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Specializing in Combination Products

Summary: Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (January 2017)

Introduction:

This document is a summary and commentary of key provisions of FDA's Final Guidance: *Current Good Manufacturing Practice Requirements for Combination Products*. It is presented for informational purposes only and should not be relied upon for regulatory purposes, as it attempts to simplify, condense and paraphrase the legalistic language of the guidance. For regulatory purposes refer to the FDA guidance.

The guidance repeats much of what is already described in the combination product CGMP rule (21CFR4), in particular its preamble, which was codified four years ago. Naturally, with a few additions, deletions and clarifications, the final guidance repeats much of that which was in the draft guidance. The following summary and commentary tries not repeat what was already known about CGMP requirements for combination products. With the exception of repeating certain important principles that mainly concern the coordination of compliance across facilities and responsibilities of management, this summary and analysis mainly identifies and discusses new insights and clarifications contained in the final guidance. As the result of having to make a judgement as to what is new and what is key, not all points of the guidance are summarized.

For the sake of clarity, some of the terminology used in this summary differs from the legalistic terminology used in the guidance. For example, the guidance uses the terms *operating system and base operating system* while in this summary, these terms are replaced with, *overall quality system and platform quality system*. Also, the guidance refers both drug/biologic CGMP and medical device CGMP as CGMP. To distinguish between these quality system regulations this summary will either refer to the regulations by CFR citation or by using the abbreviation CGMP for drug/biologic CGMP (21CFR211); QSR for medical device CGMP (21CFR820).

Coordinating Compliance Across Facilities:

- The holder of a combination product marketing authorization retains overall responsibility for product quality, even if they are not directly engaged in its manufacture.
- Quality agreements with constituent part manufacturer(s), suppliers and contractors are an important way to ensure that changes are transparent to the



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finished combination product manufacturer. If it is not possible to obtain notice of changes, the combination product manufacturer should implement additional controls to ensure that changes are identified and appropriate measures are taken to ensure that safety and effectiveness of the combination is maintained.

- Where possible, manufacturers of finished single-entity and co-packaged combination products should establish arrangements with suppliers, contractors, and consultants to receive notice of changes to the product or service, if the change might affect the downstream manufacturing process or the quality of the finished combination product.
- Some CGMP requirements concern the product as a whole, such as design controls, and some concern the overarching manufacturing process as a whole, such as CAPA. CAPA system(s) should allow for adequate information flow, appropriate investigations and the resolution of CAPA-related issues between facilities and manufacturers. Establishing a CAPA system that is shared between facilities, or facility-specific CAPA systems with established links between them, may facilitate handling of CAPA issues requiring multi-facility collaboration.
- Manufacturing activities occurring at multiple facilities and their associated quality systems should be coordinated. Each design, manufacturing and testing facility should have documentation describing its responsibilities and provide assurance that it complies with applicable regulations. As part of supplier qualification and oversight activities, the manufacturer of the finished combination product should have access to these records. Quality agreements with contractors, collaborators, suppliers and consultants should specify the activities to be performed and the documentation needed to demonstrate compliance with regulatory requirements.

Legacy Combination Products:

- FDA does not use this term.
- Combination products are subject to 21CFR211 and 21CFR 820 requirements that previously applied to their constituent parts prior to promulgation of 21CFR4.

Compliance and Inspections:

- A facility that manufactures a combination product must comply with 21CFR211 and 21CFR820 as required by 21CFR4.
- A facility that manufactures only device used to manufacture a combination product is not subject to 21CFR820. Manufacturers of APIs used to manufacture a combination product are not made subject to 21CFR211 as the result of 21CFR4.



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- The lead center for premarket review has the lead for ensuring compliance and, as necessary, other FDA components will cooperate. Inspections will typically be conducted consistent with existing compliance programs and policies.
- During an inspection, documentation should be provided describing the overall quality system, its platform quality system, and how it was supplemented to comply with additional requirements specified in 21CFR4.
- In addition to the need to demonstrate compliance with the basic requirements of the platform quality system, only compliance with the additional requirements specified in 21CFR4.4(b) must be demonstrated.
- If a streamlined quality system is being utilized, the quality system established at each facility involved in manufacture of a combination product should be described in pre-market submissions. For CDER or CBER-lead pre-market submissions this should be described in eCTD Module 3. For further guidance on placement within Module 3, the guidance refers to Section 3.3.2 of the CDER/CBER eCTD Technical Conformance Guide/Technical Specifications Document, but this seems to be an error. None-the-less, compliance information should be included in Module 3, and consistent with the flexible approach taken in the Guide there are several places that could be considered for appropriate placement of this information (e.g., 3.2.R or 3.2.P.7). For PMA submissions, this information should be described the manufacturing section.

Drug Container Closure Systems and Delivery Devices:

- Certain devices are exempt from all or parts of 21CFR820. Such exemptions may extend to device constituent parts of combination products and to the combination products of which they are a part. For these constituent parts and the finished combination product, demonstrating compliance with 21CFR820 is unnecessary as long as the quality system complies with 21CFR211.
- When a medical device is incorporated as a container closure system of a combination product, compliance with 21CFR211 must be demonstrated.
- If a device that would ordinarily be exempt from all or parts of 21CFR820 is incorporated into a container closure system this may be a new use of the device and exemptions from part 820 may no longer apply.
- Changes to the intended use of constituent parts of a combination product may require premarket review. If a manufacturer believes that a container closure drug delivery attributes should not be considered to be a medical device, or if they believe a device constituent part is exempt from any or all provisions under 21CFR820, the evaluation of this should be documented.



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Convenience Kits:

- When a kit only includes products that are legally and independently marketed, and packaged and labeled in the kit as they are when independently marketed, for the purpose of 21CFR4 compliance, the kit is considered a *convenience kit*, and demonstrating compliance with quality system requirements is only required for kit assembly, packaging, labeling, sterilization and further processing.
- If a kit includes any products that are repackaged, relabeled, or otherwise modified from the independently marketed product, then the kit is not a convenience kit
- For a device constituent part that would be considered exempt from 21CFR820 requirements when marketed outside the kit, the kit manufacturer may not be able to claim this exemption if the intended use of the device constituent part in the kit is new, or If the kit manufacturer modifies its intended use through labeling. Manufacturers believing that a kit qualifies as a convenience kit, or that a device constituent part is not subject to 21CFR820 requirements should document this evaluation.

Change Management:

- Combination product manufacturers should establish procedures for acceptance of components, containers/closures, and constituent parts to ensure detection and evaluation of changes that are critical to the safety or effectiveness of the combination product.
- For cross-labeled combination products, if one entity manufactures a constituent and another entity manufactures another constituent part, procedures should be in place to inform one another of changes that may affect the safety or effectiveness of the combination product, and that the specifications for the respective constituent parts remain appropriate, or are updated to ensure that the combination product remains safe and effective.

Specific QSR Provisions from 21 CFR 4.4(b)(1):

- **Management responsibility:**
 - Management with executive responsibility must periodically review the suitability and effectiveness of the quality system, including to ensure that the quality system satisfies established quality policy and objectives.
 - A management representative must be appointed, and the appointment formally documented, with responsibility for ensuring that quality system requirements are effectively established and maintained, and for reporting on the performance of the quality system to management with executive responsibility.



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- **Design Controls:**

- The design control process for the device constituent parts of cross-labeled combination products should address suitability for use, interactions and interrelationships between the constituent parts.
- Quality by Design principles may be leveraged in demonstrating compliance with design control requirements.
- The extent and complexity of design controls and its documentation will vary based on the complexity of the product and its phase of product development. Accordingly, if an independently and legally marketed drug product with an unchanged formulation, route of administration and intended use, is used to manufacture a combination product that incorporates a delivery device, design controls can begin once the choice of the delivery device is judged to be feasible and suitable. In this case, the properties of the drug can be used as a starting point for design inputs that focus on ensuring that the device appropriately delivers the drug and that the drug quality is not adversely affected by the device constituent part. For a novel combination product with novel drug and device constituent parts, design controls are intended to ensure that coordinated development of the drug and device constituent parts occurs, resulting in a final combination product that satisfies user needs and its intended use.
- Design inputs should address performance characteristics, safety, reliability and user needs. They should be established early in the development process to ensure that development efforts are consistent with intended use and user needs. Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA) concepts used in pharmaceutical development may be applied in combination product development conducted under design control in the establishment of design inputs and outputs. CQAs may be refined as product development continues. Design output documentation includes drawings and product specifications that can be verified against the design inputs as development progresses.
- Some design verification (e.g., bench and/or pre-clinical testing) and design validation (e.g., human factors testing) will typically be completed prior to the initiation clinical safety and efficacy studies. Clinical studies conducted to support safety and/or efficacy of the constituent parts of a combination product may be leveraged as part of the cumulative design validation efforts for the overall combination product.
- Design validation activities may include simulated use testing or clinical/nonclinical evaluations, including human factors studies and software validation. Device constituent part equivalents may be used in the conduct of final design validation activities but the manufacturer must document in detail the similarities and differences in the manufacture of the to be marketed device



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constituent part and its developmental equivalent. Where there are differences, the manufacturer should conduct appropriate testing and justify that the design validation results are representative of, and valid for, the to be marketed combination product. This should account for differences that may arise from inclusion of a drug or biological product, including equivalence of the manufacturing process for the drug/biologic constituent part, or the combination product as a whole. The equivalence rationale should be documented. Bridging studies may still be necessary.

- Risk analysis should begin early in the design process and continue throughout the lifecycle for the product to identify risks associated with its design, manufacturing processes, and intended uses of the combination product. Risk assessment and management activities performed for a drug constituent part under pharmaceutical development practices may be elements of the combination product overall risk analysis.
- The Design History File (DHF) may not need to document design and development planning for established characteristics of the individual constituent parts, for example the safety and effectiveness of a drug constituent part of a co-packaged combination product, if that drug constituent part was previously approved for the same indication. If a finished device, drug, or biological product constituent part is purchased, the combination product manufacturer is not required to retrospectively “design” that constituent part with respect to previously reviewed characteristics. If a separately developed drug or biological product constituent part requires modification in order to be used in the combination product, the manufacturer must assess what design control activities must be performed to ensure the safety and effectiveness of the combination product, and its suitability for use.
- It is appropriate for a DHF for a combination product to leverage and/or cross-reference existing developmental data. When transitioning from drug development to combination product development manufacturers should evaluate existing development documentation and systems and assess what, if any, changes may be needed to demonstrate compliance with design controls. Manufacturers should be able to explain to FDA in premarket submissions and in inspections how their practices and terminology align with design control requirements.
- **Corrective and Preventive Actions (CAPA):**
 - Combination product manufacturers have responsibility for ensuring that CAPA requirements are met and they have flexibility in coordinating CAPA systems across facilities. Manufacturers should ensure that appropriately comprehensive review of activities are undertaken at relevant facilities to determine the root



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cause of existing or potential quality problems for constituent parts and/or the combination product as a whole.

- As necessary, participating combination product and constituent part designers and manufacturers should participate in cross-facility efforts to investigate and determine and document the root-cause of quality problems and establish appropriate measures to correct and prevent their occurrence. The CAPA process for combination products also should consider implications of corrective and preventive actions for all constituent parts and for the combination product as a whole.

Specific drug/biologic CGMP Provisions from 21 CFR 4.4(b)(2):

- **Acceptance of drug product manufacturing components, containers, and closures:**
 - Combination product manufacturers do not need to demonstrate compliance with 21 CFR 211.84 for device constituent parts or materials used to manufacture of a device constituent part, unless the device constituent part is also the drug container or closure or a component.
 - In lieu of such testing, 21 CFR 211.84 allows for reliance on a supplier's report of analysis, provided that identity testing is conducted and that the reliability of the supplier's analysis can be verified. These duties augment and elaborate acceptance activity requirements established under 21 CFR 820.80. Accordingly, if a facility already has established 21 CFR 820.80-based acceptance procedures, it would be appropriate to augment these procedures to incorporate 21 CFR 211.84 compliant measures.
- **Calculation of Yield:**
 - Yield calculation requirements for drug manufacturing steps applies to the drug constituent part of a combination product; yield calculation is not required for device constituent parts. Losses in yield during a manufacturing step which are related to the rejection of device components should be captured as part of yield calculations for the drug constituent part, and investigation of the cause of that loss should identify the root of cause of device nonconformities.
 - For manufacturing operations conducted under a under a QSR platform based quality system, documentation of yield calculations may be part of the Device History Record and include actual yields, percentages of theoretical yields, and the maximum and minimum percentages of theoretical yield beyond which investigation is required for the drug constituent part, as it is processed and combined with the other constituent part(s) of the combination product.



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- **Tamper-evident Packaging of OTC Human Drug Products:**
 - Tamper-evident packaging requirements apply to the packaging of single entity OTC combination product as a whole. For co-packaged OTC combination products, these requirements can be met through appropriate packaging of the drug constituent part(s) within the larger co-package as long as such an approach is otherwise permissible under the packaging and labeling requirements applicable to that combination product.

- **Expiration Dating:**
 - The constituent parts of combination products may have individual expiration dates or the entire combination product may have an expiration date. Generally, when individual constituent parts of a co-packaged combination product can be used independently, expiration dating should be addressed separately. If a single expiration date is established for a co-packaged combination product, this date should be the earliest expiration date/shortest shelf-life for any of the constituent part(s). If marketed independently, the expiration date for a combination product may be shorter than the expiration date or shelf life for its constituent part(s). Reasons for a shorter expiration period could include interactions between the constituent parts when they are combined, the effects of additional manufacturing steps, or other differences arising from the combination of the constituent parts.

- **Release Testing:**
 - For single-entity combination products, release testing must be performed on every batch of the combination product. In lieu of testing the finished combination product FDA may allow testing of unfinished samples if they are representative of the finished combination product with respect to the characteristics and attributes being tested. The manufacturer will need to establish through quantitative testing that manufacturing differences between the unfinished combination product samples and the finished combination product do not affect the drug constituent part of the combination product.
 - For co-packaged combination products, release testing must be performed on every batch of the drug constituent part(s).

- **Stability Testing:**
 - With adequate justification FDA may allow the use of bracketing and matrixing approaches. FDA may also allow the leveraging stability data for an already marketed combination product if the new product modification of an existing marketed combination product that would not impact the stability of the drug constituent part.



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- Should a combination product manufacturer purchase a drug product from another manufacturer for inclusion in a co-packaged combination product, the combination product manufacturer is responsible for ensuring the stability of the drug product, as marketed in the co-packaged product, through appropriate mechanisms, (e.g. by implementing purchasing controls) to ensure the adequacy of the drug product manufacturer's stability testing or by conducting additional stability testing.
- If a drug constituent part of a co-packaged combination product has an expiration date, the combination product manufacturer may be able to rely on that expiration date in lieu of conducting new stability studies, if it can be documented that additional manufacturing operations are expected to impact the drug constituent part and its container-closure system.
- **Reserve Samples:**
 - For co-packaged combination products the requirement to keep reserve samples of drug products can be met by maintaining samples of the drug constituent part in its immediate container-closure system, without the need to retain samples of the device or portions of it.
 - For single-entity combination products, reserve samples should be of the drug constituent part, in or upon the device constituent part, or components that come into contact with the drug product as packaged for distribution. For a drug-eluting stent or disc, or a prefilled syringe reserve samples should generally be kept of the entire combination product.
 - Manufacturers that choose to retain reserve samples that are representative of, but not identical to, a finished drug constituent part or the entire combination product should provide adequate justification and data to support that any differences in the manufacturing process for the reserve sample and the finished combination product do not affect the drug constituent part, that the immediate container/closure has the same characteristics as the immediate container/closure for the drug as packaged in the combination product for distribution, and the proposed representative samples are suitable for required testing of the drug constituent part for which those reserve samples retained.
 - As an alternative to retaining complete samples for all testing, it may be possible to keep properly defined and validated equivalents for some testing while retaining complete samples of the entire combination product for other testing. Bracketing and matrixing approaches may be acceptable, and the use of samples from representative sub-lots of a larger batch of representative samples of each size from within a batch that includes multiple sizes from the same family of coated combination products.



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Commentary:

- **Remaining Uncertainties:**
 - The guidance does not address the impact of the addition an unapproved or uncleared constituent part to a kit, or the impact of changing the intended use or labeling of a constituent part that has been previously independently and legally marketed. It is not clear under such circumstances, when the kit is no longer recognized by FDA as a convenience kit, what CGMP and QSR activities need to be conducted by the kit manufacturer. It may not be possible for the kit manufacturer to assume CGMP and QSR responsibilities that are the responsibility of the manufacturers of the previously independently marketed constituent parts.
 - A change in intended use of a previously independently and legally marketed medical device from a general-use device to a specific-use device constituent part of a combination, seems likely when it is incorporated into a kit with a specific intended use. This seems to be a “Catch 22”. This conundrum also seems to apply to device constituent parts that are exempt from all or parts of the QSR. When an QSR-exempt (or partially exempt) general use device is intended to be used for a specific intended use, the regulatory benefits of existing exemptions or regulatory discretion that would have applied to the independently marketed device seem likely to be lost as the result of a change in intended use.
 - FDA has stated elsewhere that it does not intend to develop a Compliance Policy Guide for combination products. How will an FDA inspector assess a streamlined quality system that combines elements of a flexible QSR regulation with rigid drug/biologic-CGMP requirements?
 - How are Design Controls are to be applied to the drug constituent part throughout single-entity and kit combination product development? The guidance addresses this for cross-labeled combination products but it is silent on single-entity and kit combination products.
 - How do Design Controls apply to clinical supply kits which are not intended for commercialization?
 - Should compliance information be included in 510(k) applications for combination products?
- Why is FDA retrospectively applying QSR requirements to combination products when the preamble to the Final QSR rule specified that the regulation would not be applied retrospectively to marketed medical devices?