

US FDA ISSUES FINAL RULE FOR COMBINATION PRODUCT QUALITY SYSTEMS

On January 22, 2013, the US FDA published the long-anticipated Final Rule: “*Current Good Manufacturing Practice Requirements for Combination Products*”, with the purpose of clarifying regulatory requirements for quality systems used to design, develop and manufacture combination products and to help ensure consistent and appropriate application and enforcement of these requirements. In this article, Michael Gross, PhD, RAC, Principal Consultant, Chimera Consulting North America, focuses on how the Final Rule effects the development and manufacture of drug delivery systems, such as prefilled syringes and auto-injectors.

The US FDA Final Rule: “*Current Good Manufacturing Practice Requirements for Combination Products*”, codified as 21CFR4,¹ is largely unchanged from its initial publication as a Proposed Rule on September 23, 2009.² It applies to marketed combination products and many products in development.

Manufacturers of combination products have 180 days to comply with the Final Rule.

“THE FINAL RULE DOES NOT CREATE NEW REQUIREMENTS, NOR DOES IT MODIFY EXISTING PREDICATE RULE REQUIREMENTS; RATHER IT CLARIFIES HOW TO APPLY THESE REQUIREMENTS TO COMBINATION PRODUCTS”

FDA intends to apply a risk-based approach to combination product facility inspections and has stated that it will offer manufacturers a reasonable opportunity to correct quality system deficiencies before taking compliance or enforcement actions.

THE FINAL RULE

The Final Rule states that Current Good Manufacturing Practice regulations for drugs and biological products (21CFR210 and 211) apply to combination products that include a drug or biologic constituent part. Current Good Manufacturing Practice regulations for medical devices or the Quality System Regulation (QSR, 21CFR820) apply to combination products that include a device constituent part. Additional regulatory requirements and standards apply if certain biological products described in

21CFR 600-680 are incorporated as a constituent part into a combination product. And,

Current Good Tissue Practice requirements, including donor eligibility requirements, for human and cellular and tissue-based products (HCT/Ps) described in 21CFR1271 apply to combination products that incorporate an HCT/P.

With respect to manufacturing components, device manufacturing components are not subject to Final Rule but drug manufacturing components are. Prefilled drug delivery systems, including prefilled syringes, are combination products subject to the Final Rule.

Compliance with combination product quality system regulations must be achieved by utilising a quality system that is demonstrated to comply with Predicate Rules (for example, drug-cGMP and device-QSR regulations) applicable to each constituent part of a combination

product. Two options exist for demonstrating compliance with applicable regulatory requirements: demonstration of compliance with the specifics of all quality system regulations applicable to each constituent part or, under certain conditions, demonstrating compliance with the specifics of either the drug-cGMP or device-QSR regulations, rather than both. Under the later circumstance, to demonstrate full compliance with both regulations, a manufacturer that chooses to base its quality system on a cGMP-platform is required, as applicable, additionally to demonstrate compliance with specified provisions of the QSR, thus creating a streamlined (i.e. hybrid) quality system. These specified provisions are:

- Management Responsibility (21CFR820.20)
- Design controls (21CFR820.30)
- Purchasing controls (21CFR820.50)
- Corrective and preventive action (21CFR820.100)
- Installation (21CFR820.170)
- Servicing (21CFR820.200)



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Additionally, for combination products that incorporate certain types of biological products, compliance with the requirements of 21CFR 600-680 must also be demonstrated. For a combination product that incorporates human cells or tissues (i.e. HCT/Ps) compliance with the requirements of 21CFR1271 must be demonstrated.

When two or more types of constituent parts to be included in a single-entity or co-packaged combination product are held at the same facility, or when the manufacture of a combination product proceeds at the same facility while utilising these constituent parts, compliance with all applicable quality system regulations must be demonstrated.

DISCUSSION

The Final Rule does not create new requirements, nor does it modify existing Predicate Rule requirements; rather it clarifies how to apply these requirements to combination products. Entities that engage in only certain regulated manufacturing operations are subject only to those portions of Predicate Rules that apply to those operations.

The Final Rule preamble states that certain container closure systems which also serve as drug delivery devices (such as a prefilled syringes, for example) may be considered as drug manufacturing components. Yet they are still in fact constituent parts of combination products and are thus subject to the Final Rule. Therefore, if a facility is manufacturing a finished prefilled syringe from drug and device components, the facility must comply with both QSR and cGMP regulations.

The preamble also addresses “convenience kits”, which are combination products that only include two or more types of medical products which are legally and independently marketed and subsequently co-packaged for independent marketing with the same labelling as that used for independent marketing. Generally no additional cGMP requirements apply to these kits, except for those requirements applicable to the assembly, packaging, labelling, sterilisation, or further processing of the kit itself.

However, if any of the products included in a kit are repackaged, relabelled or otherwise modified for the purpose of their inclusion in the kit, the kit is no longer considered to be a convenience kit. Under these circumstances all of the quality system requirements which are applicable under the Final Rule apply.

The preamble discusses how combination product manufacturers are required to demonstrate compliance with the Predicate Rules as they apply to a particular combination product. Demonstrating compliance includes establishing and maintaining written procedures and records that document and verify the utilisation of applicable quality system requirements described in the respective Predicate Rules.

Under cGMP Requirements for Combination Products, each of the constituent parts of a combination product when manufactured and marketed separately, are subject only to the individually applicable predicate quality system regulations pertaining to that type of constituent part. The constituent parts of a single-entity and co-packaged combination product retain their drug, biologic or medical device regulatory status before and after they are combined. Thus, facility where a single type of constituent part is manufactured must demonstrate compliance with the quality system requirements applicable to that type of constituent part. Quality system requirements that apply to the individual constituent parts of a combination product continue to apply even after they are combined to form of a single-entity or co-packaged combination product.

The Design Controls requirements of the QSR apply when a device constituent part is incorporated into a combination product. The QSR requires device manufacturers to establish and maintain Design Controls procedures that ensure that design requirements are appropriately established and that intended use and user needs are considered and satisfied. In utilising Design Controls, manufacturers may rely on existing information for the constituent parts. Should a combination product developer wish to use an existing or off-the-shelf product as a constituent part of a combination product, the utilisation of Design Controls must ensure that the existing product meets appropriate and prospectively established design requirements which assure that the combination product will be safe and effective.

This may result in modification of the existing product for use as part of the combination product. Modification of such a device must occur under Design Controls.

Within the meaning of the Final Rule, a device constituent part of a combination product is a finished device and a drug constituent part of a combination product is a drug product. Specification developers



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FDA has issued a new quality system regulation with important implications for developers and manufacturers of drug delivery systems and their constituent parts and components.

Prefilled syringes and drug delivery devices and systems are subject to the regulation. Developers and manufacturers of have 6 months to implement required changes to their quality systems.

A comprehensive analysis of the regulation can be found at

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Chimera Consulting assists companies in complying with the new regulation by conducting:

- Quality system gap assessments and mitigation
- Review and updating of SOPs
- Review and updating of purchasing agreements
- Internal and supplier audits
- Preparing for FDA inspection

“MANUFACTURERS OF DEVICE COMPONENTS, SUCH AS SYRINGE PLUNGERS, STOPPERS OR BARRELS, ARE NOT CONSIDERED TO BE DEVICE MANUFACTURERS UNDER THE QSR AND ARE THEREFORE NOT SUBJECT TO THE FINAL RULE”

and contract manufacturers are considered to be manufacturers subject to the Final Rule if they manufacture combination products or combination product constituent parts. However, manufacturers of device components, such as syringe plungers, stoppers or barrels, are not considered to be device manufacturers under the QSR and are therefore not subject to the Final Rule, even if that component will be incorporated into a combination product or constituent part of a combination product at another facility.

The Final Rule does not change any quality system requirements described in Predicate Rules for constituent parts (i.e. drug, biologic, device) described in master files (DMFs or MAFs for example). If the manufacture of an article described in a master file is subject to cGMP or QSR requirements, these requirements must still be met under the Final Rule. If the manufacture of such an article is exempt from

certain Predicate Rule requirements, it may still be subject to other Predicate Rule Requirements (e.g. QSR Purchasing Controls in the case of device constituent parts).

CONCLUSION

Manufacturers of combination products and combination product constituent parts have six months from the date of publication of the Final Rule to implement changes to their quality systems, at all affected manufacturing facilities, to demonstrate full compliance with the requirements of the Final Rule. Prudent manufacturers will assess the impact of the Final Rule on their manufacturing and quality operations and those of their suppliers and contractors. Risk-based gap assessments should be applied which should include review of purchasing agreements, SOPs and

conducting audits. Additional SOPs and training programmes may be needed, and implementing this will take time and planning.

REFERENCES

1. *Final Rule: “Current Good Manufacturing Practice Requirements for Combination Products”*. *Federal Register*, 2013, Vol 78(14), p 4307.
2. *Proposed Rule: “Current Good Manufacturing Practice Requirements for Combination Products”*. *Federal Register*, 2009, Vol 74(183), p 48423.

ABOUT THE AUTHOR

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