Combination Products Regulation – A Guide to Compliance

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Abstract *— The Food and Drug Administration (FDA or Agency) has issued a regulation on the current good manufacturing practices (CGMP's) requirements applicable to combination products. The new rule is intended to promote the public health by clarifying which CGMP requirements apply when drugs, devices, and biological products are combined to create combination products. In addition, the rule sets forth a transparent and streamlined regulatory framework for firms to use when demonstrating compliance with CGMP requirements for "single entity", "co-packaged", "cross-labeled", and "investigational cross-labeled" products. New regulations for combination products (new rule) were made effective in July 22, 2013 and are made available in the 21 Code of Federal Regulations (CFR) Part 4. The new rule does not contain new statutes or requirements for the Life Sciences Industry, but encompasses elements from the three existing regulations for drugs, devices and biologics. The purpose is to ensure that an industry manufacturing health products that combine two or more of the aforementioned elements complies with the requirements and has the controls in place to provide a product with the lowest risk to the patient. This is a change in paradigm from the previous ways of the agency where only one of the regulations for drugs, devices, or biologics applied to any given manufacturer, depending on the primary mode of action of their product. The project will focus on the development of a strategy to implement the new combination product regulation in relation to pharmaceutical (drugs) and medical device products that merge to conform a final product.*

Key Terms and Acronyms:

Term	Definition
FDA	Food and Drugs Administration
CGMP's	Current Good Manufacturing Practices
CFR	Code of Federal Regulations
QMS	Quality Management System
CAPA	Corrective and Preventive Action
HCT	Human Cell and Tissue
PMOA	Primary Mode of Action
NDA	New Drug Application
ANDA	Abbreviated New Drug Application
IND	Investigational New Drug Application
AER	Adverse Event Reporting
BLA	Biologics License Application
PMA	Premarket Approval
510K	Pre-Market Notification (equivalence)
IDE	Investigational Device Exemption
MDR	Medical Device Reporting
CDER	Center Drug Evaluation & Research
CBER	Center Biologics Evaluation & Research
CDRH	Center Devices & Radiological Health
Combination Product	A combination product is composed of any combination of a drug and a device; a biological product; or a drug, device, and a biological product.
Single entity combination product	A product comprised of two or more regulated components, i.e drug/device, that are physically, chemically, or otherwise combined and produced as a single entity
Co-pacakged combination product	Two or more separate products packaged together in a single package or as a unit and comprised of two or more components, i.e., drug/device
Cross-labeled combination product	A drug, device, or biological product packaged separately that according its investigation plan or proposed labeling is intended for use only with another approved specified drug, device or biological product

LITERATURE REVIEW

The FDA regulatory documents reviewed and used for this project were:

21 CFR Parts 210 and 211 – Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Finished Pharmaceuticals, respectively. [1]

The regulations contained in these parts contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of drug products for administration to humans or animals.

21 CFR Part 820 – Quality System Regulation or Current Good Manufacturing Practices for Medical Devices [2]

The regulations contained in this part govern the methods used in, and the facilities and controls used for the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use.

21 CFR Part 600-680 – Current Good Manufacturing Practice for Biological Products

The regulations contained in this part govern the methods used in, the handling and manufacturing of Biological products.

21 CFR Part 4 – Current Good Manufacturing Practice for Combination Products (New Rule) [3]

The regulations contained in this part are intended to promote the public health by clarifying which GMP requirements apply when drugs, devices, and biological products are combined to create combination products. The regulatory area covered by the new rule can be represented with Figure 1.

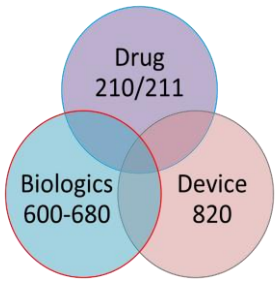

Figure 1
Common Regulatory Space

THE NEW RULE – 21 CFR PART 4

21 CFR §4.4 defines the CGMP requirements for single entity and co-packaged combination products;

§4.4 (a) (1) provides the option to implement the appropriate GMP for each type of constituent product included in the combination product (drug/device/biologic/HCT). [3]

Following §4.4(a)(1) would require that a full drug quality system be in place to control the drug constituent part and that a full device quality system be in place to control the device constituent part. However the new rule provides a streamline approach for compliance. Figure 2 illustrates the most common examples for compliance depending on the Primary Mode of Action (PMOA) for a medical device or a drug driven industry following the aforementioned streamline approach. [4]

Drug Primary Mode	Device Primary Mode
21 CFR Parts 210/211 and ✓Management Responsibility (820.20) ✓Design Control (820.30) ✓Purchasing Controls (820.50) ✓CAPA (820.100) ✓Installation (820.170) ✓Servicing (820.200)	21 CFR Part 820 and ✓Testing of Containers (211.84) ✓Calculation of Yield (211.103) ✓Tamper-evident Packaging (211.132) ✓Expiration Dating (211.137) ✓Testing/Release (211.165) ✓Stability Testing (211.166) ✓Special Testing (211.167) ✓Reserve Samples (211.170)

Figure 2
Streamline Approach for Combination Product Regulation Compliance

As shown in Figure 2, if the PMOA is a drug, then in order to comply with the new rule for combination products when combining a drug and a device, the manufacturer can choose the streamline approach and comply with all of the requirements for the CGMP's for drugs (parts 210 and 211), plus comply with some specific requirements for the medical devices CGMP's (part 820). The same principle is applied vice-versa if the PMOA is a device.

REGULATORY GALAXY

The Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (Draft Guidance), was issued by the FDA for clarification of some topics to the industries and to elaborate a

"current thinking" document of the FDA in respect the combination products theme.

The regulatory requirements for filing, making requests for new products, product investigations, event reporting and others should be directed to the office related to the constituent part (based on the PMOA).

The aforementioned regulatory requirements con by summarized with the illustration in Figure 3.

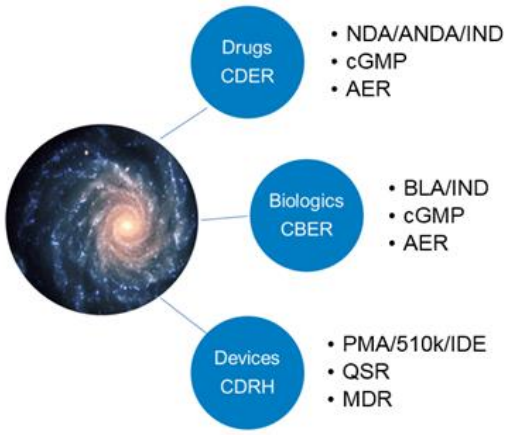

Figure 3
Regulatory Galaxy for per FDA Office

METHODOLOGY

The following is a recommended method of assessment, execution and implementation steps to effectively make a successful transition from a Drug (Pharmaceutical) based Quality Management System (QMS) to a Combination Product (drug-device) based QMS using the Streamline Approach discussed in section 2.4.1. Similar steps can be adapted to accomplish a transition in the other direction (device to device-drug), by making the necessary adjustments to comply with the Streamline Approach methodology proposed by FDA. The QMS provides the structure and control for cGMP operations at any facility. Note that a robust QMS is designed to accomplish three main objectives, which are:

- To deliver products that meet the needs of customers
- To establish and maintain a state of control for process performance and product quality
- To facilitate continuous improvement

As noted, the case to be analyzed in this project is the transition from a drug based QMS to a drug-device QMS combined product. As shown in Figure 4, the proposed Streamline Approach gives the topics to be added to the CGMP's for drugs (parts 210 & 211) from the CGMP's for medical devices (part 820) as shown below:

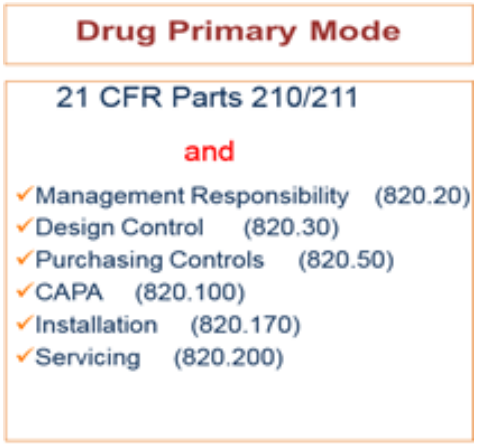

Figure 4
Streamline for Drug PMOA-Device

For the purposes of this discussion, the Installation and Servicing requirements will not be analyzed, since not all manufacturers provide them.

A description of the methodology follows:

Selecting a strong team to lead the way of such a transformation is vital to the success of a project involving the incorporation of the new combination products rule to an existing company. The team should be experience in GMP matters and from multidisciplinary areas. Coverage on all possible areas (manufacturing, change control, quality, purchasing, etc.) is a must.

After an adequate team is in place, it is important to assess compliance. It is needed to define how to make the assessment and which members of the team will execute it. Once this process is agreed upon, then a list of documents (SOP's, legacy products, pending transfers, company policies) should be prepared. Notice that the FDA believes that compliance with the new combination product regulation applies for new products as well as existing products.

After all assessments have been completed and all impacted documents are identified, it is time to enter into the four (4) aspects of the device regulation that need to be incorporated into the drug based quality system. The idea is have a QMS (Quality Management System) that encompasses drugs, devices, and combination products.

As part of the Management Responsibilities requirements, assure that the Quality Policy, Organization, Management Review and Quality System procedures are adjusted to welcome the new device component changes related to the combination product regulation. For the case being analyzed, the five (5) main requirements that must be reviewed and adapted to comply with the new rule for combination products within the Management Responsibilities area are:

1. Quality Policy
2. Organization
    a. Responsibilities and authority
    b. Resources
    c. Management Representative
3. Management Review
4. Quality Planning
5. Quality System Procedures

Design Control is a process implemented during the design, development, and manufacturing of a combination product, and remains in effect throughout its life. It ensures the product meets the users' needs, is safe and effective, and satisfies its regulatory requirements. In the same fashion as with Management Responsibility, the Design Controls requirements need to be satisfy by reviewing all documents related to design verification, validation, Input/Outputs, and Design History File. These are all documents that need to include the requirements of the device constituent part of the combination product. The aspects of Design Controls that must be reviewed in relation to the new rule are:

1. Design Planning
2. Design Input
3. Design Output
4. Design Reviews
5. Design Verification
6. Design Validation
7. Design Transfer
8. Design Changes
9. Design History Files

The CAPA system, which is maybe the most closely audited requirement, should include risk based considerations of the device part and combine them with the requirements already established for drugs when assigning severity, detection and controls of the combination product. The documentation must be adapted or reviewed to make sure the following aspects are covered in relation to CAPA's:

1. Analyzing
2. Investigating
3. Identifying
4. Verifying
5. Implementing
6. Ensuring
7. Submitting
8. Documenting

CAPA is an integral part of what can be characterized as two (2) inter-related quality systems which are:

1. NC (Nonconforming) process for investigating and controlling nonconforming product, and identifying actions to correct and prevent recurrence, which lead to…
2. CAPA (Corrective Action-Preventive Action) process for executing those identified actions, and for verifying or validating those actions to complete and close the loop.

Together, these processes fulfill both medical device and pharmaceutical NC/CAPA requirements.

Purchasing Control requirements are commonly overlooked because not much attention is put in the suppliers by several companies, assuming that the responsibility for a component manufactured outside of their facility is solely of the supplier. It is imperative to apply process rigor and oversight to suppliers of anything that might touch or affect the device and other constituent

parts of the combination product. These controls need to take into consideration the device component so that it complies with all regulations the same as if these components are manufactured in the base company itself.

The FDA is clear on the requirements for Purchasing Controls stating that each manufacturer shall establish and maintain the requirements, including quality requirements that must be met by suppliers, contractors, and consultants. These includes [2]:

1. Evaluation and selection of potential suppliers, contractors, and consultants.
2. Definition of the type and extent of control to be exercised.
3. Establishing and maintaining records of acceptable suppliers, contractors, and consultants.

The FDA is also clear on the type of data that expects from suppliers, stating that each manufacturer shall establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product and services. Related to the documentation, it also states that Purchasing documents shall include, where possible, an agreement where the suppliers, contractors, and consultants agree to notify the manufacturer of changes in the product or service so that manufacturers may determine whether the changes may affect the quality of a finished device.

The items that may be purchased from an independent supplier are classified as follows:

1. Raw Materials include all items that touch the product from its design and development stage through its entire lifecycle.
2. Components and Services include service providers, contractors, and consultants.

To ensure consistency and compliance with the new combination product regulation,

1. Develop an approved supplier list for use across the company.
2. Alignment of company-wide processes for qualifying, approving and monitoring of suppliers for all components and services.

Finally, a strong and detailed training and communication plan needs to be in place to assure all areas and personnel are informed of the changes of policies, procedures and methods related to the new combination product regulatory compliance.

A flowchart of the proposed steps is shown in Figure 5.

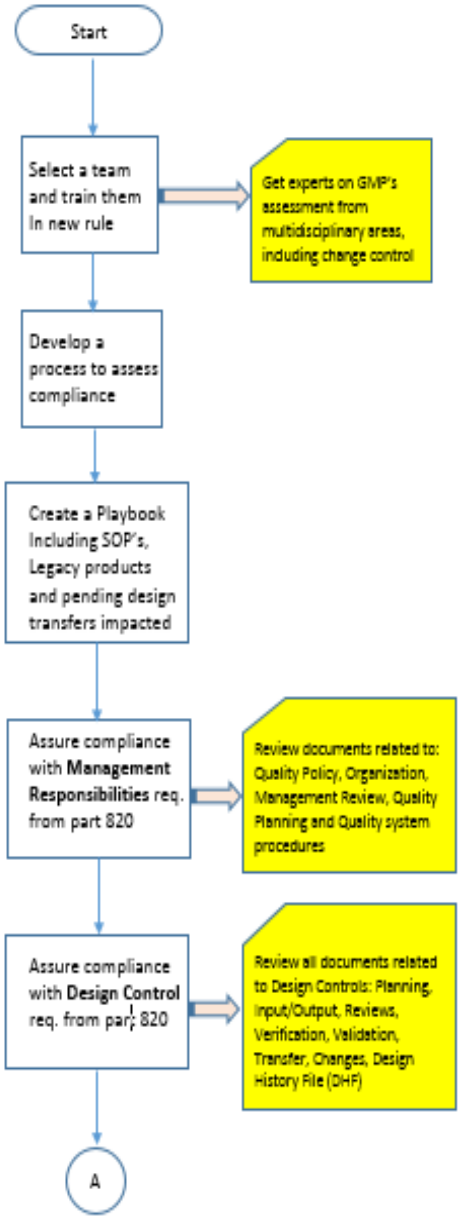

Figure 5
Flowchart for CFR Part 4 Compliance

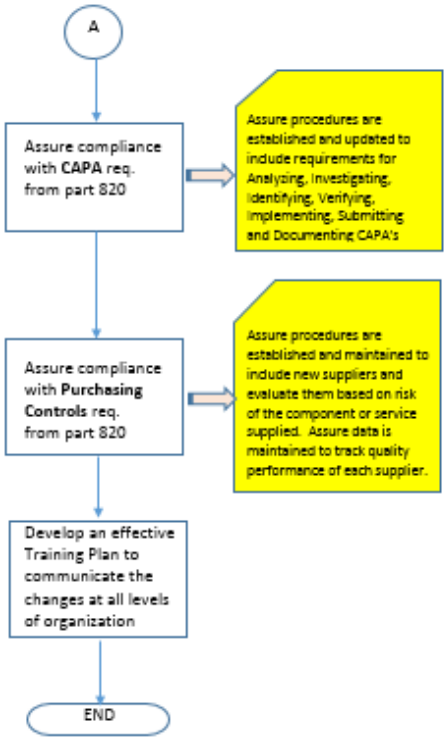

Figure 5
Flowchart for CFR Part 4 Compliance

THE CONTINUOUS IMPROVEMENT LIFE CYCLE

In order to maintain compliance with the new and in fact, all regulatory requirements in the life sciences industry, a life cycle like the one in Figure 6 should be implemented to Plan, Do, Check and Act on the different areas of regulatory compliance. The Management Review is the ideal forum to track, discuss and initiate any required action supporting the continuous improvement of the Quality Management System (QMS).

Figure 6
Continuous Improvement Life Cycle

CONCLUSIONS AND RECOMMENDATIONS

The new Combination Product GMP Regulation ensures that all constituents of Combination Products are properly controlled under a GMP system. A well planned implementation strategy that includes product and documents assessments, SOP's listing and review of the Quality Policy is vital to a successful transition. The initial assessment and implementation team should be well experience in GMP's and should be multidisciplinary, so that no area is left uncovered.

A comprehensive Training Plan is needed in order to communicate effectively the changes and modifications made to all levels of the organization.

The methodology for implementation of the combination product regulation to a drug based company contains also contains the steps to be followed if the implementation of the new rule is desired for a device based company incorporating a drug constituent part. For this, the streamline approach needs to be the one that incorporated the elements of the drug regulation (21 CFR parts 210 & 211) into the quality system for devices.

REFERENCES

[1] *Current Good Manufacturing Practice in Manufacturing, Processing, Packaging, or Holding of Drugs; General and Current Good Manufacturing Practice for Finished Pharmaceuticals*, 21 CFR Parts 210 & 211, Effective date: September, 1978.

[2] *Current Good Manufacturing Practice (CGMP) for Medical Devices, Quality Systems Regulation*, 21 CFR Part 820, Effective date: December, 1978

[3] *Current Good Manufacturing Practice Requirements for Combination Products*, 21 CFR Part 4, Effective date: July, 2013.

[4] *Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products*, (Draft).