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

**Reference:** FDA Guidance for Industry Good Manufacturing Practices for Combination Products; Docket [FDA-2015-D-0198](#)

Dear Sir/Madam:

PDA commends FDA for developing such a detailed guidance document and providing significant clarifications to address many of the remaining questions regarding application of GMPs to combination products. PDA appreciates the many examples provided by FDA but recommends that FDA go further, with more specificity and more examples to provide an additional level of clarity. Perhaps even a question and answer type document could be developed. PDA has made several suggestions in the attached comments, developed some language specifically addressing the situation with legacy products, and suggested a revision to the prefilled syringe example more relevant to most commercial situations. In addition, PDA recommends that FDA consider future examples to address outstanding issues regarding cross-labeled combination products.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical, biological and device manufacturing including members representing our Combination Products Interest Group, Regulatory Affairs and Quality Advisory Board, and Board of Directors.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson

## General Comments

1. PDA commends the FDA for the development of this draft guidance and the examples provided to illustrate the complexities of combining two different sets of Good Manufacturing Practices for combination products. PDA believes this document goes in the right direction to reduce confusion and clarify FDA expectations but believes additional explanation and examples would strengthen the guidance and provide additional benefit to industry and to FDA. A few general comments and several detailed comments and suggested clarifications are provided in the sections below.
2. PDA recommends FDA develop a separate guidance document to cover cell-based combination products as human cell-device combination products are too specialized for a general guidance such as this. HCT/P products need various blends of some parts of 21 CFR Part 600 (not all) with or without 21 CFR Part 1271 compliance depending on whether cell-based combination products are from unique donors or from immortal cell lines. The new guidance should include specific examples of cell-device products.
3. PDA finds the use of the terms manufacturer and sponsor with seemingly different intended meanings in different contexts in this draft causes confusion and recommends the use of the term Marketing Authorization Holder. In cases where the manufacturer may be a contract organization to the MAH, the responsibilities noted in this guidance may be more appropriately assigned to the MAH. A specific definition is proposed below in section III.C.4.2. PDA recommends FDA look at these terms throughout the document to ensure the use is clear. Another possible term to consider is “owner” as defined in FDA Guidance for Industry Contract Manufacturing Arrangements for Drugs: Quality Agreements as “the party that introduces (or causes the introduction of) a drug into interstate commerce.” This Quality Agreement guidance states “Quality Agreements described in this guidance should also be used by Owners of combination products as they are subject to requirements under 21 CFR 211, 21 CFR 820.”
4. The final rule defines the statutory requirements for implementing and complying with the required sections in the CGMPs. As stated, if a required section is not applicable, the manufacturer or MAH must document this determination. PDA recommends that FDA should make clear in this guidance that this determination should not preclude a manufacturer or MAH from using a provision from ANY of the CGMPs, *even if not required by the statute*. If use is appropriate and justified, MAH or manufacturers should not be penalized for using non-required sections from an alternative CGMP system (e.g., implementing Design Controls to establish component part suitability or implementing a Device Master Record in a drug CGMP-based operating system); neither should they be subject to regulatory action if they do not use it in all cases.
5. As the CGMPs allow manufacturers to use any and all systems and methods at their disposal to meet the requirements of the regulations, it is up to the MAH to provide adequate justification to establish that the system(s) and procedures used meet all regulatory requirements. For example, for combination products and constituent parts, manufacturers/MAH may use systems from Drug Guidance (e.g., ICH Q8 Quality by

Design) in order to meet some of the device QS regulation requirements (e.g., Design Controls).

6. Throughout the document “Device Constituent Parts” and “Drug Constituent Parts” are described as if they are always physically discreet and separate entities. This is not always the case, particularly for integrated combination products, and can cause significant confusion when trying to apply the appropriate CGMPs. For example, syringe components (syringe barrel, plunger, etc.) are considered drug components when manufactured and received at the fill finish facility. These syringe components are then filled with a drug to become a subassembly, subject to drug CGMPs. It is not until the syringe is assembled with a plunger rod or assembled with autoinjector device components to become a finished prefilled syringe or finished prefilled autoinjector (ie, capable of drug delivery), that a finished “Device Constituent Part” and finished combination product exists. PDA recommends the Agency explain this continuum in manufacturing and part definitions to provide additional clarity.

## Specific Comments to the Text of this Draft Guidance

### II. B Overview of the Final Rule

1. PDA recommends that FDA add additional clarification confirming that no other CGMP requirements exist for the constituent parts or the cross-labeled combination product, regardless if the combination product is approved under one or two separate marketing applications.

As Stated in paragraph 2 of this section:

The final rule on CGMP requirements for combination products applies to all combination products. As stated in the preamble to the final rule, the CGMP requirements for constituent parts of cross-labeled combination products that are manufactured separately and not co-packaged are the same as those that would apply if these constituent parts were not part of a combination product (e.g., for a drug/device combination product, 21 CFR parts 210 and 211 would apply to the manufacture of the drug constituent part(s) of the cross-labeled combination product, and 21 CFR part 820 would apply to the device constituent part(s)).

New text to be added at the end of paragraph 2:

Compliance of each constituent part of a cross-labeled combination product to the CGMPs applicable to that constituent part only ensures manufacturers of combination products comply with ALL required CGMPs. That is, a drug manufacturer of the drug constituent part of a cross-labeled combination product would not be required to implement ANY of the QS regulations (21 CFR part 820) and the device manufacturer of the device constituent part of a cross-labeled combination product would not be required to implement ANY of the drug CGMPs (21 CFR part 210 and part 211). Each MAH or manufacturer would use the systems and procedures specific under the CGMPs required by their constituent part to establish that each product is safe and effective for its intended use, which means that the combination of the constituent parts is safe and effective for use together. The streamlined approach for CGMPs is not applicable to cross-labeled combination products. This would apply regardless as to whether the combination product was authorized under one or two separate marketing authorizations.

2. The agency recommends that MAH and manufacturers who choose to operate under a streamlined approach clearly identify in their premarket submissions and at the initiation of an inspection whether they are operating under the drug CGMP-based or QS regulation-based streamlining approach (2<sup>nd</sup> paragraph, page 7). As stated in the text modifications below, PDA recommends that a summary of the quality system approach to compliance would be sufficient and the agency's recommendation should not in any way suggest that: (1) any CGMP procedures establishing quality system compliance are necessary to be provided as part of the submission; (2) if procedures are submitted, they are for information only and are not to be viewed by the agency as commitments in the Marketing Authorization. It is only necessary for MAH and manufacturers to have all documentation needed to demonstrate compliance with 21 CFR part 4 available to FDA during an inspection.

Recommended Text Modification to last paragraph in section II.B.

"To facilitate efficient inspection, the agency recommends that MAH and manufacturers who choose to operate under a streamlined approach clearly identify in their submissions and at the initiation of an inspection whether they are operating under the CGMP-based or QS regulation-based streamlining approach. Inclusion of a summary of drug CGMP-based

or QS regulation-based streamlining approach is sufficient.

3. If a constituent part is purchased from another manufacturer it may not be possible to have the documentation for this constituent part available at the premises of the combination product manufacturer. Therefore the second paragraph, page 7, is amended to give clarification in accordance with the concept described in D.3. Pg. 14.

Recommended Text Modification (second paragraph page 7)

Marketing authorization holders using either a streamlined approach or opting to implement all applicable CGMP requirements should be able to identify and readily access all documentation needed to demonstrate compliance with 21 CFR part 4 for FDA inspection. If a components of the constituent part, or the entire constituent part of the combination product, is designed or manufactured by another manufacturer at another facility and the documentation relevant to the design and/or manufacture is not readily available at the manufacturer's premises, a manufacturer may provide evidence of adequate supplier oversight instead (i.e. agreed specification, signed contract, supplier audit).

## II. C The role of the lead center and other agency components

4. PDA recommends providing an example and other clarification to the last two paragraphs on page 7 as noted below.

“It is important to note.....may choose to adopt the QS regulation-based streamlining approach.” To illustrate further, where the final combination product might be a drug contained in, and delivered by, a prefilled syringe, and where the PMOA is the drug, either drug CGMPs or device QS regulations could be the primary applicable quality system and the other used secondarily to accomplish the streamlined approach.

“For a combination product, the lead center is a manufacturer’s primary point of contact.” For a product for which a lead center has not been formally designated, including legacy combination products, the center that has granted Marketing Authorization is considered the lead center.

### III.C. 4.2 Definitions

5. PDA recommends not introducing new categories or definitions in this guidance for terms already defined in existing guidance or regulation. "Convenience kit" is not a type of combination product itself, but falls under the definition of a co-packaged combination product. Reference: CFR 3.2(e) 2

Recommended Text Modification to 1<sup>st</sup> paragraph in this section:

It also addresses the meaning of “convenience kit” as a type of co-packaged combination product.

### III.C 4.2. 3. Drug containers and closures versus delivery devices

6. This section on containers and closures has caused significant confusion and PDA recommends adding more specific wording, explanations, clarifications and examples as follows.

Recommended Text Modifications:

“The agency draws a distinction between drug containers and closures and delivery devices. The essential distinction is whether the article is designed to deliver the drug it contains *to the patient* or merely to hold it *during transport and storage from which the drug must be transferred for final delivery to the patient.*”

If the article merely holds the drug, it is only subject to drug CGMPs as a container or closure. *Specialized or unique connectors (i.e. luers) and/or other elements that are part of the primary container closure to facilitate connection and/or transfer are not considered device functions. Therefore, addition of such an element to a container or closure does not create a combination product.* A container closure system is the sum of packaging components that together contain and protect the drug product. *This includes primary and secondary packaging components if the latter are intended to provide additional protection to the drug product. A packaging system may be considered a container closure system.* A packaging component is any single part of a container closure system. Examples of primary packaging components are containers, ampules, vials, cartridges, syringe barrels, screw caps, stoppers, and stopper overseals. Examples of secondary packaging components are plungers, needle safety shields.

An article that does not merely hold or contain the drug, but also delivers it *directly to the patient*, is not merely a container or closure and may also be subject to the QS regulation. A finished piston syringe *when filled with drug by the manufacturer*, for example, is not only a primary container or closure. A finished piston syringe *intended for medical purposes* is a device used to deliver fluids, as described in 21 CFR 880.5860, and is subject to the QS regulation. Accordingly, a syringe filled with a drug, for example, is a combination product and must demonstrate compliance with both the drug CGMPs and QS regulation. This includes syringes filled with saline or WFI that fulfill the definition of drug per 21 U.S.C. 321, (g)(1).

*The facility responsible for the manufacture of any component or subassembly of the piston syringe is not subject to QS regulatory requirements, as stated in III.C.2 (page 10 paragraph 4).*

There are other delivery devices, ...included in the kit.

Note, however, that a class 1 device constituent part incorporated *as part of a kit or directly* into a drug container raises additional considerations. For example, when establishing batch testing and release and product stability testing criteria under 21 CFR 211.165 and 211.166, a dropper incorporated into a drug kit or directly into a container's cap would need to be addressed as part of the drug container because it would come into contact with the drug product. Similarly, when such a dropper is used in conjunction with the drug, the dropper 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 the device constituent part is class 1, and exempt from the applicable section of the QS regulations relevant to combination products, design controls specific to the use of the dropper and its contact with the drug product DO NOT apply under 21 CFR 820.30. The suitability of the device constituent part, either included in the kit or integrated with the container as the device constituent part, can be fully addressed under a drug CGMP-based streamlining approach operating system (21 CFR parts 210 and 211). 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

#### III.C.4.2 4. Convenience Kits

7. PDA suggests the definition of convenience kits, and concepts surrounding how CGMPs are applied to might be confusing. Although the guidance is very helpful, it would benefit users of the guidance if this section contained additional examples and clarifications.

PDA recommends adding the following text to the end of the section on convenience kits.

In Section 3 above it was stated that when a class 1 device is included in a convenience kit, generally speaking no additional CGMP requirements would apply to that device or to the combination product under 21 CFR part 820 simply because that device is included in the kit with a drug. This will also be the case when a class 2 or class 3 device is included in a convenience kit with a drug and also if a drug is included in a convenience kit with any class device or devices. When a combination product is created by the co-packaging of an approved drug and an approved/cleared device, generally speaking no additional CGMPs apply to the device or the drug solely due to their inclusion together in a kit. The CGMPs that apply to each constituent part are the same as if the combination were cross labeled instead of co-packaged. As stated earlier, there are additional expectations regarding any additional processing, such as the manufacturing steps associated with any assembly, packaging, labeling, sterilization, or further processing of the kit itself. In addition, the MAH must consider the suitability of the two products when used together. However, these additional manufacturing steps and the suitability of the combination can be addressed by the CGMPs or quality system established by the MAH.

This means that a medical device manufacturer packaging an approved drug into a convenience kit with an approved/cleared device must ensure that any further processing and testing to establish that the combination is suitable are addressed under the requirements of their 21 CFR part 820 compliant quality system without a requirement to implement any elements of 21 CFR parts 210 or 211 under the streamlined approach. Conversely, if a drug manufacturer packages an approved/cleared device (e.g., a syringe) with their approved drug, they must address all additional processing and testing to establish that the combination is suitable only under their established 21 CFR parts 210 and 211 compliant quality system, ie, elements of 21 CFR part 820 under the streamlined approach are not required. This is independent of the class of the device and type of drug, as long as the intended use of the constituent parts do not change and the constituent parts are not modified.

Also, the intended use of a device cleared or approved with a general use classification (e.g., a drug delivery device approved for use with more than one drug or unrestricted to any drugs) is not considered to have changed solely because the device is now packaged with, and therefore intended for use with one drug. Any issues that might arise will be addressed when the MAH assesses the suitability of the combination under their established CGMPs. The addition of a logo, or new branding on a device placed in a kit would not be considered a modification of the product and not impact the determination of the kit as a convenience kit or the requirement for the implementation of additional CGMPs.

#### III.C.4.2 Definitions

8. PDA suggests adding a definition of marketing authorization holder, owner, or investigation study application holder/sponsor to the end of this section and using in lieu of manufacturer or sponsor where appropriate throughout the document.

5. Marketing Authorization Holder (MAH)

For the purposes of this guidance, the marketing authorization holder is the company that submits and is granted authorization to investigate (under an IDE or IND) or to market (under a 510(k), PMA NDA, ANDA, BLA) the combination product. Elements of the rule and guidance that apply to activities executed prior to the submission, apply to the company that intends to submit the application for the combination.

### **III D. 3 What CGMP responsibilities apply to specific manufacturers and facilities, and how should CGMP compliance be coordinated across facilities?**

9. In the first paragraph, PDA suggests that the guidance clarify whether a device is exempt before it is part of a combination product. The design and manufacture of the device should not lose that exemption when packaged as part of the combination, particularly if the intended use has not changed. Also, the co-packager should not be held to any requirements not already applicable to the constituent part. PDA also recommends clarifying the requirement for Master Manufacturing Records.

Recommended addition to the first paragraph:

“The combination product sponsor at that specific facility.” *Only those drug CGMP or QS regulation requirements that would be applicable to the constituent part as a standalone product would be applicable to the constituent part as part of the combination product and the combination product as a whole. For example, a class 1 device in a co-packaged combination product that is exempt from the QS regulation as a standalone product is still exempt as a part of the combination product. (See explanation on page 10 above) Also, the MAH using a streamlined approach quality system is not subject to any of the QS regulation as part of their Combination Product CGMP requirements under 21 CFR Part 4, as the device is exempt. If a device is exempt before it is part of a combination product, the design and manufacture of that product should not lose that exemption when packaged as part of the combination, particularly if the intended use has not changed. Also, the co-packager should not be held to any requirements not already applicable to the constituent part.*

10. PDA recommends adding the following text after the second paragraph on page 14 to address Device Master Records (DMR) vs. Master production and control Records (MPCR) :

“Some CGMP requirements may concern..... handle issues requiring multi-facility collaboration.” *Master record(s) are required under 21 CFR 820.181 (Device Master Record) or under 21 CFR 211.186 (Master production and control Record - MPCR). Neither of these was cited in 21 CFR part 4a so it can be concluded that either is an acceptable method of documenting the master record for the product under the requisite CGMP. A manufacturer who has a 21 CFR part 820 compliant quality system would use a DMR and a manufacturer under a 21 CFR part 211 and part 211 compliant quality system would use a MPCR. Although Design controls under 21 CFR 820.30 is a required sub-system for application of the streamlined approach and the definition of design outputs, a design control element, includes the requirement for a DMR (reference 21 CFR 820.3(g), a manufacturer*



may choose to, but is NOT REQUIRED to, develop a DMR for the combination product under a drug CGMP-based streamlined approach operating system such as at the facility where a prefilled syringe combination product is finished. The MPCR for the prefilled syringe combination product example is sufficient to meet CGMP requirements according to the streamlined approach.

### III. E. Control of changes to a combination product

#### IV A 2 Design Controls (21 CFR Part 820.30)

11. As Design Controls are a critical element required by 21 CFR Part 4a to be implemented by companies that have a 21 CFR part 210 and part 211 compliant quality system, PDA recommends the following additional clarifications and examples to help enhance the understanding of the requirements. PDA recommends eliminating the reference to the preamble of the proposed rule and the associated footnote. In PDA's opinion, a preamble to a proposed rule after the rule is final has no value and little availability/visibility. PDA also recommends adding an additional clarifying footnote referencing the Design Control Guidance for Medical Device Manufacturers, March 1997 and modifying existing footnote 25.

Recommended Text Modifications:

~~The preamble to the proposed rule discusses design control requirements for combination products at some length.~~ As specified in the final rule, design controls apply to any combination product that includes a device constituent part unless exempted under the underlying classification regulations (e.g. most class I devices). Guidance for industry on pharmaceutical development addresses product design and development procedures, reflecting "quality by design" principles. The establishment of a framework that manufacturers must use when developing and implementing design controls is described in the Guidance for Design Control Guidance for Medical Device Manufacturers\*\*.

The QS regulation includes requirements for design development with which compliance must be demonstrated (21 CFR 820.30(b)). The following is a description of design control requirements and the documentation that must be maintained for co-packaged and single-entity combination products<sup>25</sup>.

Add New Footnote \*\*: Design Control Guidance For Medical Device Manufacturers, published March 11, 1997.

Revision to Footnote 25: While outside the scope of 21 CFR 4.4(b)(1), it bears noting that the design control process and design history file for the device constituent parts of cross-labeled combination products should address the suitability of the device for use as part of the combination product, including the interactions and interrelationships between it and other constituent parts of the combination product. Also, the manufacturer of the drug constituent part of the cross-labeled combination product, who is not required to comply with QS regulation requirements, can address the suitability of the drug for use as part of the combination product, including the interactions and interrelationships between it and other constituent parts of the combination product using established systems and procedures under 21 CFR parts 210 and 211.

12. PDA recommends the following addition to the second paragraph under Design controls, bottom of page 17.  
"Design control procedures apply to activities undertaken....should include appropriate documentation or reference it, to ensure readily available access to this documentation for FDA inspection. At a minimum, the combination product MAH should have a design specification of the device components available and provisions regulating the

responsibilities regarding design control and design documentation and access to this documentation, i.e., a Quality Agreement. In addition, the MAH should make provisions regarding the accessibility of design control documentation that resides at a remote facility supporting the design of a device constituent part. If this documentation is requested during FDA inspection, every effort should be made to provide access to such documentation considering that the documents may be at a different company, in different time zones, in a foreign language and may need to be extracted from documents that involve another company's products. FDA and the MAH should try to reach a mutually agreeable time frame for access to these records.

13. At the top of page 19, first full paragraph, PDA recommends FDA distinguish changes made during the design of the product from those made under “design changes” after design transfer.

“In accordance with 21 CFR 820.30(i), manufacturers are also required to have procedures to ensure that any changes to design requirements are identified, documented, validated or verified where appropriate, reviewed, and approved prior to implementation. A change control process is essential to ~~incorporate~~ capture and document design changes ~~appropriately both~~ during the original design process for the combination product in the design history file. The records of these changes must be maintained as part of the design history file. In addition, a change control process must be implemented to capture and document design changes and after the design has been transferred to manufacturing. These are likely to be two different systems. Together, they create a history of the evolution of the design, which can be important when investigating failures or evaluating the appropriateness of proposed modifications or changes to the product.”

14. PDA recommends the following additional clarification be added starting on page 19 second paragraph

“The design history file for a combination product should address ..... such previously reviewed characteristics. Rather, if the manufacturer intends to modify the device, or use the device for a purpose inconsistent with the approved/cleared intended use, then 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. If the product is not modified, and is to be used in a manner consistent with its approved/cleared intended use, the kit is a convenience kit and the manufacturer is not required to implement any additional systems and can address the product under its established CGMPs (See convenience kits).

15. In the next paragraph on Page 19, PDA recommends the following modifications in the last sentence of the paragraph to add that the combination product manufacturer must comply with design control requirements for any modifications that need to be made to any 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).

“In addition, the combination product manufacturer must assess the impact of all changes made to any constituent part of a combination product with a device constituent part and comply with design control requirements for any modifications ~~that need to be made to a constituent part for use in the combination product~~ that impact the safety or effectiveness of the product (e.g., new formulation of the drug or new features of a device) under 21 CFR 820.30(i).”

16. PDA also recommends modification to footnote 33 on the bottom of page 19

“Similarly, if a combination product market authorization holder 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 or refer to such elements in developing the overall design controls for the combination product. The information leveraged should be listed in a formal agreement between the manufacturer and supplier and the two parties may decide to maintain the elements related to components at the supplier level. If the device component supplier does not follow the QS regulation, the combination product market authorization holder's design control activities for the device constituent part will likely need to be more extensive.

**IV. B. 7. Special testing requirements (21 CFR 211.167)**

17. Special testing may include the option of using parametric release for sterilization. Both devices and drugs have a long history of effectively applying Sterile Parametric practices. USP <1222> acknowledges the limits of sterility testing and the process for utilizing parametric release for drug products. Similarly this is covered for devices under ISO 11135, ISO 11137-1 & -2, ISO 17665-1, and ISO 20857. It might also be recommended that the guidance include as a reference USP 38 <1222> Terminally Sterilized Pharmaceutical Products – Parametric Release. This is an Agency accepted practice under 21 CFR 211.167 for the elimination of batch specific sterility testing.

Recommended Text Modifications to second paragraph

“With respect to 21 CFR 211.167(a), batch testing requirements would apply both to the drug constituent part and to the finished combination product for a single-entity combination product (such as a prefilled syringe) to ensure the combination product is sterile and pyrogen free when distributed. For terminally sterilized products, sterility test requirements may be met utilizing parametric release (e.g., sterilization validation).”

**IV B 8 Reserve samples (21 CFR 211.170)**

18. There are many devices where a Retain Sample of the entire combination could be cost prohibitive and unnecessary to achieve the intent, however when only considering a part of the combination product a rationale for this should be generated.

Recommended Text Modifications to first paragraph at the top of page 27

“Accordingly, as explained below, for co-packaged combination products, manufacturers should maintain samples of the drug constituent part, and for single-entity combination products, they should maintain samples that include the device constituent part or components thereof as appropriate. When choosing components or equivalent from a device constituent as the reserve samples containing the drug constituent part, a scientific rationale must be included.”

**Legacy Products (new proposed section)**

19. The issue of Legacy Products has engendered a significant level of confusion for MAH who were not previously required to address a second CGMP with regard to their combination product. Also, although the document provides some guidance, it is included as one element of one paragraph under “Design Controls” and it does not provide adequate visibility of, nor the full scope of the issue. PDA recommends that FDA expand the guidance to more clearly and fully address Legacy Products and suggests including the following as a separate section in the guidance at the end of IV.A.2. As added to the text below, Although it is FDA assertion that all of these products were subject to both sets of GMPs even before the existence of the Combination Product GMP rule, it is not possible to implement systems to address and control activities that have already occurred nor practical to implement the systems and controls then repeat the activities. PDA’s approach to the legacy product section below is to recommend establishment of information and standards adequate to assess future changes and protect the patient.

Recommended Text Modifications:

Legacy Products are combination products that were developed, designed and in some cases approved/cleared for marketing and commercialized without considerations of the requirement for addressing the quality systems for both of the constituent parts. In most cases, these combination products were approved/cleared for marketing before the effective date of the final rule (21 CFR Part 4a), but others may have been designed and developed, but not submitted or approved/cleared prior to that date.

Although it is FDA assertion that all of these combination products were subject to both sets of CGMPs even before the existence of the Combination Product GMP rule, it is not possible to implement systems to address and control activities that have already occurred nor practical to implement the systems and controls then repeat the activities. As such, FDA has stated that they will use discretion during the inspection of Legacy Product establishments, but requests the following approach to ensure the manufacturer has taken appropriate measures and has documentation to establish that the Legacy Product meets all requirements and there are adequate documents and systems to manage the product going forward.

With respect to Legacy Products, the organization should perform a full retrospective gap analysis of the product to identify that sufficient data necessary to support the manufacture of the product, ensure its safety and effectiveness, and support any future changes *so that product is available*. In order for this to be effective, the company must first establish the set of requirements that would satisfy a company that the current device (legacy product) is safe and effective and that would serve as a baseline for future changes. This is sometimes called a *Product Requirements Specification (PRS)*. For example, existing specifications may become part of the requirements. *In order to identify the data or information available to support the final requirements* it is appropriate to leverage existing data and/or testing already performed, as evidence that the product has been effectively verified and validated and meets all requirements. *Any gaps in available data must be remediated or an analysis and justification as to why the existing experience is sufficient to confirm that the product is acceptable.*

Another gap that must be assessed is whether the risk profile of the product has been documented and determined to be acceptable. Risk assessments are usually performed prior to and in conjunction with the design process, however it is possible and appropriate to implement a risk management program and apply risk assessment techniques to establish that the risk profile of the existing product is acceptable and no risk mitigation are required.

If this is not the case, the risk mitigations must be implemented and the product appropriately re-verified and revalidated.

Both the PRS and Risk Management File will be necessary to address any complaints, adverse events, non-conformances and changes going forward. The information as the output of this exercise would be sufficient to meet the requirements of a design history file and can be used as a design history file going forward.

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.

Another area that must be addressed is the control of suppliers of components and constituent parts of the combination product. An assessment must be performed to ensure that the requirements, including quality requirements that must be met by suppliers, are established and that the performance of the supplier has been acceptable. If these are not adequate, additional testing may be required. The MAH should demonstrate that 1) oversight and controls are appropriate, 2) suppliers are on an approved vendor list and 3) written, signed agreements for the communication of all appropriate changes are in place.

Manufacturers do not need to retrospectively provide evidence that they evaluated and selected the potential suppliers, contractors, on the basis of their ability to meet specified requirements, including quality requirements.

All other 21 CFR Part 4 required systems (Management Responsibilities and CAPA) cannot be applied retroactively, but must be implemented if applicable and maintained going forward.