February 5, 2010

VIA ELECTRONIC SUBMISSION

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Current Good Manufacturing Practice Requirements for Combination Products; Proposed Rule; Docket No. FDA–2009–N–0435

Dear Sir or Madam:

The Combination Products Coalition ("CPC") is pleased to offer its comments on the Proposed Rule for Current Good Manufacturing Practice Requirements for Combination Products.[1] This proposed rule is a critical first step in providing clarification to the combination product industry on the application of GMP regulations. The proposed rule clearly is the product of a tremendous amount of time and effort, and we would like to thank the Agency for its thoughtful analysis.

By way of background, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination products area. One of the principal goals of our organization is to work with the Agency on issues affecting combination products, in order to advance our common missions of providing the best possible health care for patients. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

GENERAL COMMENTS

We appreciate the Agency's hard work in developing and issuing the proposed rule. The rule is a needed advancement beyond current guidance and historical case-by-case decisions by FDA, and its publication has already enabled important dialogue between the Agency and regulated industry on GMP issues. For example, on January 12, 2010, Agency and industry representatives participated in a workshop hosted by the Regulatory Affairs Professionals Society ("RAPS"), in collaboration with our organization. The workshop centered on applying the proposed rules to detailed case studies, with the overarching goal of

[1] 74 Fed. Reg. 48423 (Sept. 23, 2009) (the "GMP Proposed Rule").

analyzing and discussing the practical strengths and weaknesses of the rule. Our comments incorporate many of the key issues discussed during the workshop, as well as additional comments from our members. RAPS also has submitted a complete summary of the issues discussed during the workshop as comments on the proposed rule.

Overall, the proposed rule sets forth a sound foundation for meeting the GMP obligations that are necessary to ensure a product's safety and efficacy. However, several important clarifications are warranted to ensure that the rule is optimally flexible and efficient and that regulated industry and FDA personnel can implement the new requirements appropriately.

We are also concerned about aspects of the implementation of the new rules, including how the rules will be implemented for existing, well established products (i.e., "legacy" products) and that the proposed rule significantly underestimates its impact on manufacturers. In particular, the impact of the proposed rule on small firms, and innovation in general, could be substantial given the rule is in some cases unnecessarily prescriptive with regard to requirements. The rule needs to accurately gauge the type and amount of work required in order to develop an appropriate implementation plan. In this regard, implementing guidance issued for comment ***before*** the final rule is issued is of paramount importance.

Below we offer our specific comments on the proposed rule.

SPECIFIC COMMENTS

1. The Definition of "Constituent Part"

The term "constituent part" is pivotal under the proposed requirements. Because of its importance, Agency personnel and manufacturers need a clear, practical definition. Currently, much of the ambiguity in the proposed rule regarding the application of a "streamlined" system stems from ambiguity over what constitutes a "constituent part."

As written, it seems the definition of a constituent part would encompass ***any*** device or drug component or ingredient. Specifically, the proposed rule defines a constituent part to include ***any*** drug or ***any*** device that is part of a combination product. As we know, the statutory definitions of a device and a drug include components.[2] Thus, a component or ingredient that is or becomes part of a combination product is defined as a constituent part. To state it another way:

[2] The term "device" … means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, ***including any component, part, or accessory*** (21 USC 321(h) (Emphasis added). The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) *articles intended for use as a component of any article specified in clause (A), (B), or (C)* (Emphasis added). 21 U.S.C. § 321(g) and (h).

Proposed rule says: Constituent Part = Drug or device that is part of a combination product

Existing law says: Drug or Device = Components and Ingredients

Unintended consequence is: Constituent part = Components and ingredients

Further, under the proposed rule, a device that is a constituent part of a combination product is considered a finished device, and a drug that is a constituent part is considered a drug product.[3] So in effect, the proposed rule *reaches back* to grab components and ingredients, subjecting them to GMP requirements as though they were finished drugs or devices.

Such consequences may not be appropriate for components that have not yet been assembled into a finished device or even a device assembly. Indeed, there are many components and ingredients in devices and drug products whose manufacturers are not required to comply with GMPs. (This point is discussed in more detail below under our second specific comment.) Based upon the proposed definition and without clarifying guidance, confusion may also result with regard to drug container closures (i.e., drug components) and when these components constitute a device constituent part. The proposed provisions also could have the unintended effect of requiring manufacturers of components and inactive ingredients to register their facilities as a manufacturer, because the "constituent part" they produce is defined as a "finished" device or drug.

Proposed Solution: The final rule should clarify the definition of a constituent part and add a definition for components. In particular, we suggest the definitions in proposed § 4.2 be revised as follows:

> "Constituent part is a drug, device, or biological product that is part of a combination product as defined in § 3.2(e) of this chapter and that contains a drug substance as defined in § 314.3 of this chapter or that is a finished device as defined in § 820.3 of this chapter, or a biological product as defined in § 600.3 of this chapter."
>
> Add the following definition: "Component means any raw material, substance, piece, part, software, firmware, labeling, assembly or inactive ingredient that is intended for use in the manufacture, or to be included as part of the finished, packaged, and labeled combination product. This regulation does not apply to manufacturers of components of finished combination products, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidance."

[3] Proposed § 4.2.

Further, the implementing guidance should address and provide examples of constituent parts, in order to illustrate and describe the dividing line between components and ingredients and finished products. In providing these and other examples, the terms "drug substance" and "drug product" should be used carefully. As described above, we believe the most appropriate term – and one that reflects historic practices – with respect to the definition of constituent part is "drug substance."

2. Application of GMP Requirements to Components Before and After Arrival at a Facility Where a Combination Product is Produced

As discussed above, the proposed rule defines a constituent part to include any device or drug that is part of a combination product. Under existing GMPs, components – which include any raw material, substance, piece, part, software, firmware, labeling, or assembly for medical devices and active and inactive ingredients for drug products[4] – are not defined or treated as finished devices or drugs. Rather, they are only addressed and covered by GMPs when they are received by the manufacturing facility. In this way, medical device components and drug inactive ingredients and components are not *directly* subject to GMPs, although the final manufacturer has responsibility for ensuring appropriate quality requirements at the supplier facility and in the case of devices are encouraged to use the GMPs as guidance.

In many cases, the drug or device part of a combination product is comprised of components or ingredients that are assembled with the drug or device into a finished combination product. They are *not* in and of themselves finished medical devices or drugs (and should not be a "constituent part") *until* such time as they are assembled. Before that time, they are components or ingredients, and would not have previously been directly subject to GMPs.[5] This GMP regulation should ensure that constituent parts of combination products are treated the same as if they were to be final manufactured or assembled into a finished medical device or drug. That they end up combined with a drug or device in a combination product should not introduce a new, more burdensome requirement.

For example, consider the case of syringe components that become the syringe portion of a pre-filled syringe combination product. The components are manufactured and supplied separately to the final product manufacturer, where they are assembled and filled with the

[4] 21 CFR §§ 210.3(b)(3) and 820.3(c).

[5] The QSR provides: "This regulation does not apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidance." (21 CFR 820.1(a)). The *Medical Device Quality Systems Manual: Small Entity Compliance Guide* elaborates on this regulatory language, stating: "A 'component' is defined by 820.3(c) as "any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device." *Component manufacturers are excluded from the QS regulation by 820.1(a)(i). Current FDA policy is to rely upon the finished device manufacturer to assure that components are acceptable for use. . . .*When finished device manufacturers produce components specifically for use in medical devices they produce, whether in the same building or another location, such production of components is considered part of the device manufacturing operations, and the production should comply with the QS regulation." (Emphasis added).

drug. These are never intended, offered or sold as finished devices, and in the state they are provided (unassembled) do not meet the definition of a medical device. Further, these manufacturers have historically been considered providers of container closure components, have quality systems that are required and monitored by the final drug manufacturer's GMP requirements (and usually covered in a quality agreement), and have Drug Master Files available for FDA review. These companies should not be required to implement device quality systems or be subject to this rule.

> ***Proposed Solution:*** In terms of specific regulatory language, revising the regulatory definitions of "constituent part" and adding a definition for "component" as described above would avoid these problematic consequences. Adding an explanation in the final rule or implementing guidance that combination product GMPs are consistent with other existing sets of GMPs, in that those systems and processes do not apply directly to manufacturers of device and drug components and drug inactive ingredients, would also be helpful. Further, the final rule and implementing guidance should provide that container closures currently treated as drug components will continue to be handled in the same fashion – i.e., treated as a drug/biologic container closure as defined under 21 CFR § 211.84, and not as a device constituent part that is subject to the QSR. The final rule should not change the long-standing definitions and interpretations of these systems applied by the Agency.

3. Responsibility for GMP Compliance

a. *Responsible Entity*

The proposed rule sets forth requirements for entities that "manufacture" a combination product. The rules would define "manufacture" as including, but not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage. One point of confusion with respect to this definition is that it is not entirely consistent with the definitions of manufacture under the drug GMPs and device QSR. For example, the QSR definition of manufacturer provides that it includes "those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions."

> ***Proposed Solution:*** The final rule or implementing guidance should clarify that the combination product GMPs are intended to encompass the types of entities and activities defined as manufacturing under drug GMPs and the device QSR.

The rule also should clarify who the responsible entity is in the case of situations involving specification developers, contract manufacturers, component manufacturers, and the like. For example, under the QSR, both manufacturers and contractors may be held jointly

liable for QSR violations.[6] Ultimately, though, the Agency typically looks to the finished device manufacturer – which may be a specification developer – to ensure overall compliance with GMP requirements.

Proposed Solution: The combination product GMP rule should remain consistent with this established framework.

b. *Location and Duplication of GMPs*

GMPs are comprised of two elements – systems (i.e. policies, procedures, methods, etc) and records (e.g. calibration, process validation, batch records, audit records, etc). When manufacturing takes place in one facility, both of these elements are usually implemented and utilized in that regulated, registered facility. However, many combination products are the result of two different technologies, expertise, processes and, in many cases, facilities. Thus, in most cases in which two constituent parts are brought together as contemplated under the proposed regulation, there is only one final manufacturer responsible for registration of the product and whose name appears on the product.

When the GMP part is specifically covering the manufacture of the product, applicable requirements are easily parsed to the facility that performs that operation (e.g. calibration, pest control, documentation control, batch records, etc) or are identified as inapplicable to the given facility's operations. However, when the GMP system applies to the *whole* product, the existence of two systems may be more burdensome at the least and disruptive at worst.

Further, certain device QSR provisions are not tied to a facility and could be implemented at any company or facility involved in the process. In particular, design controls, management controls, and purchasing controls ideally should be implemented *before* supplemental quality system requirements are officially triggered by a product "arriving" at a facility. Importantly, though, as explained above, these systems could be located in any of the companies, as long as the responsibilities are appropriately defined and allocated between the manufacturers (e.g., in a written Quality Agreement).

To take a specific example, consider design controls. A medical device manufacturing facility may have an existing and compliant design control system that requires design input, design review, risk management, and other required elements. This system, with the proper agreements, inputs, and participation by the drug company, could be applied to the entire product and meet the GMP requirement without having the drug company create an unnecessary and duplicate system. The Design History File (records) could be located at either facility, or there could be relevant records located at both facilities. Either way, the relevant records would be available to FDA during an inspection of the combination product facility.

[6] FDA, Medical Device Quality Systems Manual, Ch. 1, available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/ucm122391.htm (last accessed Dec. 29, 2009).

Proposed Solution: To avoid duplicative and unnecessary requirements and ensure flexibility to address complex virtual development and manufacturing arrangements, the combination product GMP regulation should envision and allow for the existence of a system that is *implemented* at any facility, can be *utilized* by more than one facility, and, for systems that are not tied to the manufacture, can be at a facility remote from the product manufacture. The responsibility for ensuring that all requirements are met and are appropriate should always fall to the manufacturer who holds the marketing application.

4. Scope and Impact of the Triggers for a Combined GMP System

Proposed § 4.4(d) says that a combined GMP system may be used when two or more constituent parts "have arrived at the same facility" or when "manufacture … is proceeding at the same facility." Due to the complexity of manufacturing operations for combination products, the final rule and implementing guidance should clarify the ambiguities inherent in these approaches.

In particular, a key ambiguity of the rule is how and when to comply with the supplementary elements necessary to form a streamlined quality system. For example, when constituent parts come together in a single entity or kit combination product, it is not clear if compliance with the additional requirements must extend both backward and forward or only forward from the point when the constituent parts are brought together. Interpreting the rule to apply in "both directions" (backward and forward) in order to achieve compliance with a streamlined quality system would be overly burdensome.

Proposed Solution: Clarify that the rules regarding a streamlined system will apply "forward" only – i.e., during and after the time the constituent parts arrive at the manufacturing facility or when manufacture is proceeding at the facility. Importantly, though, this "forward" application must be consistent with the concepts described above with respect to the location and duplication of GMPs. That is, even though the requirements apply on a "forward" basis, they may nevertheless be implemented by manufacturers that are involved in the manufacturing process (e.g., by manufacturing a constituent part) *before* the constituent part arrives at a manufacturing facility or when manufacture is proceeding at a facility.

Manufacturers also will need to address important nuances when applying these rules to their manufacturing operations and the practice of "bringing together" constituent parts. In particular, often such operations may not be as simple as "arrival", but rather may involve *forming* drug and device constituent parts when components are brought together (for example, a prefilled syringe).

Proposed Solution: The final rule and implementing guidance should clarify the dividing line in cases like these. In particular, the additional set of quality system requirements should not apply until a constituent part is formed or assembled. Going

back to our discussion above, the constituent part should be considered a drug, device, biological, or HCT/P in finished form.

Finally, the final rule and coordinating guidance also should recognize circumstances in which the manufacture of a combination product occurs in a large facility that has unrelated drug and device operations.

Proposed Solution: Clarify that the manufacturer could simply choose to implement separate GMP systems for the differently regulated articles.

5. Change Controls

An established overall change management system for changes that may occur in a constituent part of a combination product is important. However, the proposed rule does not address how combination product manufacturers should implement existing change control requirements to ensure changes in constituent parts are managed and monitored between and among manufacturers. Assessing such changes is particularly important for products that are distributed separately and assembled and used by an end user versus a manufacturer.

Proposed Solution: As part of implementing change control requirements, companies should ensure that changes are assessed by both companies prior to implementation. The Agency should consider requiring constituent part manufacturers to notify the manufacturer of the combination product before making changes to a constituent part. Importantly, though, manufacturers must have flexibility in implementing such a change control system. For example, in many instances, manufacturers enter into a quality agreement describing each firm's roles and responsibilities with respect to quality system compliance, including change controls. Because of the widely-varying products and arrangements between and among manufacturers, this is a key example of an issue that needs to be addressed in implementing guidance.

6. Implementation Issues

a. *Products Already on the Market*

The Agency needs to supply much more detail on how manufacturers should implement the new GMP requirements. As published, the proposed rule does not adequately address transition issues associated with currently marketed products not subject to public health or safety concerns. In the absence of more information from FDA and a detailed plan to deal with these types of products, the potential impact of the rule on manufacturers could be enormous. For example, confusion could result from the potential for retroactive implementation of the new requirements (e.g., if a manufacturer is incorporating elements of the QSR, there could be a potential for the impractical task of retroactively creating a Design

History File where one did not previously exist). This would not only create unnecessary burden on manufacturers; it would also cause problems from a field inspection standpoint.

> ***Proposed Solution:*** The final rule and implementing guidance should address how the rules will be applied to products already on the market, which reflect regulatory approaches, product clearances and approvals, and individual Agency decisions that span decades. For example, for some older, well-established products, retroactive application of the rules will be unnecessary.

b. *Implementing Guidance*

We are pleased that the proposed rule recognizes that "coordinating guidance" is needed to fully implement the final rule. This guidance is absolutely critical for the smooth and timely implementation of combination product GMPs. As a practical matter, many manufacturers will not be able to implement the rules adequately without detailed guidance.

> ***Proposed Solution:*** Obviously, the guidance should address the ambiguities identified in comments on the proposed rule and in other avenues of communication with the Agency (e.g., in conjunction with product clearances or approvals). Importantly, in terms of timing, the guidance should be published *before* the final rule is published. Such an approach will help ensure a more coordinated approach to implementation.

c. *Impact Analysis and Effective Date*

The proposed rule estimates that manufacturers will only need about 25 hours per product to assess compliance with the proposed rule and "perhaps alter[] some standard operation procedures." We believe this estimate drastically underestimates the time required for firms to come into compliance with the rules. Indeed, until now, the Agency has expressed its interpretation of GMPs applicable to combination products through a *draft, non-binding* guidance document. Although many firms experienced in combination product issues have incorporated the principles expressed in the 2004 draft guidance into their operations, other firms that are new to the combination product area may not have incorporated such practices. The impact of the proposed rule on small firms, and innovation in general, could be substantial. Further, even firms that are experienced in combination products will need to take a close look at the implementation of GMPs throughout their facilities when the final rule and coordinating guidance are published. This process and analysis requires the coordination of many functions and extensive communications and analysis among company personnel.

> ***Proposed Solution:*** A more accurate estimate of the time required for firms to come into compliance with these rules is in the triple-digit range.

Additionally, as a result of the significant work required, the effective date of the final rules should be adjusted based upon specific regulatory requirements a firm must implement. In particular, the implementation of device management controls and design controls may entail a significant amount of time for firms that are not experienced in these requirements. When the Agency originally promulgated device design controls, device firms were given an

additional year (in addition to the eight months applicable to other provisions of the QSR) to comply with the new design control requirements.

Proposed Solution: Drug and other companies not already experienced in design controls should be given one year to comply with design control requirements. The Agency should review the feasibility of a 180-day delay for other portions of the rule after re-assessing the time and economic burden, as discussed above.

d. *Responsibility for Compliance Oversight*

The proposed rule also does not provide much detail on precisely who within the Agency will be responsible for overseeing compliance with the rules. Clarification on such issues is necessary to ensure the smooth implementation of the new rules by both regulated industry and the Agency.

Proposed Solution: The implementing guidance should apply to FDA staff and should address, at a minimum, the following issues:

- Who within the Agency is directly responsible for overseeing the implementation of and compliance with the rules? For example, will this responsibility rest within the individual Centers, OCP, or some other function?

- How will Agency personnel communicate with regard to GMP requirements applicable to combination products? For example, such communication may be needed in the context of product development activities and meetings, approving product applications, and field force actions.

- How will the Agency train field force on these requirements and on inspections of combination product manufacturers?

7. Cross-Labeled Combination Products

Although the preamble to the proposed rules explains how GMPs apply to combination products that are distributed separately, the proposed regulatory language does not seem to address this issue. In particular, the regulatory language should clarify that when the constituent parts of a combination product are manufactured and distributed separately, they are subject only to GMPs otherwise applicable to their constituent part.

Proposed Solution: It seems that this clarification can be accomplished through a relatively simple change to proposed § 4.3. Instead of "The current good manufacturing practice requirements in parts 210 and 211 of this chapter apply to a combination product that includes a drug constituent part …", the regulatory language could be clarified to state: "The current good manufacturing practice requirements in parts 210 and 211 of this chapter apply to the ***drug constituent part*** of a combination

product." The language would be changed in the same manner for device and biologic constituent parts.

Another discrete issue with respect to cross-labeled products is that the proposed rule does not address handling customer complaints associated with products distributed separately but combined and administered by the end user.

Proposed Solution: Manufacturers of constituent parts of cross-labeled combination products should continue to comply with their respective GMP/QSR requirements. If the manufacturer's investigation into the complaint indicates a potentially reportable adverse event, ideally the manufacturer should report the incident to the other manufacturer. This issue is covered by the proposed rule on postmarket safety reporting requirements; however, final requirements probably will not go into effect for some time. Therefore, in the meantime, the Agency should acknowledge that companies will follow existing adverse event reporting frameworks.

8. Clarifications Regarding "Applicable" GMPs

The description of the streamlined system in proposed § 4.4(b) should be clarified to recognize that, if a manufacturer chooses to adopt a streamlined approach, the manufacturer only needs to incorporate the "applicable" requirements set forth in § 4.4(b)(1)-(2). This is consistent with long-standing rules regarding application of GMPs.[7]

In particular, the wording of these sections is overly restrictive in that it does not allow the company to assess and determine the applicability of the supplemental GMP/QSR provisions, with the manufacturer documenting the justification for not implementing inapplicable provisions. Therefore, the rule may require implementation of specific GMP or quality system provisions at facilities where they are not appropriate or necessary and where existing controls are adequate.

This can be true for single entity drug-device combination products regulated by the Center for Devices and Radiological Health and produced under a streamlined GMP system with the QSR as the baseline system. In these cases, specific elements of the drug GMP testing requirements and other compendial testing requirements for finished therapeutic drug formulations are often not applicable. Specific examples of this issue include:

- It is unclear when the proposed rule intends calculation of yield under § 211.103 to occur. In some cases, calculation of yield does not appear to be demonstrable in a credible scientific manner in the manufacturing process for combination products with a device primary mode of action. There are other ways to ensure appropriate amount and concentration and therefore the safety and effectiveness of the combination product (process requirements, design control specifications).

[7] *See* 21 CFR §§ 210.2(b) and 820.1(a).

- Requiring reserve samples of the final combination product under § 211.70 seems overly burdensome and impractical, particularly when there are multiple sizes and shapes. If interpreted as written, companies would need to retain large numbers of a final product to be able to meet the quantity requirement for testing the drug constituent part (currently twice the quantity necessary for release testing retained for one year after expiration date of the product).

- Stability testing (expiry testing) for drugs have similar problems as reserve samples, in that is would be impractical to perform annual stability for each size and shape.

This over-restrictiveness also can be true for combination products regulated by the Center for Drug Evaluation and Research and produced under a streamlined system with the drug GMPs as the baseline system. In this case, the addition of some of the device QSR elements may not be appropriate. Specifically, in many cases installation and servicing will not apply, and also there may be instances where other systems (e.g. management controls, purchasing controls) may not add any additional controls or quality to the product that are not already required under the drug GMPs.

> ***Proposed Solution***: In general, the proposed rule should recognize the need for flexibility for manufacturers when interpreting and applying applicable portions of GMPs to combination products that are manufactured under a streamlined system. Taking § 4.4(b)(1) as a model, we suggest the following changes: "If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply ***with applicable parts of*** the drug GMPs, the following ***applicable*** provisions of the QS regulation must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the QS regulation need be made, ***and for those parts of either regulation that are determined not to apply to the specific product, a discussion and justification as to the inapplicability must be documented and maintained at the facility:***"

9. "Demonstrating" Compliance

Throughout the proposed rule, the Agency repeatedly says firms must "demonstrate" compliance with combination product GMPs. For example:

> "Accordingly, the written procedures for a streamlined system would have to assure that the firm could demonstrate compliance with the cGMP requirements specified in the proposed rule."[8]

[8] GMP Proposed Rule at 48426.

> "… the [GMP] operating system for that constituent part must be demonstrated to comply with all [GMP] requirements applicable to that type of constituent part …"[9]

The way in which the Agency uses the term "demonstrate" seems ambiguous. Specifically, we are concerned the Agency somehow intends it to connote some type of independent, additional requirement.

> ***Proposed Solution:*** The rule should clarify that "demonstrate" is used the same as it always has been with respect to GMPs. Specifically, the requirements for firms to demonstrate compliance are set forth in the rules, for example, through the implementation of written procedures, internal auditing, and other requirements. Importantly, "demonstrate" also encompasses demonstrating and justifying that specific provisions are inapplicable to a facility, as described in our comment above.

10. Combination Products Created "In Situ"

The proposed rules do not address combination products in which there is only one constituent part, and the other portion(s) of the combination product is created *in situ*. Typically, such products are devices that create a drug.

> ***Proposed Solution***: For these types of products, the final rule should clarify that the manufacture of the combination product is subject to the GMP rules applicable to the constituent part that is manufactured and distributed to the user.

11. Application of the Rules to Biological Products

In general, we believe the proposed rule should provide more detailed information regarding its implementation with respect to biological products. For example, although the proposed rule describes specific differences between drug and device GMPs, it does not discuss specific differences as between biological and other GMPs. A more explicit description would help ensure stakeholders understand how to implement GMPs in a practical way.

> ***Proposed Solution***: The final rule and implementing guidance should incorporate a table similar to the one used in the September 2004 draft guidance on combination product GMPs setting forth the key GMP provisions to consider when implementing a streamlined GMP system.

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[9] *Id* at 48431 (proposed § 4.4(c)).

We are pleased that the Agency has issued the proposed rules, and we look forward to the implementing guidance and the final rule. Because of the important implications of these rules, we urge the Agency to carefully consider stakeholder comments as it develops and issues an implementing guidance and the final rule. We are happy to help in any way we can.

Respectfully submitted,

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