant danger to health is

involved, the agency is obligated to follow its response unless it is amended or revoked pursuant to the relevant regulatory requirements. The agency will not recommend legal action against a person or product with respect to an action taken in conformity with an advisory opinion that has not been amended or revoked.

If the agency revokes or amends an advisory opinion, we will either give notice in writing or by publishing a notice in the *Federal Register*. Action taken in conformance with an advisory opinion that is subsequently amended or revoked is acceptable to FDA unless the agency determines that substantial public interest considerations preclude continued acceptance. If possible, an amended or revoked advisory opinion will state when action previously undertaken does not remain acceptable.

Please see 21 CFR § 10.85 and related sections for additional information.

Q.27. What if I have a question about how cGMP regulations apply to a particular combination product or combination product constituent part?

A. Manufacturers are encouraged to seek FDA's input on the implementation of cGMPs throughout combination product development, including the pre-investigational phase. Manufacturers may seek this input through written correspondence or informal meetings with the agency.

In general, when making a request, manufacturers should include the same elements as described in the answer above – i.e., a statement of the issues involved, specific questions on which the manufacturer requests an opinion, and all relevant facts and legal points. The information submitted should include the product's risk and its technology. If possible, a proposed plan for compliance with cGMP regulations is also helpful. After the agency receives a request, it will review information submitted to determine if the agency needs more facts. If we do, we will let the manufacturer know this.

OCP will work with manufacturers to ensure that all appropriate agency personnel are involved and will assist in obtaining their input and collaboration on relevant issues. Because of this, manufacturers may wish to first contact OCP to ensure that this coordination occurs. You may reach OCP at (301) 427-1934 or by e-mail at combination@fda.gov. In addition to OCP staff, FDA staff involved in discussions about the application of cGMP regulations to a combination product may include, but are not limited to, reviewers in the lead and consulting product review divisions (CBER, CDER, and CDRH), cGMP experts in the Offices of Compliance, in the lead and consulting centers and the district office, and Office of Regulatory Affairs national expert advisors.

We understand that manufacturers may also be concerned about how best to participate in agency discussions to ensure that the agency has all necessary information to make an informed decision. Certainly, manufacturers should include all relevant information with their requests. In addition, if a manufacturer has suggestions on the extent to which the manufacturer should participate in agency meetings, OCP is interested in hearing that as well. Overall, OCP firmly believes that open communication between a manufacturer and the agency throughout the product development process is key to ensuring compliance with applicable regulatory requirements.

We also understand that manufacturers are typically anxious to receive responses from the agency on their requests. We will always endeavor to respond to industry requests in a timely manner. Unfortunately, due to the wide variation in complexity of products and issues, it is impractical for us to provide a standard timeframe in which we will respond. We encourage manufacturers to let us know when a request is particularly critical, and in turn, we will let manufacturers know when we need additional information as soon as we identify this need. Additionally, manufacturers should always feel free to contact us to determine the status of a request.

FDA will document its recommendations concerning a manufacturer's proposal in FDA meeting minutes, letters, or other permanent communication records, as appropriate. FDA staff will also communicate decisions to the appropriate District Office.

Q.28. Can a manufacturer propose a plan to FDA describing how the manufacturer will achieve compliance with cGMPs, particularly for novel combination products?

A. Yes, manufacturers are encouraged to seek FDA comment on their plans to achieve compliance with cGMPs. FDA recommends that these plans include a full description of how the manufacturer intends to comply with applicable cGMP regulations. For single entity combination products, the plan should address when the constituent parts are combined, merged, or joined, what cGMP regulations apply at that point, and how the manufacturer intends to comply with those regulations. The plan should also consider the risk of the combination product, its technology, and any anticipated postmarket development and post-approval changes. FDA recommends that applicants include input from all critical manufacturers in these plans and include information on critical steps that may be conducted by third party service providers and any special testing. You may reach OCP at (301) 427-1934 or by e-mail at combination@fda.gov.

Q.29. Are there multiple pathways for obtaining advice from the agency with regard to the application of cGMP regulations to combination products?

A. Yes. This guidance document describes two pathways that we believe will be most useful to combination product manufacturers. First, a manufacturer may request a more formal "advisory opinion" through the process described in Question 26. Second, a manufacturer may request advice through more informal correspondence and meetings as described in Question 27. Manufacturers can also request advice from other agency offices or centers. However, as described above in Question 27, OCP believes that submitting a request to OCP will allow better coordination among agency personnel and will help ensure that all relevant personnel are included in discussions.

Q.30. What factors does FDA consider when determining which pathway is appropriate for a given product?

A. In general, the advisory opinion pathway is appropriate when a manufacturer has a question about how cGMP regulations apply to combination products generally or to a particular type of combination product. The "informal" pathway is appropriate when a manufacturer has a question about how the regulations apply to a specific combination product – e.g., a particular brand.

Q.31. What if a manufacturer disagrees with the agency's decision regarding applicability of cGMPs?

A. FDA has defined a process for manufacturers to raise suspected instances of inconsistency in the application of cGMP regulations to combination products by the FDA field force.

VII. Enforcement

Q.32. How are inspectors alerted that they are inspecting a combination product manufacturer?

A. When CDER is the lead center, the field force is sent a copy of the CMC section of an NDA when it is submitted to FDA or other documentation that identifies that a combination product manufacturer is being inspected. Additionally, we have recently developed an analogous process for circumstances in which CDRH is the lead center. This process will ensure that field force inspecting manufacturers for which CDRH is the lead center will receive copies of a PMA, a 510(k) submission, or other documentation letting the inspectors know that they are inspecting a combination product manufacturer.

Q.33. Do only certain inspectors or types of inspectors inspect combination product manufacturers?

A. Inspectors that are charged with responsibility for inspecting combination product manufacturers are cross-trained on applicable GMP regulations. Such inspectors are also trained on the unique issues that face combination products. Additionally, FDA endeavors to coordinate its inspections such that combination product manufacturers may be inspected by a team of two or more inspectors with complementary knowledge, skills, and experiences when appropriate.

Q.34. How does FDA ensure that inspectors are appropriately trained?

A. As described above, FDA will ensure that inspectors who inspect combination product manufacturers are cross-trained on relevant regulations. Inspectors of combination product manufacturers are also trained on combination product specific issues.

Q.35. To the extent that different sets of cGMP regulations apply to a combination product, will the lead center oversee the enforcement of all of those regulations?

A. The lead center will oversee and have ultimate responsibility for the inspections. However, the lead center must consult with other centers as appropriate.

Q.36. How does assignment of a lead center affect assignment of inspection personnel?

A. FDA personnel from the lead center assigned to the combination product will conduct or lead the inspection of a combination product manufacturer. As described above, inspectors who inspect combination product manufacturers will have been trained on relevant regulations. For example, inspectors from CDRH will have been trained on relevant drug and biologic cGMP regulations in addition to the device regulations. The lead center is also charged with consulting with other centers as necessary, for example, to obtain input on a unique regulatory issue or to coordinate an inspection. Sometimes it may be appropriate to have a team of inspectors that is comprised from inspectors from different centers, and the lead center must make this determination and coordinate the inspection. More detail on making this decision is provided below.

Q.37. How does FDA determine if a cross-center team of inspectors, or separate inspections, are needed to inspect a combination product manufacturer?

A. As mentioned above, sometimes FDA will determine that inspectors from more than one center are needed to inspect a combination product manufacturer. Many factors may play into this determination, for example:

- Complexity of the combination product;

- Familiarity of the investigators with the product and the manufacturer;

- Investigators' experience with inspecting combination product manufacturers generally;

- Length of time since previous inspection, and whether this particular manufacturer and/or product line has ever been inspected before;

- Manufacturer's recommendation; and

- Inspectional resources.

The lead center will evaluate these factors and make a determination about the type of inspection that is warranted and will oversee the inspection.

VIII. Case Studies

Below follow case studies that address how the principles discussed in this guidance document apply to specific fact patterns. While the case studies illustrate how this guidance document and the relevant regulations may apply in a given situation, they are only examples. Depending upon the facts and circumstances surrounding a situation, there may be more than one way to apply this guidance and/or to achieve compliance with applicable regulatory requirements.

Case Study 1

Company A manufactures medical devices and has developed a unique injection device that is intended to be used to inject drugs. Company A is considering different ways to market the device and the cGMP obligations that apply to each of the scenarios.

Scenario 1. **Company A manufactures a standard set of injection device components, according to its own specifications, for the intended use of filling with drugs to make a prefilled injection combination product. Company B, a pharmaceutical company, buys the standard device components, assembles them, and fills the finished device with Company B's drug to make a prefilled injection combination product.**

What cGMP requirements apply to Company B?

Company B will assemble and fill the device with drug at its own facility; therefore, Company B must consider what cGMP requirements apply to its manufacture of the finished product, a single entity combination product.

Because Company B is a drug manufacturer, and because the product is a single entity combination product, Company B should use Algorithm A to analyze its cGMP requirements. In response to the first question – Did you develop specifications for the device – Company B should answer "no", because the injection device components are manufactured according to Company A's specifications. Next the algorithm asks Company B to consider whether it is changing the intended use of the device constituent part. This question is not relevant to this scenario because Company B is purchasing only the components for a container closure for its drug and is assembling them into a finished product. Therefore, Company B should skip this question and proceed to the next question in the algorithm.

Company B must next consider whether the device is a container for the drug. Company B will answer "yes" to this question, because Company B has purchased the device components for the purpose of assembling a container closure. The algorithm then asks Company B to perform a risk analysis to ensure that the device is a proper container for the drug. As long as the risk analysis indicates that it is a proper container, the algorithm directs Company B to consider whether it ensures that the device supplier (Company A) complies with the relevant controls for the device. If Company A does not comply with the QSR, then Company B must implement design controls, purchasing controls, and/or CAPA to the degree needed to ensure product quality. (Note that in this scenario, Company A may not be required to comply with the QSR because it is manufacturing components, so Company B may have to comply with these controls.) If, however, Company B ensures that Company A complies with the QSR, then Company B should answer "yes" to this question and thus reach the conclusion that Company B does not have to implement design or purchasing controls at its facility but, if it has not already

done so, Company B would have to implement CAPA to the degree needed to ensure product quality.

Scenario 2. **Company A partners with Company C, a pharmaceutical company, to produce a prefilled version of the injection device. Under this arrangement, Company A produces the injection device according to Company C's specifications and sells Company C the device components. Company C fills the injection device with its drug at its own facility.**

What cGMP requirements apply to Company C?

Company C will assemble and fill the device with drug at its own facility; therefore, Company C must consider what cGMP requirements apply to its manufacture of the finished product, which is a single entity combination product.

Because Company C is a drug manufacturer, and because the product is a single entity combination product, Company C should use Algorithm A to analyze its cGMP requirements. In response to the first question – Did you develop specifications for the device – Company C should answer "yes", because Company A manufactures the device according to Company C's specifications. Next Company C should perform a risk analysis to assess the impact of possible design changes. As discussed above (see Question 17), the relevant design changes to be considered include all possible design changes. For example, if Company A is contractually permitted to make changes, then Company C should consider the impact of the possible changes. If design changes in the device would pose a significant safety-related risk or would change the effectiveness of the combination product, Company C should consider whether quality system controls could adequately control the risk. If such controls could not control the risk, then the device must be redesigned. If quality system controls can control the risk, then Company C should implement the relevant control (design controls, purchasing controls or CAPA) as needed to adequately ensure product quality. If changes in the device would neither pose a significant safety related risk nor change the effectiveness of the product, then Company C does not need to implement design controls or purchasing controls; however, Company C should implement CAPA or should integrate CAPA requirements with its existing system to the degree needed to ensure product quality.

Also note that as with Scenario 1, Company A may not be required to comply with the QSR because it is manufacturing components.

Scenario 3. **Company A partners with Company D, a pharmaceutical company, to produce a prefilled version of the injection device. Company D ships its drug to Company A, and Company A fills the injection device with its drug at its own facility.**

What cGMP requirements apply to Company A?

Company A must consider what cGMP requirements apply to its manufacture of the finished product, which is a single entity combination product.

Because Company A operates under Part 820, and because the product is a single entity combination product, Company A should use Algorithm C, which addresses the situation where a device facility adds a drug constituent part to a single entity combination product. Under this algorithm, Company A will analyze the unique controls in Parts 210/211 to determine whether Company A's existing system addresses those provisions. If Company A's system does not address the specified provisions of Parts 210/211, Company A should implement the relevant control to the degree necessary to ensure product quality (and consider the next requirement). After Company A has analyzed the specified provisions of Parts 210/211, the algorithm then directs Company A to consider whether the drug supplier – Company D – complies with the controls for the drug constituent part. If Company D is not in compliance with the relevant controls, then Company A should implement the control to the degree necessary to ensure product quality. If, however, Company D is in compliance, Company A's analysis is complete.

<u>Scenario 4.</u> **Company A enters into an arrangement with a pharmaceutical company, Company E, to co-package its assembled unfilled injection device with Company E's drug. Company A sterilizes the injection device before it ships the device to Company E's facility where it is co-packaged with Company E's drug. No additional sterilization of the kit is performed.**

What cGMP requirements apply to Company E?

When a drug is co-packaged with a device, the final product is a kit combination product. Because Company E is a drug company that operates under Parts 210 and 211, it should analyze its cGMP obligations using Algorithm B, which addresses adding device components to a kit combination product.

The first question is whether the device is exempt from design controls, purchasing controls, and CAPA. If the answer is "no", Company E should consider the next three questions in the algorithm, which address whether Company E has systems that effectively address the requirements relating to design controls, purchasing controls, and CAPA. (See Algorithm B for the specific questions.) If Company E does not have the relevant controls already implemented, it should implement the controls to the degree needed to ensure product quality. For example, Company E might need to implement design controls and purchasing controls to ensure that changes to the device do not affect the quality of the finished kit. Next Company E should consider whether component suppliers comply with the controls at issue for the device component. As long as Company A complies with the QSR, the answer to this should be yes, so Company E would simply implement controls as previously instructed by the algorithm.

Scenario 5. **Company A enters into an arrangement with a drug company, Company F, to co-package Company A's assembled unfilled injection device with Company F's drug. Here, Company F ships Company A the drug, and Company A packages its device and Company F's drug together. Company A sterilizes the device before it packages the kit, and does not sterilize the drug.**

What cGMP requirements apply to Company A?

When a drug is co-packaged with a device, the final product is a kit combination product. Because Company A is a device company that operates under the QSR, it should analyze possible obligations under Parts 210 and 211 using Algorithm D, which addresses adding drug or biologic components to a kit combination product.

The first question that Company A must answer is whether it will sterilize all of the kit's constituent parts (as opposed to just the device constituent part). The answer to this question is no, because the facts indicate that Company A will only sterilize its device. Additional controls pursuant to Parts 210 and 211 might be warranted if Company A sterilized the drug constituent part or the entire kit, because such sterilization could affect the integrity of the drug constituent part. Next Company A must consider whether it is changing or modifying the kit's constituent parts or whether the kit's configuration itself changes or modifies any of the kit's constituent parts. As part of this analysis, Company A should consider whether the kit's configuration changes the intended use of any of the constituent parts or whether Company A is directly changing the intended use of any of the kit's constituent parts. (However, note that we are addressing only GMP issues here, not approval-related issues.) As long as the drug and device constituent parts are both used in accordance with their cleared or approved uses and Company A makes no other changes or modifications to the constituent parts, the answer to this question will be no. Therefore, according to the algorithm, Company A is co-packaging the kit, and Company A does not need to implement provisions of Parts 210/211 at its facility.

Case Study 2

Company ABC is a small biopharmaceutical company that is developing a monoclonal antibody (MAB) that would be administered through IV infusion.

Company ABC contracts for the manufacture of MAB by Company SS. Company SS makes, labels, and releases the final bulk MAB. Company SS operates under Parts 210 and 211. Additionally, Company ABC has audited (and will continue to audit) Company SS, and Company SS ships samples from the product lots to Company ABC for standard stability studies.

Example 1 – Marketed Infusion Bag

Company ABC wishes to supply the MAB in a kit that would include one vial of MAB and a marketed infusion bag. Company ABC would purchase the bag from Company BAG. Company BAG operates under the QSR. Company BAG and Company SS would ship the bag and MAB, respectively, to Company A&S for assembly, labeling, and sterilization. Company A&S also operates under the QSR. Company A&S would then ship the kits to Company ABC, which distributes the kits for sale.

What are Company BAG's cGMP obligations?

The infusion bag is a medical device. Company BAG's compliance with the QSR is sufficient.

What are Company A&S's cGMP obligations?

Company A&S is assembling and sterilizing a kit combination product. Company A&S is a third party service provider for Company ABC. Company ABC, as the manufacturer of the finished product, is responsible for ensuring the overall quality of the product and thus should ensure that Company A&S complies with the necessary cGMP regulations. The starting point for evaluating Company A&S' cGMP obligations is under what cGMP system Company A&S currently operates, which as the facts indicate is Part 820.

Because Company A&S operates under the QSR, Company ABC should consider whether it needs to incorporate any provisions of Parts 210/211. Algorithm D can help Company ABC with this analysis. Company ABC would need to answer "yes" to the first question in Algorithm D, which asks whether the facility sterilizes the finished kit or all of the kit's components. Because Company A&S is sterilizing the entire kit, Company A&S may need to implement provisions of Parts 210/211 to ensure that the sterilization of the MAB biological product is performed under adequate quality system controls. The algorithm directs Company ABC to use Algorithm C to evaluate the relevant provisions of Parts 210/211. Algorithm C poses several questions that address whether Company A&S has systems in place to address requirements of Parts 210/211. If Company A&S does not have the relevant controls already implemented, it should implement the controls to the degree needed to ensure product quality. Next Company ABC should consider whether component suppliers comply with Parts 210/211 for the drug and/or biological components of the kit. The facts indicate that Company SS, which makes MAB, does comply with Parts 210/211, so the answer is yes.

What are Company ABC's obligations?

Company ABC is responsible for ensuring the quality of the finished product. The appropriate quality assurance activities depend upon what is necessary to ensure the kit's quality, in light of such factors as the risk level of the kit. A manufacturer may ensure quality in a variety of ways; for example, entering into written agreements with service providers, conducting inspections or audits, or performing other quality assurance activities. Company ABC might also audit the service providers prior to engaging them to perform manufacturing functions. Company ABC should also ensure that its third party service providers comply with the necessary cGMP obligations.

Finally, Company ABC's obligations with respect to the infusion bag include ensuring that it functions correctly for administering MAB, both before and after sterilization. This obligation is part of product design. Additionally, as discussed, Company ABC should ensure that Company BAG is in compliance with the QSR obligations that apply to the infusion bag. Contrast these obligations with respect to an off-the-shelf bag with those illustrated by example 2, below.

Example 2 – Custom Infusion Bag

What if the infusion bag was manufactured according to Company ABC's specifications?

If the infusion bag were manufactured according to Company ABC's specifications and was not an "off-the-shelf" device, Company ABC would have a responsibly to ensure the quality of the custom-made infusion bag itself, as opposed to the quality of the finished combination product kit. Assuming that the infusion bag would still be shipped directly to Company A&S for assembly and sterilization, Company ABC could ensure the bag's quality by performing appropriate quality assurance activities with respect to the bag and the bag manufacturer. This might include quality audits, sample testing, and other appropriate activities.

Case Study 3

Company DRG is a pharmaceutical company that has developed a drug and a monoclonal antibody for combination therapy. The drug and monoclonal antibody combination is administered through IV infusion from the same bag, although each product will be contained in separate vials and will be combined shortly before administration.

Company DRG contracts for the manufacture of the drug and the monoclonal antibody to other companies as follows:

- Company DD manufactures, labels, and releases the final bulk drug.

- Company MM manufactures, labels, and releases the final bulk monoclonal antibody.

Companies DD and MM both operate under Parts 210 and 211.

Companies DD and MM ship the drug and monoclonal antibody, respectively, to Company DRG. Company DRG, operating under Parts 210 and 211, puts the vials of drug and monoclonal antibody into a kit.

What are Company DRG's cGMP responsibilities?

Company DRG is packaging two constituent parts together in a single package to make a drug-biologic combination product. The obligations in Parts 210 and 211 apply to drugs and most biological products; therefore, those obligations would apply to this combination product. Certain biological products also have obligations under 21 CFR Parts 600-680. If any of those obligations apply to this product, Company DRG needs to implement them. Otherwise, Company DRG's compliance with Parts 210 and 211 should be sufficient. The algorithms in this guidance document address only drug-device and biologic-device situations; therefore, they do not apply here.

Case Study 4

Company XYZ has developed a combination product that is intended to treat cold sores on a patient's face or lips. The combination product would treat cold sores with a device that delivers the drug to the cold sore via an iontophoretic current.

The product consists of a control unit, a drug cartridge, and a moist towelette that the patient wraps around his or her finger. Below follows a more detailed description of these parts:

- The control unit contains, among other things, a circuit board, a computer chip, software, and batteries to power the unit.
- The drug cartridge, which snaps onto the front of the control unit, contains a foil-sealed single dose of the drug that treats the cold sore. The cartridge consists of a receptacle (a polypropylene disc containing a metal electrode and a pad) that is filled with the drug and sealed with a foil lid. The receptacle also has mechanical and electrical connections to the control unit.
- The towelette contains a conductive solution that is used to ensure that there is proper conductivity of the user's finger for use with the product.

To use the product, the patient snaps the cartridge onto the front of the control unit. The patient then wraps the towelette around his or her finger and inserts their finger into a ring on the control unit. The patient next turns on the control unit and peels the foil lid from the drug cartridge. The patient then holds the exposed drug cartridge to the cold sore for ten minutes. The control unit alerts the patient when ten minutes have elapsed.

Company XYZ developed all of the specifications for the product and its constituent parts. Company XYZ has received a determination that the PMOA of the product is that of a drug.

Company XYZ plans to contract with several companies to manufacture and assemble the product. These companies, and their respective cGMP compliance, are described below.

- Company 1 will manufacture the control unit in a facility that operates under Part 820.
- Company 2 will manufacture the towelette in a facility that operates under Parts 210 and 211.
- Company 3 will manufacture the receptacle. Company 3 is a plastic molding company that does a variety of manufacturing work. Company 3 does not operate under any cGMP system.
- Company 4, which operates under Parts 210 and 211, makes the drug final bulk.

Companies 3 and 4 ship the receptacle and drug final bulk, respectively, to Company 5.

- Company 5 manufactures the drug cartridge by filling the receptacle with drug final bulk using an automated machine that it built specifically for this project. This machine seals the receptacles with the foil lid. Company 5 operates under Parts 210 and 211.

Companies 1, 2, and 5 ship the products that they make (the control unit, towelette, and drug cartridge, respectively) to Company 6.

- Company 6 assembles and packages the product's constituent parts into a "kit" consisting of a control unit and multiple drug cartridges and towelettes. Company 6 also labels the final product. Company 6 operates under Parts 210 and 211.

What are Company XYZ's obligations?

Although Company XYZ contracts out the manufacturing functions, Company XYZ is the specification developer and thus is considered the manufacturer of the finished product. As the manufacturer of the finished product, Company XYZ has a responsibility to ensure the overall quality of the product. Company XYZ therefore should determine whether its third party service providers' cGMP compliance is adequate and should ensure that the third party service providers are producing quality constituent parts for the finished combination product. Company XYZ's oversight of the third party service providers to ensure product quality could include a wide variety of measures, for example:

- Visually inspecting product before it leaves the service provider. (Though typically the service provider will do this, Company XYZ may perform this function itself. For example, Company XYZ personnel may be on-site at a service provider to visually inspect the product when the product is in the development phase or when the product first hits the market.)
- Requiring or conducting lot or sample testing.
- Requiring a certificate of analysis for each lot of product.

The actual measures chosen will depend on the product in question, its risk profile, and possible activities required or suggested by FDA.

Typically manufacturers also conduct quality assurance activities before engaging a third party service provider, although again this is not a regulatory requirement. Such activities might include an inspection or audit of the service provider or other due diligence measures, such as reviewing the service provider's policies and procedures.

Finally, though again not a regulatory requirement, the specific obligations and roles of each party (as between Company XYZ and a particular third party service provider) will often be addressed in a written agreement. Such an agreement will allocate quality control and/or assurance responsibilities such as adherence to standard operating procedures and documentation of quality testing.

What are Company 1's cGMP obligations?

Company 1 manufactures the control unit, which is the device constituent part of the overall combination product. The facts do not indicate that Company 1 manufactures a

combination product or a drug or biologic constituent part; therefore, Parts 210 and 211 do not apply to its operations. Company 1's compliance with the QSR is sufficient.

What are Company 2's cGMP obligations?

As described above, Company 2 operates under Parts 210 and 211. The facts do not address whether the towelette is a drug or device; however, operating under Parts 210 and 211 will be sufficient as long as the quality system is sufficient to ensure the quality of the towelette. Similarly, if Company 2 were a device company operating under Part 820 (and not under any provisions of Parts 210 and 211), such compliance with Part 820 would be acceptable as well, again as long as the quality system was sufficient to ensure the quality of the towelette. The important point is that the towelette is manufactured under quality controls that are sufficient to ensure its quality.

What are Company 3's cGMP obligations?

Company 3 manufactures the receptacle, which is part of the container closure for the drug product. (The final container closure includes the lid as well as the receptacle.) As with the other parts of the system, Company XYZ developed the specifications for this custom container closure (i.e., it is not an "off-the-shelf" product). Company 3 does not operate under a cGMP system. This is appropriate as long as the quality of the receptacle is ensured through the performance of appropriate quality control measures (for example, a visual check of the receptacle). As discussed above, either Company 3 or Company XYZ could perform these quality functions.

What are Company 4's cGMP obligations?

Company 4 manufactures the drug final bulk and operates under Parts 210 and 211. The facts do not indicate that Company 4 manufactures a combination product or a device constituent part; therefore, the QSR does not apply to Company 4's operations. Company 4's compliance with Parts 210 and 211 is sufficient.

What are Company 5's cGMP obligations?

Company 5 fills the receptacle with the drug final bulk, thus creating the drug cartridge. The drug cartridge is the drug constituent part of the finished combination product. The facts do not indicate that Company 5 manufactures a combination product or a device constituent part. (The drug cartridge is not a combination product if the receptacle and lid are not medical devices.) Therefore, Company 5's compliance with Parts 210 and 211 is sufficient to ensure the quality of the drug cartridge.

What are Company 6's cGMP obligations?

Company 6 assembles, packages, and labels the finished combination product. The final product is a single entity combination product because it is comprised of two or more regulated constituent parts, i.e., a drug and a device, that are physically combined into a single entity. (21 CFR 3.2(e)(1)). The final product is not a kit because neither the drug constituent part (the cartridge) nor the device constituent part (control unit) will be approved or marketed separately. They are each made to work only with the other part and will only be approved and sold together as a combination product.

Because this is a single entity combination product and because Company 6 operates under Parts 210/211, the algorithm in Appendix A should be used to determine its necessary compliance with certain provisions of the QSR. As the manufacturer of the finished product, Company XYZ is responsible for the overall quality of the finished product and thus can use the algorithm to assess Company 6's cGMP obligation, or can delegate that responsibility to Company 6. In this case study, we will assume that Company XYZ is using the algorithm to assess Company 6's obligations.

The algorithm's questions will be answered in terms of the facility in which the product is manufactured. The first question in Appendix A is whether the facility's existing quality system addresses requirements for design controls, purchasing controls, and CAPA. If the answer is "no," Company XYZ should then consider whether Company 6 developed design specifications for the device constituent part. Company XYZ (not Company 6) developed specifications for the device (i.e., the control unit), so the answer to this question is "no". Next Company XYZ should assess whether Company 6 will change the intended use of the device constituent part. The answer seems to be "no", because Company XYZ designed the device specifically for the finished combination product. Therefore, Company 6's actions with respect to the device should be within the device's intended use. The algorithm then instructs Company XYZ to consider whether the device is a container for the drug. Again the answer is "no." The algorithm next instructs Company XYZ to ensure that the device is an appropriate constituent part for the finished combination product. As long as the analysis indicates that the device constituent part is appropriate, Company XYZ should assess whether the device supplier (Company 1) complies with the relevant controls for the device. The facts indicate that Company 1 fully complies with the QSR, so the answer to this question is "yes." Company XYZ then reaches the conclusion that Company 6 does not need to implement the relevant QSR control at its facility, as long as the control being considered is either design or purchasing controls. If, however, Company 6 does not have an adequate CAPA system implemented at its facility, it should implement these requirements to the degree needed to ensure product quality.

What change control regulations apply to this product, given that the change validation for the drug is based on a molecular and chemical analysis and the change validation for the device is based on a materials, scientific, and engineering analysis?

Changes made to any part of the overall product (i.e., to the drug cartridge, device, towelette, or receptacle) can impact the other pieces of the combination product. For example, if the cartridge is changed, it may no longer work with the control unit in the same way, or it may no longer deliver the drug in the same way. Therefore, change controls that only consider one constituent part (e.g., only the drug or only the device) typically will not be adequate for a finished combination product. In light of this, Company XYZ, as the manufacturer of the finished product, should ensure that it knows when any part of the finished product is changed. Additionally, changes should be reviewed across the combination product as a whole to assess the impact on the entire system.

One approach to ensuring appropriate change controls would be for Company XYZ to have in place a high-level oversight document that addresses the general minimum requirements of each constituent part of the combination product. Such a document would require that if any of the general minimum requirements change for a part, that change must be vetted with the other system parts to ensure that it does not adversely affect the other system parts.