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Combination Products: A 40 Year Regulatory Evolution

Technological advances in healthcare products and the delivery of those products will continue to straddle the traditional boundaries of regulatory authority between the U.S. Food and Drug Administration's (hereafter referred to as FDA or the Agency) medical product centers. Since the first combination products came under the FDA's purview over 40 years ago, the Agency has taken various actions to organize, delegate, and outline how it will regulate the manufacture and distribution of these products in the U.S. and on July 22, 2013, issued a Final Rule entitled, "Current Good Manufacturing Practice Requirements for Combination Products" (21 CFR Part 4). However, over the past year, FDA has taken enforcement action with specific reference to 21 CFR Part 4, providing insight into how the regulation of combination products will look in this ever expanding product space. On January 27, 2015, the Agency released a draft guidance document entitled, "Current Good Manufacturing Practice Requirements for Combination Products" to accompany the Final Rule. Over the coming year, FDA is also expected to release guidance on human factors for combination products, adverse event reporting and other documents that may impact combination products. Moreover, there are particular regulatory challenges that face traditional pharmaceutical and medical device companies when manufacturing or distributing combination products in the U.S. This document discusses these challenges and how industry can prepare to meet them.

BACKGROUND

The first combination products to fall under FDA's regulatory authority were developed in the 1970s, including products such as radiobiologicals and in vitro diagnostics. During the proceeding decades, combination products were regulated by the Agency through a particular center on an ad hoc basis including the use of intercenter agreements. The Safe Medical Devices Act (SMDA) of 1990[1] included provisions for the regulation of combination products and eventually regulation fell under the FDA Modernization Act of (FDAMA) 1997.[2] In 2001, the Executive Director of the Medical Device Manufacturers Association, Stephen Northrup, recommended the formation of an Office of Combination Products to the U.S. House Committee on Energy and Commerce, to address industry-perceived shortcomings in the FDAMA to "prevent jurisdictional disputes or inefficient review processes that result from disagreements on how to regulate [combination products]."[3]

Office of Combination Products

The Office of Combination Products (OCP) was established on December 24, 2002 as part of the enactment of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA). The OCP's main responsibility is to "develop and implement policies and processes to streamline the review and regulation of drug-device, drug-biologic and device-biologic combination products as defined in 21 CFR 3.2(e)."[4] The OCP acts as a facilitator between industry and FDA and among the FDA centers. It develops guidance and regulations to clarify the regulation of combination products and supports the Agency with premarket review and postmarket rules. Specifically, the OCP manages the Request for Designation (RFD) process by reviewing a submitter's RFD for a new entity, determining the product's primary mode of action and assigning the FDA center which will have primary jurisdiction for review of both combination and single-entity products where the jurisdiction is unclear or in dispute.[5]

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Combination Products: A 40 Year Regulatory Evolution

FDA REGULATORY APPROACH TO COMBINATION PRODUCTS

In its October 4, 2004 draft guidance entitled, "Current Good Manufacturing Practices for Combination Products," FDA outlined its proposed requirements for the regulation of combination products.[6] Specifically, it outlined the current Good Manufacturing Practice (cGMP) provisions from the regulations for drugs and biological products under 21 CFR Parts 210 and 211, for certain biological products under 21 CFR Parts 600-680, and the Quality System Regulation (QSR) for devices under 21 CFR Part 820, that would apply to combination products as defined under 21 CFR 3.2(e).[7] The Agency received numerous comments from industry and determined that rulemaking was warranted "to facilitate the manufacture of safe and effective combination products by providing a clear and transparent regulatory roadmap for the application of cGMP requirements."[8] The proposed rule was published in the Federal Register on September 23, 2009.[9] This publication generated much industry discussion, which FDA grouped into 25 sets of comments. Most of the comments were supportive and centered on the need for a clear regulatory framework that accounts for the fact that combination products are composed of drug, device and biologic product constituent parts. The Final Rule was issued on and effective as of July 22, 2013.[10]

Final Rule

21 CFR Part 4 does not include new regulations and does not introduce any new requirements; the Final Rule clarifies how existing regulations for drugs (21 CFR Parts 210 and 211), biological products (21 CFR Parts 600-680), medical devices (21 CFR Parts 803, 806, and 820), and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (21 CFR 1271) are expected to be implemented with respect to combination products. All existing and new combination products are expected to be compliant with the applicable drug and/or medical device regulations, including those for biologics or HCT/Ps if the combination product contains those constituent parts. In other words, no products are grandfathered and there is no grace period for a combination product to meet the applicable drug and/or medical device regulations. 21 CFR Part 4 is "intended to streamline demonstrating compliance with cGMP requirements for [combination products] and to help ensure appropriate implementation of requirements while avoiding unnecessary redundancy in cGMP operating systems for these products."[11] This "streamlined approach" provides a manufacturer operating a quality management system under either drug cGMPs or device QSR the opportunity to demonstrate compliance with the other set of regulations when it manufactures a combination product containing both a drug and a device. The following sections detail the application of 21 CFR Part 4 in practice.

Important Definitions

FDA defines drugs as "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" (Section 201(g) of the FD&C Act [21 USC 321(g)]).[12] FDA defines a medical device as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is […] Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or [...] Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes" (Section 201(h) of the FD&C Act [21 USC 321(h)]).[13]

From the FDA perspective, a definition was needed to clarify the requirements for the drug and medical device components of a combination product. Specifically, FDA defines, in 21 CFR Part 3.2, a constituent part as "a drug, device, or biological product that is part of a combination product."[14] Constituent parts retain their regulatory status after they are combined, and the associated cGMP or QSR requirements for each constituent part continue to apply to each when together in a combination product. Furthermore, "in the event of a conflict between regulations applicable […] to combination products, the regulations most specifically applicable to the constituent part in question shall supersede the more general."[15]

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Recent Enforcement[16]

Although the Final Rule has been available for over a year, it was not until 2014 that any enforcement actions were levied specifically pertaining to the current regulations governing combination products and citing 21 CFR Part 4. In one recent example, a company that traditionally manufactures pharmaceuticals and biologics received a warning letter[17] from FDA with observations pertaining to design control (21 CFR 820.30) and purchasing control (21 CFR 820.50(a)). The warning letter specifically highlighted that the device constituent parts of the combination product were considered adulterated and included observations such as:

- The firm failed to establish and maintain design validation procedures to ensure that the devices conform to defined user needs and intended uses.
- The firm failed to establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes.
- The firm failed to evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements, and document the evaluation.

In another example of regulatory enforcement, a firm which traditionally manufactured pharmaceuticals and biologics, but now manufactures combination products, received a warning letter[18] citing observations pertaining to complaints (21 CFR 820.198), corrective and preventive actions (21 CFR 820.100) and statistical techniques (CFR 820.250). Those observations included:

- Failure to review, evaluate, and investigate, where necessary, complaints involving the possible failure of a device to meet any of its specifications.
- Failure to adequately establish procedures for corrective and preventive actions.
- Failure to establish and maintain corrective and preventive action procedures that include requirements for ensuring the corrective and preventive action is effective.
- Failure to adequately establish procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics have not been adequately established.

Warning letters such as these most likely will continue to be issued against traditional drug and medical device manufacturers as they develop and implement advanced technologies that are considered combination products. As manufacturers expand into other regulated environments, they may make themselves vulnerable to regulatory action if they are not compliant with the regulations of a constituent part, particularly when the technologies include existing or new products that are outside of their core traditional product lines. Companies who have or can develop a bilateral understanding for FDA requirements for drugs and biologics as well as medical devices can assess, plan, and execute product development, manufacturing, and surveillance operations that are in compliance with 21 CFR Part 4, and handle the implications that the Final Rule and guidance documents have on industry.

IMPLICATIONS OF 21 CFR PART 4 AND GUIDANCE FOR MEDICAL DEVICE AND PHARMACEUTICAL INDUSTRIES

Application of 21 CFR Part 4 in Practice

FDA offers two options for demonstrating compliance with the cGMP requirements applicable to co-packaged or single-entity combination products:

- "To demonstrate compliance with the specifics of all cGMP regulations applicable to each of the constituent parts included in the combination product;
- To demonstrate compliance with the specifics of the drug cGMPs or the QS regulation, rather than both, when the combination contains both a drug and a device, under certain conditions."[19]

The second option refers to the "streamlined approach" offered by the Agency to allow manufacturers of combination products that include both a drug and a device constituent part to demonstrate compliance with either set of regulations, rather than demonstrating full compliance with both, and thus avoid possible redundancies in complying with both sets of regulations in full.[20] The following sections explain differences and some particular concerns for traditional manufacturers of drugs or medical devices in complying with 21 CFR Part 4.

Overlap and Differences

Drug cGMPs and medical device QSR have clear commonalities in areas such as requirements for management and recordkeeping, and they each grant flexibility to manufacturers in terms of how to meet the intent of the regulations. The Agency considers the regulations to be similar, and they are intended to achieve the same goals.

The regulations do, however, differ because each was developed to address the characteristics of products to which they pertain. Both the drug cGMPs and device QSR contain specific requirements for various quality concepts that are only more generally addressed in the other set of regulations. For example, the device QSR has detailed CAPA requirements (21 CFR 820.100), while CAPA principles are included in multiple parts of the drug cGMPs, particularly in Organization and Personnel (21 CFR 211.22) and Records and Reports (21 CFR 211.180(e) and 21 CFR 211.192).[21]

Figure 1: Requirements to Consider in Combination Product Manufacturing Under a Streamlined Approach to Demonstrating Compliance to cGMPs

If The Operating Manufacturing Control System Is Part 820 (QS Regulation)		If The Operating Manufacturing Control System Is Part 210/ 211 (cGMP Regulation)	
cGMP Requirements	**Title**	**QSR Requirements**	**Title**
211.84	Testing and approval or rejection of components, drug product containers, and closures	820.20	Management responsibilities
211.103	Calculation of yield	820.30	Design controls
211.132	Tamper-evident packaging requirements for over-the-counter (OTC) human drug products	820.50	Purchasing controls
211.137	Expiration dating	820.100	Correction and preventive actions
211.165	Testing and release for distribution	820.170	Installation
211.166	Stability testing	820.200	Servicing
211.167	Special testing requirements		
211.170	Reserve samples		

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With any combination product there are some important considerations when determining which regulations apply and how to design a quality system to meet those regulations. The previous figure from FDA's draft guidance on cGMP for Combination Products[22] describes which drug cGMP regulations should be considered for a combination product in which the operating manufacturing control system is designed to meet the QSR, and vice versa.

INDUSTRY CONSIDERATIONS AND FDA NEXT STEPS

- **Office of Pharmaceutical Quality:** The Center for Drug Evaluation and Research (CDER) is undergoing reorganization, including establishing the Office of Pharmaceutical Quality (OPQ) dedicated to product quality by providing better alignment among all drug quality functions at CDER, such as review, inspection and research.[23] OPQ officially launched January 2015 and will include updated systems for processing applications and will implement integration of 21 CFR Part 4 evaluation milestones.[24]

- **Combination product inspections:** FDA is now sending investigation teams of both pharmaceutical and medical device investigators to combination product manufacturers to schedule, perform and review 21 CFR Part 4 inspections. This approach will ensure the Agency's review of a firm's quality system is not inadvertently imbalanced to either drug cGMP or medical device QSR requirements. During an inspection, manufacturers should ask the investigator(s) about the scope of the inspection to learn which sections of the drug cGMPs and medical device QSR are being considered.[25] Moreover, FDA recommends that manufacturers that follow a streamlined approach clearly identify whether they are operating under a drug cGMP-based or device QSR-based approach at the beginning of an inspection and have all appropriate documentation required by either set of regulations available to access during the inspection.[26]

- **Internal audit programs** for traditional drug or medical device manufacturers will likely not be sufficient to assess the manufacturer against 21 CFR Part 4. Manufacturers will have to expand those programs to meet regulatory and compliance requirements for drugs, devices and biologics. In particular, their internal auditors need to have appropriate qualifications and expertise in applying the 21 CFR Part 4 requirements, or be trained in such manner.

- **Adverse event (AE) reporting** is an area of concern for companies that traditionally manufacture either drugs or medical devices, and have begun to manufacture combination products. If an AE is determined to be a "side effect" or contraindication, and if it is related to the delivery of a product, the manufacturer needs to consider medical device reporting (MDR, 21 CFR 803) and also needs to identify the types and depth of investigations required for complaints, as well as the most appropriate reporting of outcomes (complaint investigation report, CAPA, MDR, etc.). OCP has not yet provided guidance on the manner in which postmarket AE reporting for combination products should be handled, but it is working to clarify the most appropriate method of reporting AEs for combination products. In general, MDR requirements for medical devices are more stringent than Postmarketing Adverse Drug Experience (PADE) reporting requirements in terms of both timing as well as reportability.[27]

- **Drug-device interactions** need to be better understood by all combination product manufacturers. 21 CFR 211 Subpart E describes the cGMP requirements for component parts and drug product containers and closures,[28] which include requirements for testing leachables, biocompatibility and extractables on the primary container to ensure compatibility with the drug. Similar testing needs to be done on the device and its interaction with the drug product to ensure drug-device compatibility and avoid adverse interactions. Traditional medical device manufacturers should be particularly aware of this concern as there are no similar regulations under the QSR. Additionally, the Agency highlights the differences between a container or closure and a delivery device, and the need to be in compliance with the appropriate regulations, depending on the complexity of the delivery mechanism.[29] Risk management is the essential element for assessing drug-device interactions. Manufacturers need to demonstrate that they have the appropriate strategy and have performed adequate due diligence with regard to risk.

- **Co-packaged** and **cross-labeled** combination products have subtle differences that require clarification. Co-packaged combination products are two or more products in a single package that can be individually marketed. Cross-labeled products are packaged separately but are intended to be used only with a specific approved product, and cannot

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be individually marketed. **Convenience kits** are a form of co-packaged combination product that includes multiple products that are legally marketed and labeled independently so that each product retains its respective labeling. Manufacturers need to be aware of the packaging procedures and require a supplier to include all instructions for use (IFUs). Manufacturers of cross-labeled products would need to be cognizant of the distribution of their products to ensure they are not marketed individually.

- Although the **streamlined approach** outlines how a combination product manufacturer can demonstrate compliance with the drug cGMP and device QSR when both are applicable to its facility[30], manufacturers should consider reviewing and cross-referencing the equivalent regulation for good business practices. The following sections describe considerations for both traditional pharmaceutical and medical device manufacturers to be in compliance with the appropriate regulations as well as to establish good business practices when developing a compliant, robust, and efficient quality system for combination products.

Considerations for Pharmaceutical Companies

- **CAPA requirements** under 21 CFR 820.100 are more rigorous than similar cGMP requirements for drugs (21 CFR 211.198(b) and 211.22) and biological products (21 CFR 600.14[31] and 21 CFR 606.171[32]). In particular, all medical device CAPA subsystem quality data, including examples such as complaints, internal audits, change control, design controls, manufacturing data, purchasing controls data, etc., will have to be analyzed and trended for potential sources of corrective and preventive actions. Moreover, CAPA has direct linkages into the MDR process and the Agency will examine how manufacturers investigate complaints and determine whether a complaint is reportable under MDR, if the timing and timelines are appropriate, whether the manufacturer is following up with supplemental reports and how objectively those reports are submitted.[33]

- **Complaint handling** requirements for medical devices are slightly different than the requirements for pharmaceuticals and biologics. Specifically, QSR requires a formal unit designated for complaint handling. The reporting of adverse events also follows different regulations (21 CFR 310.305[34] for drugs and 21 CFR 803[35] for devices). On the drug side, there is a timeframe of 15 calendar days to report an AE to the FDA. For devices, depending on severity of harm, there are two options: no later than 30 calendar days, or no later than 5 work days if the reportable event requires remedial action to prevent an unreasonable risk of substantial harm to public health.[36] Also, 820.30(d) states that documentation related to reportable events needs to be clearly identified and maintained in a separate portion of the complaint files.

- **Design controls** have to be implemented for all phases of combination product development in order to account for appropriate drug, device and biologic regulatory and compliance requirements. In particular, the application of statistical techniques will be required to ensure rationales are documented for determining the appropriate valid statistical technique for the analysis being conducted. A manufacturer should be able to demonstrate the history of how its products evolved, and traditional pharmaceutical manufacturers do not have design validation and verification (21 CFR 820.30(f-g)) in place. Ultimately, it is the responsibility of the combination product manufacturer to understand how combining two constituent parts will work and how the product will function as a whole. For example, if a manufacturer uses a specification developer to design a constituent part, that manufacturer needs to have assurance that the specification developer has an acceptable design control system and also has access to the design control records.[37]

- **Purchasing controls** will have to incorporate the application of risk management techniques in the process for selecting suppliers and addressing remedial and corrective actions for noncompliant products. Moreover, traditional pharmaceutical manufacturers will need to implement purchasing controls when using suppliers for medical device constituent parts. The QSR preamble states: "…quality system regulation now explicitly requires that the finished device manufacturer assess the capability of suppliers, contractors, and consultants to provide quality products pursuant to Sec. 820.50 Purchasing controls. These requirements supplement the acceptance requirements under Sec. 820.80. Manufacturers must comply with both sections for any incoming component or subassembly or service."[38] Purchasing controls are called out by the Agency as a QSR requirement for traditional pharmaceutical manufacturers to consider when following the streamlined approach.[39] For example, a combination product manufacturer receives complaints

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specific to the needle component of its prefilled syringe. After investigation, the manufacturer identifies that mold cavity changes were made to the syringe by its supplier, which impacted the delivery of drug. cGMPs under 21 CFR 210 and 211 do not include purchase controls that would require notification of such a change; however, because the constituent part (needle) is a device, purchasing controls (21 CFR 820.50(b)) would apply, requiring the supplier to notify and gain approval for making any change to the needle, in addition to assuring verification of those changes (21 CFR 820.30(f)).[40]

- **Document control** requirements are more specifically described in the QSR (21 CFR 820.40)[41], particularly with regard to design changes. Pharmaceutical cGMPs require written procedures, including any changes, for production and process controls (21 CFR 211.100)[42]; however, the rigor of documentation requirements on the medical device side is more defined in the need for design history files (DHF) and device history records (DHR) that describe design verification and validation and a history of how the device manufacturer followed its plan for the design of the product. While a drug master file (DMF) is comprehensive in its content requirements, the documentation requirements are focused specifically on the manufacturing and processing of the drug (21 CFR 314.420).[43] The combination product manufacturer also needs to consider how it manages internal documentation for demonstrating compliance with the applicable cGMP requirements.[44]

- **Management responsibilities** are specifically detailed in the QSR (21 CFR 820.20)[45] but not explicitly described in the pharmaceutical cGMP regulations. The QSR requires having an adequate organizational structure in place and conducting periodic management reviews of the quality systems. The pharmaceutical cGMPs are general in that they require all employees to be qualified and trained for their job responsibilities (21 CFR 211.22).[46] Therefore, according to the QSR, the burden lies with executive management to establish and enforce the organization's quality policy, while also setting up the appropriate organizational structure to be able to comply with and meet regulations.

Considerations for Medical Device Manufacturers

- **Change control requirements** are applied differently under 21 CFR 211, in that changes may be implemented after approval of drug components. Device risk impact assessment as part of change control would require approval prior to implementation of a change. OCP has released a draft guidance document entitled, "Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA."[47] The guidance document only addresses the type of submission to provide when making a change to a constituent part of a combination product under one of these marketing applications, and further guidance will be issued on the technical content of the submissions and how manufacturers can address changes for products not approved under BLA, NDA or PMA, or approved under more than one application.[48] Moreover, all manufacturers of combination products need to implement change control protocols with their suppliers of constituent parts that account for the appropriate cGMPs.[49]

- **Design control** needs to account for the timing of the integration of the active pharmaceutical ingredient (API) during the manufacture of a combination product to ensure stability and product retention programs meet the 21 CFR 211 Subpart E requirements. For example, a suture manufacturer designs a new suture and plans to impregnate it with an antimicrobial pharmaceutical. If the drug constituent part is finished, the manufacturer needs to incorporate the stability and product retention dates. If the drug constituent part is not yet finished during the development of the suture, the manufacturer needs to incorporate timing for the completion of the drug into the device development and planning. It is important for the manufacturer to consider the combination product as a whole, rather than just as individual constituent parts.

- **Packaging and labeling operation** (21 CFR 211.130)[50] requirements for incoming inspection procedures need to be implemented by traditional medical device manufacturers to ensure that the components, drug product container and closures meet the requirements, and that there is documented evidence for skip lot testing.

- **Laboratory controls** (21 CFR 211 Subpart I)[51] need to be followed to qualify laboratories of combination product manufacturers to ensure that drug product components meet specifications when combined with the device constituent parts. This step needs to happen at the design verification stage. These test methods being used for the verification study have to be qualified and the specifications for what is being tested need to be approved and released.

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- **Retention and holding requirements** are detailed in drug cGMPs (21 CFR 211 Subparts E and H), but there are no similar regulations in the device QSR. Traditional medical device manufacturers need follow the drug cGMP requirements if they manufacture combination products that include drug products that have sterility and hold dates included on the product. Additionally, manufacturers need to have a retain program to ensure the drug constituent part is separate from the device constituent part, in addition to the finished combination product, to allow for an effective complaint investigation.

- **Stability and reserve samples requirements** (21 CFR 211.166(b)[52] and 21 CFR 211.170,[53] respectively) need to be taken into account by traditional medical device manufacturers as they receive and/or add drug constituent parts during the manufacture of combination products. For example, a manufacturer receives a drug product constituent part from a supplier to be used with a medical device constituent part in the manufacture of a combination product. The drug constituent part has an expiration date and stability data recorded in the documentation that the manufacturer needs to recognize and document. The device QSR states that the manufacturer is responsible for purchased constituent parts and therefore would need to appropriately account for the expiration date on the product.[54]

Future OCP Activities and Enforcement

On January 27, 2015, FDA released a companion guidance document to 21 CFR Part 4 to provide further information regarding the Agency's expectations for compliance with cGMPs for combination products and to help manufacturers comply with these requirements. FDA has released the guidance with the intention of providing information on the "implementation of regulatory requirements for use of a streamlined cGMP operating system for single-entity and co-packaged combination products." [55] This guidance refines the Final Rule and addresses industry concerns described in the preamble to the Final Rule, including:[56] the requirements for design controls for consistent parts, requirements for postmarketing change submission and premanufacturing design control requirements for products currently on the market, distinctions between devices and containers/closures, corrective and preventive actions particularly for products with multiple manufacturers, sample retention, batch release testing and stability testing, as well as other areas the Agency decided to clarify.[57] The Agency is expected to sponsor or co-sponsor a workshop in 2015 to solicit feedback on this guidance and then release a final guidance.[58] Over the coming years, OCP is developing IT infrastructure to better support intercenter coordination for premarket review and enhance information sharing with access to postmarket safety reporting (PSR) data. It is also expected to release the following guidance documents and final rules:

- Draft guidance on human factors
- Final guidance on cGMP for combination products
- Final rule for PSR[59]
- Final guidance on coronary drug-eluting stents – nonclinical and clinical studies
- Draft guidance on cross-labeling requirements[60]

Enforcement activity around 21 CFR Part 4 compliance can be expected to increase in the coming years, as more manufacturers of pharmaceuticals or medical devices develop technologies that straddle the traditional definitions of a drug or medical device, as FDA develops and clarifies regulations around specific combination products, and as the Agency uses more teams of investigators to support combination product inspections. Ultimately it is the manufacturer's responsibility to comply with these requirements. Furthermore, if manufacturers choose to follow the streamlined approach to demonstrate compliance with the applicable requirements of drug cGMP or device regulations in addition to their respective established quality system, they should also consider reviewing and cross-referencing certain aspects of the corresponding regulations to develop good business practices.

Combination Products: A 40 Year Regulatory Evolution

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Combination Products: A 40 Year Regulatory Evolution

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[1] Federal Register. November 21, 1991. Final Rule. Assignment of Agency Component for Review of Premarket Applications. FDA.gov. http://www.fda.gov/ohrms/dockets/98fr/91-27869.pdf

[2] Schillinger DC. 2004. The Office of Combination Products: Its Roots, Its Creation, and Its Rule. Harvard.edu. http://dash.harvard.edu/bitstream/handle/1/8852096/Schillinger05.html?sequence=2

[3] Committee on Energy and Commerce. 2001. Evaluating the Effectiveness of the Food and Drug Administration Modernization Act. GPO.gov. http://www.gpo.gov/fdsys/pkg/CHRG-107hhrg72831/html/CHRG-107hhrg72831.htm

[4] Food and Drug Administration. 2004. Guidance for Industry and FDA Staff - Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126006.htm

[5] Food and Drug Administration. 2010. RFD Process. FDA.gov. http://www.fda.gov/CombinationProducts/RFDProcess/

[6] Federal Register. October 4, 2004. Draft Guidance for Industry and the Food and Drug Administration; Current Good Manufacturing Practices for Combination Products; Availability. GPO.gov. http://www.gpo.gov/fdsys/pkg/FR-2004-10-04/pdf/04-22205.pdf

[7] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[8] Federal Register. January 22, 2013. Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf

[9] Federal Register. September 23, 2009. Current Good Manufacturing Practice Requirements for Combination Products. GPO.gov. http://www.gpo.gov/fdsys/pkg/FR-2009-09-23/pdf/E9-22850.pdf

[10] Federal Register. January 22, 2013. Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf

[11] Federal Register. January 22, 2013. Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf

[12] Federal Food, Drug, and Cosmetic Act (FD&C) Sec. 201. [21 U.S.C. 321] Definitions. FDA.gov http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterslandIIShortTitleandDefinitions/ucm086297.htm

[13] Federal Food, Drug, and Cosmetic Act (FD&C) Sec. 201. [21 U.S.C. 321] Definitions. FDA.gov http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterslandIIShortTitleandDefinitions/ucm086297.htm

[14] Code of Federal Regulations. 2014. 21 CFR Part 3.2. Definitions. FDA.gov http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=3.2

[15] Federal Register. January 22, 2013. Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf

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[16] FDA maintains a database of all Warning Letters that is searchable by company, subject, issuing office and certain content. http://www.fda.gov/iceci/enforcementactions/WarningLetters/default.htm#browse

[17] Food and Drug Administration. 2014. Amgen, Inc. Warning Letter. FDA.gov. http://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm385288.htm

[18] Food and Drug Administration. 2014. Baxter Healthcare Corp. Warning Letter. FDA.gov. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm384682.htm

[19] Federal Register. January 22, 2013. Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf

[20] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[21] Federal Register. January 22, 2013. Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf

[22] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[23] Food and Drug Administration. Office of Pharmaceutical Quality. FDA.gov. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm418347.htm

[24] Hertz, S. 2014. PDA-FDA CGMP Conference Presentation: cGMPs for Combination Products. PDA.org. http://www.pda.org/docs/default-source/attendee-presentations/north-america/2014/2014-pda-fda-joint-regulatory-conference/steven-hertz.pdf?sfvrsn=8

[25] Hertz, S. 2014. PDA-FDA cGMP Conference Presentation: cGMPs for Combination Products. PDA.org. http://www.pda.org/docs/default-source/attendee-presentations/north-america/2014/2014-pda-fda-joint-regulatory-conference/steven-hertz.pdf?sfvrsn=8

[26] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[27] Harold Pellerite Interview. Former Assistant to the Director, OC, FDA. September 18, 2014

[28] Code of Federal Regulations. 2014. 21 CFR Part 211. Current Good Manufacturing Practice For Finished Pharmaceuticals. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1&subpartNode=21:4.0.1.1.11.5

[29] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[30] Federal Register. January 22, 2013. Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf

[31] Code of Federal Regulations. 2014. 21 CFR Part 600.14. Reporting of biological product deviations by licensed manufacturers. FDA.gov http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.14

>>>

[32] Code of Federal Regulations. 2014. 21 CFR Part 600.14. Reporting of biological product deviations by licensed manufacturers. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.14

[33] Harold Pellerite Interview. Former Assistant to the Director, OC, FDA. September 18, 2014

[34] Code of Federal Regulations. 2014. 21 CFR Part 310.305. Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=310.305

[35] Code of Federal Regulations. 2014. 21 CFR Part 803. Medical Device Reporting. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=803

[36] Harold Pellerite Interview. Former Assistant to the Director, OC, FDA. September 18, 2014

[37] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[38] Federal Register. October 7, 1996. Medical Devices; Current Good Manufacturing Practice (cGMP) Final Rule. FDA.gov. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/ucm230127.htm

[39] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[40] Code of Federal Regulations. 2014. 21 CFR Part 820.30. Design controls. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=820.30

[41] Code of Federal Regulations. 2002. 21 CFR Part 820.40. Document controls. GPO.gov. http://www.gpo.gov/fdsys/granule/CFR-2002-title21-vol8/CFR-2002-title21-vol8-sec820-40

[42] Code of Federal Regulations. 2011. 21 CFR Part 211.100. Written procedures; deviations. GPO.gov. http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol4/pdf/CFR-2011-title21-vol4-sec211-100.pdf

[43] Code of Federal Regulations. 2014. 21 CFR Part 314.420. Drug master files. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.420

[44] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[45] Code of Federal Regulations. 2014. 21 CFR Part 820.20. Management responsibility. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=820.20

[46] Code of Federal Regulations. 2014. 21 CFR Part 211.22. Responsibilities of quality control unit. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.22

[47] Food and Drug Administration. 2013. Draft Guidance for Industry and FDA Staff – Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA. FDA.gov. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336230.pdf

Combination Products: A 40 Year Regulatory Evolution, continued...

[48] Federal Register. January 22, 2013. Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf

[49] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[50] Code of Federal Regulations. 2014. 21 CFR Part 211.122. Materials examination and usage criteria. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1&subpartNode=21:4.0.1.1.11.7

[51] Code of Federal Regulations. 2014. 21 CFR Part 211.160. General requirements. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1&subpartNode=21:4.0.1.1.11.9

[52] Code of Federal Regulations. 2014. 21 CFR Part 211.166. Stability testing. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.166

[53] Code of Federal Regulations. 2014. 21 CFR Part 211.170. Reserve samples. FDA.gov. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.170

[54] Federal Register. October 7, 1996. Medical Devices; Current Good Manufacturing Practice (cGMP) Final Rule. FDA.gov. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/ucm230127.htm

[55] Federal Register. January 22, 2013. Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf

[56] Interview with John B. Weiner. Associate Director for Policy, Office of Combination Products. January 21, 2015

[57] Food and Drug Administration. 2015. Draft Guidance for Industry and FDA Staff - Current Good Manufacturing Practice Requirements for Combination Products. FDA.gov. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

[58] Interview with John B. Weiner. Associate Director for Policy, Office of Combination Products. January 21, 2015

[59] Concepts for Comment Purposes Only – Not for Implementation. Postmarket Safety Reporting for Combination Products. http://www.fda.gov/downloads/combinationproducts/requestsforcomment/ucm108195.pdf. FDA.gov

[60] Email from John B. Weiner. Associate Director for Policy, Office of Combination Products. February 6, 2015

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