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VIA ELECTRONIC DELIVERY

Stephen Ostroff, M.D.
Commissioner of Food and Drugs (Acting)
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2015-01410 – Comments on “Current Good Manufacturing Practice Requirements for Combination Products; Draft Guidance for Industry and Food and Drug Administration Staff”

Dear Commissioner Ostroff:

The Combination Products Coalition¹ welcomes the opportunity to comment on FDA’s *Current Good Manufacturing Practice Requirements for Combination Products; Draft Guidance for Industry and Food and Drug Administration Staff* (“Draft Guidance”). We believe that the Draft Guidance is a great step forward in clarifying FDA’s cGMP expectations for combination products, and appreciate the many detailed examples that the Agency has provided to clarify its thinking on the application of 21 CFR Part 4. We offer these comments to suggest a few small, but important, ways in which we think the Draft Guidance could be improved by providing additional clarity regarding:

- I. Distinctions between convenience kit and other co-packaged combination product requirements;
- II. Design History Files for combination products that were not developed under design controls;
- III. Design controls for combination products with simple liquid dosing devices and similar products;
- IV. Requests for cGMP information in marketing applications;

¹ The “CPC” is a diverse group of drug, biological product, and medical device manufacturers with substantial experience in the combination products area. Our members range in size from small start-ups to multi-billion dollar manufacturers. These companies all share an intense interest in policy issues affecting combination products. Because of our diverse, cross-industry membership, the CPC brings a broad and unique perspective to issues affecting combination products. For more information, see <http://www.combinationproducts.com>.

- V. Obligations of combination product “sponsors” (marketing authorization holders);
- VI. Standard practices for coordination amongst manufacturers of cross-labeled combination products;
- VII. Design controls for early-phase investigational combination products;
- VIII. The meaning of the term “delivery” in reference to delivery devices; and
- IX. Development and implementation of a combination products inspection guide.

We address each of these issues in greater detail, below.

I. Distinctions Between Requirements for “Convenience Kits” and Other Co-Packaged Combination Products

Per the Draft Guidance, a ‘convenience kit’ is comprised of constituent parts that are (1) legally marketed independently, and (2) included in the kit as already packaged for independent marketing and with the same labeling as required for independent marketing.² A convenience kit manufacturer is only required to demonstrate cGMP compliance with “kitting activities,” namely the assembly, packaging, labeling, and any sterilization, or further processing of the kit; other requirements of Part 4 (e.g., design controls) would not apply.³ We agree with the Agency’s proposed approach to convenience kits, but believe that the Draft Guidance would benefit from additional clarification in the following respects.

1. Co-packaged Combination Products Made from Bulk Finished Devices May Only Need to Demonstrate Compliance With Kitting Activities

Often, co-packaged combination products include finished devices that are customarily sold in bulk without independent packaging and/or labeling accompanying each unit. Although these are considered finished devices, when included in a co-packaged combination product, they do not appear to meet the definition of a convenience kit as they are not suitable for independent marketing without, e.g., attaching labeling or placing the device in independent packaging. However, the CPC feels that there should be no additional requirements placed on these types of co-packaged combination product “kits” than there would be on convenience kits.

For example, syringes are customarily sold in bulk and not independently labeled for unit sale. Complying with cGMPs for kitting activities, including labeling requirements that address any necessary directions about use of the syringe with the drug, should be sufficient for kits built with these products; nothing is lost by the omission of the individual syringe labeling, so we believe it would be reasonable to treat these kits like convenience kits. We therefore request that FDA revise the Draft Guidance to recognize that kitting with units of products marketed in bulk (and not independently packaged and/or labeled) should only require compliance with kitting activities.

² Draft Guidance, 11 (emphasis added).

³ *Id.*

2. *Kits Should Retain Their Identity When Combined with Other Products*

If a kit is combined with additional constituent parts, our understanding is that the kit would retain its independent identity as a kit. For example, if a cGMP-compliant kit containing marketed devices is combined with an investigational drug intended for Phase 3 clinical investigations, under 21 CFR Part 4, the manufacturer would only be required to assess the combining of the kit and the investigational drug constituent part product. However, we suggest that the Draft Guidance clarify this point.

3. *Modification of Constituent Parts Prior to Packaging*

The Draft Guidance states that –

“[i]f a kit includes any products that are repackaged, relabeled, or otherwise modified for purposes of their inclusion in the kit, these activities for the constituent parts would be additional aspects of the manufacture of the combination product, thus the kit manufacturer would also have to demonstrate compliance with CGMP requirements with respect to these manufacturing steps.”⁴

Our understanding is that this statement refers to modification of constituent parts (e.g., changes to packaging or labeling) prior to kitting, and not the act of bringing the parts together to create the kit. Therefore, the act of kitting alone would not be considered to “modify” constituent parts. However, it would be helpful if this point was made clearer in the guidance.

Recommendations:⁵

The CPC recommends that FDA –

1. Clarify that when co-packaging constituent parts that are customarily sold as finished devices in bulk, cGMP-compliance with kitting activities is sufficient to meet the requirements of 21 CFR Part 4. We recommend accomplishing this through making revision to Section III.C.4 as shown below:

As explained in the preamble to the final rule, a kit that includes two or more types of medical products (e.g., a device and a drug) is a co-packaged combination product and, therefore, the manufacture of the kit is subject to part 4. The CGMP requirements applicable to a kit manufacturer depend on what products are included in the kit. The preamble to the final rule also states that if the kit includes only products that are 1) also legally marketed independently and 2) included in the kit as already packaged for independent marketing and with the same labeling as required for independent marketing, it is a “convenience kit,” and the only manufacturing steps for the combination product would be the assembly, packaging, labeling, any sterilization, or further processing of the kit itself. In addition if constituent parts are customarily marketed in bulk packaging, and do not have independent unit packaging and/or labeling (e.g., piston syringes, liquid medicine dispensers, bandages), cGMP requirements for co-packaging (kitting) with the parts would be the same as for convenience

⁴ *Id.*

⁵ Recommended revisions to the Draft Guidance throughout these comments are presented in *italic underline* and ~~strikeout~~.

kits assembly. Accordingly, the ~~kit~~ manufacturer would only have to demonstrate compliance with CGMP requirements with respect to those manufacturing activities. . .

2. Clarify that when the manufacturer combines a new constituent part with a cGMP-compliant kit, the manufacturer is only required to consider the combination of kit with the new constituent part under 21 CFR Part 4.

3. Revise the statement on page 11 to reinforce that it refers to modification of constituent parts prior to kitting as follows:

“[i]f a kit includes any ~~products~~ constituent parts that are repackaged, relabeled, or otherwise modified ~~for purposes of prior to~~ their inclusion in the kit, these activities for the constituent parts would be additional aspects of the manufacture of the combination product, thus the kit manufacturer would also have to demonstrate compliance with CGMP requirements with respect to these manufacturing steps.

II. Design History Files for Products that were not Developed under Design Controls

Pharmaceutical and biotechnology companies have been manufacturing safe and effective prefilled syringes and other simple combination product presentations for several decades without formal design controls. Although benefits may flow from adopting design controls for these products, in light of this long and successful regulated history of manufacturing under pharmaceutical standards, these new controls should be (1) narrowly tailored to focus on the combination only, (2) leverage existing, highly regulated, drug manufacturing cGMP systems to create DHFs for products that have not been developed under design controls, and (3) leverage existing postmarket surveillance data and other available information to understand the risk profile for the product, and guide the level of DHF remediation that is necessary.

Therefore we greatly appreciate that FDA has emphasized throughout the Draft Guidance that “[t]he design history file [“DHF”] for a combination product should address all design issues relating to the combined use of the constituent parts in the context of its intended use,”⁶ and does not need to revisit the design history of the individual constituent parts. We also appreciate FDA’s recognition that existing information can be leveraged to build a DHF for a product not developed under design controls, e.g., (a) use of existing specifications may become part of the design output documentation, or (b) testing performed prior to distribution to serve as validation and verification documentation. We do, however, offer recommendations on strengthening some of the statements regarding leveraging past work, and clarifying how design history files for products not developed under design controls can be developed.

⁶ Draft Guidance, 19.

Recommendations:

1. The CPC recommends revising the second and third full paragraphs on page 19 as follows to further emphasize that the DHF for the combination product is to focus on the combination issues only:

The design history file for a combination product should address all design issues relating to the combined use of the constituent parts. The design history file ~~may~~ does not need to document design and development planning for established characteristics of the individual constituent parts, such as the safety and effectiveness of a drug constituent part of a co-packaged combination product if that drug constituent part was previously approved for an ~~the same~~ indication consistent with that of the device constituent (e.g., a drug indicated for subcutaneous injection co-packaged with a general use subcutaneous piston syringe). If a finished device, drug, or biological product is purchased, the combination product manufacturer is not required to retrospectively “design” that constituent part with respect to such previously reviewed characteristics. Rather, the combination product manufacturer should understand the constituent part’s existing design specifications thoroughly in order to perform design controls properly for its use in the combination product.⁷ In addition, the combination product manufacturer must comply with design control requirements for any modifications that need to be made to a constituent part for use in the combination product (e.g., new formulation of the drug or new features of a device) under 21 CFR 820.30(i).

It is appropriate to leverage existing data in developing a design history file for a combination product that may not have been developed under design controls.⁸ For example, existing specifications may become part of the required design output documentation. Similarly, testing performed prior to distribution of the combination product may be included as documentation of design verification and validation. The combination product manufacturer is responsible for assembling available information and assessing what, if any, additional information and evidence may be needed, such as additional testing or documentation of the design control activities, to address all aspects of design control that are needed to support the manufacture of the product as currently marketed, ensure its safety and effectiveness, and support any future changes to that product. However,

⁷ Similarly, if a combination product manufacturer is purchasing device components for inclusion in a combination product, and the device component supplier is manufacturing a finished device from the same or similar components and is therefore subject to the QS regulation, the combination product manufacturer may be able to leverage elements of that supplier’s design controls in developing the overall design controls for the combination product. If the component supplier does not manufacture a related finished device, the combination product manufacturer’s design control activities for the device constituent part will likely need to be more extensive.

⁸ If a constituent part of a combination product was not developed under design controls because it predates adoption of the design controls in the Quality System Regulation, there is no requirement to develop a design history file for that constituent part, only for the combination product and only focusing on those issues relating to use of the specific drug and/or biological product with the specific device with which it is being combined.

manufacturers do not need to prepare a development plan or conduct design review meetings for the product as currently marketed because the development stages that these activities would support have already occurred.

2. The CPC recommends that FDA provide specific examples of documentation sources that could be used to create a DHF for a product not developed under design controls. For example, it would be helpful if the Draft Guidance would state whether there are specific documents typically found in cGMP files, new drug applications (“NDA”), and biological license applications (“BLA”) that FDA believes would provide the specific information needed to retrospectively develop parts of a DHF (e.g., design inputs and outputs, validation and verification, and risk analysis). One way to do this would be to illustrate how documentation can be leveraged by building on the current pre-filled syringe example in the Draft Guidance, creating a scenario that assumes the product was not developed under design controls and mapping design control elements listed on pages 32-33 of the Draft Guidance to specific kinds of documents along the lines described above. We also believe additional examples with other common drug delivery presentations (e.g., metered dose inhalers and autoinjectors) would be helpful.

III. Clarify FDA’s Example Regarding Class I Liquid Medication Dispensing Devices and Design Control Requirements

The Draft Guidance contains a very useful example explaining the applicability of 21 CFR Part 4 to certain Class I drug delivery devices –

“Delivery devices, such as simple liquid medication dispensing devices regulated under 21 CFR 880.6430, that are Class I devices exempt from [requirements at] 21 CFR 4.4(b)(1). If such a liquid medication dispenser is co-packaged with a drug as a “convenience kit” . . . generally speaking no additional CGMP requirements would apply to that dispenser or to the combination product under part 820 simply because that dispenser is included in the kit.”⁹

However, the Draft Guidance then goes on to state that “a device constituent part incorporated into a drug container raises additional considerations,” and –

“may need to meet certain specifications for dosing of the specific drug product or for maintaining its integrity while in contact with the drug product, for example. *As a result, design controls specific to the use of the dropper and its contact with the drug product **may** be needed and apply under 21 CFR 820.30.*”¹⁰

The Draft Guidance does not explain why design controls “may” apply. In the example, the device constituent still appears to meet the definition of a simple liquid medication dispenser. Also, with regard to drug delivery (device functionality), there seems to be no difference

⁹ Draft Guidance, 11.

¹⁰ *Id.* (emphasis added).

between this product and the dropper in the convenience kit example described above. To the extent that the drug and device are in contact, there would be container-closure issues, but it is unclear why this would subject the product to design control requirements.

Recommendation:

The CPC requests that FDA add the following clarifying language to the Draft Guidance regarding the example above:

Except as provided by 21 CFR 820.30(a)(2), Class I devices included in co-packaged combination products (whether they meet the definition of a convenience kit or not) are GMP exempt, meaning that the co-packaged combination product which only contains such Class I device constituents would be exempt from the provisions of the QS regulation as stated in 21 CFR Part 4.4(b)(1).

The same is true when a Class I device is integrated into the container-closure for the drug, provided the device constituent part –

- Retains the same device intended uses as the non-integrated device (e.g., a liquid medication dispenser in accordance with 21 CFR 880.6430 is a “device intended for medical purposes that is used to issue a measured amount of liquid medication”);
- Has the same functionality as the non-integrated device; and
- To the extent that the integrated device was in contact with the drug product by virtue of it also being part of the container-closure, any issues associated with contact with the drug are addressed through the container-closure compatibility requirements under drug cGMPs.

IV. Clarifying the Use of cGMP Information in Marketing Applications

Some CPC members, and other members of industry, have received requests to include cGMP procedures in marketing application submissions, and demonstrate compliance with Part 4 requirements as part of premarket reviews.¹¹ These requests can cause significant problems.

¹¹ E.g., BLA 125,504, Summary Basis of Approval, CDRH Consult Memo to CDER (Jan. 6, 2014) –

The following deficiencies were noted during the review:

1. The Applicant described and provided summarized results of the validation activities. However the firm did not provide its design control procedure covering the Design Input, Design output and Design Validation/Verification, including design changes, for the overall finished combination product in order to ensure that specified design requirements are met. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.30.

2. There was no information available for review regarding the establishment of a CAPA system compliant with 21 CFR 820.100.

(emphasis added), available at,

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125504Orig1s000OtherR.pdf.

First, cGMP procedures will become part of the application on which clearance or approval is based. Because procedures are frequently revised, applicants may need to assess marketing application updates with each procedural change and companies may feel obliged to make supplemental submissions to update cGMP procedures in applications, even if they are not truly relevant to product clearance or approval. Second, during the review process, there are typically a number of clearance or approval issues to address in a short timeframe. Adding an evaluation of cGMP compliance as part of the marketing review process can, potentially, be disruptive to the overall marketing review.

Based on recent FDA roundtable discussions at an April 1, 2015 CPC-RAPS meeting, our understanding is that the Agency agrees that marketing review and cGMP issues are separate, and that the interest in cGMP information is generally limited to gathering information on the identity(ies) of critical constituent part suppliers that will inform FDA plans for pre-approval inspections. Therefore, previous requests may reflect misunderstandings or miscommunications.

Recommendation:

Although the Draft Guidance is focused on cGMP compliance, in light of confusion regarding the need to submit cGMP procedures in marketing applications and their consideration during premarket review, we ask that FDA take this opportunity to use the Draft Guidance to clarify that (a) Part 4 compliance is not assessed during the marketing application review process, and (b) cGMP procedures should generally not be requested, although FDA might request some information regarding the roles and responsibilities of different manufacturers to aid in planning pre-approval inspections.

V. Clarify the Accountability Combination Product Sponsor, and “Sponsor” Terminology

The Draft Guidance states that a combination product “sponsor” (marketing authorization holder or “MAH”)¹² for “co-packaged or single-entity combination products that have a device constituent part must establish and maintain procedures for implementing CAPA, in accordance with 21 CFR 820.100.”¹³ If a sponsor serves as a *manufacturer*, we agree it would generally be required to maintain a CAPA system. However, a sponsor may contract all manufacturing to third parties. In that case, the sponsor is accountable for the quality of the final product, but would not be required to maintain CAPA procedures.

Also, as noted above, the Draft Guidance uses the term “sponsor” as a synonym for the marketing authorization holder for a co-packaged or single entity combination product. “Sponsor” is also a term of art referring to an entity sponsoring clinical studies,¹⁴ and is used this

¹² Draft Guidance, 14.

¹³ Draft Guidance, 21.

¹⁴ See 21 CFR § 312.3.

way elsewhere in the Draft Guidance.¹⁵ Thus, it would be helpful to use another term to avoid confusion.

Recommendations:

The CPC recommends that FDA clarify that Combination Product Marketing Authorization Holders are accountable for product quality, but would not be required to maintain CAPA procedures, or any other manufacturing procedures, unless they are actually manufacturing products. We also recommend revising the terminology to avoid the use of the term “sponsor” by, e.g., replacing with “marketing authorization holder.”

VI. Clarify that 21 CFR Part 4 and the Draft Guidance Do Not Apply to “Cross-Labeled” Combination Products

Section III.E of the Draft Guidance states that if one entity manufactures one constituent part of a “cross-labeled” combination product and another entity manufactures the other constituent part:

“[B]oth should have procedures in place to inform one another of changes that may affect the safety or effectiveness of the combination product, and to confirm that the specifications for the respective constituent parts remain appropriate or are updated as needed to ensure that the combination product remains safe and effective.”¹⁶

These suggestions reflect practices that many companies follow, and we think that mentioning these practices in the Draft Guidance is appropriate. However, we believe that FDA should clarify that these suggestions are not related to the cGMP requirements at 21 CFR Part 4. Part 4 “provides a regulatory framework for designing and implementing the current good manufacturing practice operating system at facilities that manufacture co-packaged or single-entity combination products,” not separately packaged, cross-labeled products.¹⁷ Making this clarification will help prevent confusion that Part 4 applies to cross-labeled products.

Recommendations:

The CPC recommends making the following clarifying revisions to the second paragraph of Section III.E:

Similarly, if one entity manufactures one constituent part of a cross-labeled combination product and another entity manufactures the other constituent part, ~~both should have~~ it is common (though not required under 21 CFR part 4) to have procedures, policies, or other tools in place to inform one another, formally or

¹⁵ Draft Guidance, 9.

¹⁶ Draft Guidance, 15.

¹⁷ 21 CFR § 4.1 (2015).

informally, of changes being considered that may affect the safety or effectiveness of the combination product, and to confirm that the specifications for the respective constituent parts remain appropriate or are updated as needed to ensure that the combination product remains safe and effective. For example, a change to the drug constituent part of a cross-labeled combination product might require a design change to the device constituent part for the combination product to remain safe and effective. Accordingly, awareness and assessment of drug changes to determine whether they require, in this example, a change to the device constituent part(s) may be important to compliance with design control requirements for the device under 21 CFR 820.30. Similarly, a change to a device constituent part of a cross-labeled combination product may necessitate a change to a drug constituent part that would then need to be reflected in the chemistry, manufacturing, and controls specifications and testing procedures for the drug.

VII. Additional Guidance is Needed on cGMP Applicability to Combination Products Used in Clinical Trials

The Draft Guidance states that 21 CFR Part 4 does not alter the applicability of the cGMP regulations to investigational products. Additionally, it cites the current requirements for constituent part cGMPs in the investigational phase of development: Phase 1 drugs are generally exempt from compliance with the regulations under 21 CFR Parts 210 and 211, and investigational devices are exempt from 21 CFR Part 820 with the exception of design controls (21 CFR 820.30). Although the guidance provided on existing requirements is helpful, we believe additional guidance on application of 21 CFR Part 4 cGMPs to combination products is needed.

For example, it would be helpful if the Draft Guidance was revised to state instances in which design controls will not apply to the combination product in the investigational phase of development. In addition, it would be helpful to clarify that design controls in the early phase of product development generally need not be as extensive as for to-be-marketed products.

Recommendation:

FDA should provide additional guidance on the applicability of 21 CFR Part 4 in the investigational phase of product development. At a minimum, we believe the additional clarifying language should be added to the Draft Guidance:

Design controls do not apply to combination products in every clinical study, and when they do apply the requirements can vary depending on the stage of development. The following is a non-exclusive list of examples in which design controls do not apply:

- A. *A drug is in Phase I of development, and is being administered with a marketed syringe¹⁸ that has been cleared or approved for the same*

¹⁸ *We further note that a marketed product would not be subject to any other 21 CFR Part 4 requirements beyond those for its cleared or approved uses.*

mode of administration being used in the study (e.g., the drug is for subcutaneous injection, and the syringe is cleared for subcutaneous administration);

- B. A clinical study in which –
1. The device constituent is not the focus of the investigation;
 2. The device is not being assessed for safety or effectiveness in the investigation;
 3. The sponsor does not intend to develop the device for marketing; and
 4. Data from the studies will not be used to support marketing applications;
- C. The combination product is being used in an IDE-exempt study under 21 CFR 812.2(c); or
- D. The device constituent part is regulated as a Class I device that is not subject to design controls;

When design controls do apply, the level of control should be appropriate to the phase of development and may not be the same as that required later in the development process. Early phase studies (research, early feasibility studies) may not warrant full design control implementation (often products used in these studies do not represent the final, to-be-marketed version of the product). In addition, certain design control elements may not be completed prior to initiating a clinical trial. For example Design Transfer may be completed just prior to marketing commercial product. Also, design validation may not be completed until final production models for marketing are being manufactured. However, sufficient controls need to be applied to adequately assure subject safety.

VIII. Clarify the Meaning of “Drug Delivery”

The Draft Guidance states that “[a]n article that does not merely hold or contain the drug, but also delivers it, is not merely a container or closure and may also be subject to the QS regulation.”¹⁹ However the target of the delivery is not specified. We believe that “delivers” is intended to mean direct administration to the patient as opposed to, e.g., delivering a drug into a container, but this is not explicitly stated.

¹⁹ Draft Guidance, 11.

Recommendation:

Clarify that “delivers” means administration to the patient by revising the sentence above as follows:

“[a]n article that does not merely hold or contain the drug, but also ~~delivers~~ administers it directly to a patient, is not merely a container or closure and may or may not ~~also~~ be subject to the QS regulation.”²⁰

IX. Development and Implementation of a Combination Products Inspection Guide

In the past, FDA has developed detailed inspection guides to help its field personnel in addressing specific inspection issues. The CPC believes it is important to create a similar guide to aid in assessing applicability of 21 CFR Part 4 given that prior inspection training or experiences might not be sufficient to assure smooth inspections. For example, the Quality System Inspection Technique (“QSIT”) used by inspectors who have previously inspected only for medical device compliance might not align well with terminology, processes, and procedures adopted by combination product manufacturers that traditionally maintained drug and/or biological product cGMP-compliant systems and are adopting a streamlined approach under Part 4. Similarly, inspectors with a background in inspecting pharmaceutical companies might have the same kinds of issues inspecting companies that traditionally manufactured devices.

Recommendation:

Develop and implement (e.g., train inspectors to) a Combination Products Inspection Guide that will serve as the basis for guiding inspections against 21 CFR Part 4 requirements.

* * *

Again, the CPC thanks FDA for developing the Draft Guidance, and appreciates the opportunity to offer suggestions on making a few improvements to what we believe, overall, is a very well written and useful guidance document.

Sincerely,



Bradley Merrill Thompson
On Behalf of the Combination Products Coalition

²⁰ “Examples of direct administration include intramuscular, subcutaneous, oral, inhalation, and intravenous modes of administration. If the instructions for use indicate that the user and the device must interact to administer the dose (e.g., removing pills from a pill bottle), then it is not a delivery device and might not be a device at all.”