Combination Product Quality Systems

By Michael Gross, PhD, RAC

This article, the fifth in a series on the regulation of combination products in the US, considers the state of the quality system regulatory framework for combination products. This article is not a commentary on the recently published proposed rule[1] or the previously published draft guidance[2] on quality systems for combination products. Rather, it describes approaches based on existing regulations that may be taken now to establish a compliant quality system for the manufacture of a combination product in anticipation of the final rule.

Manufacturers should prepare for the day when the quality system regulation for combination products is final. Six months after the final rule is issued it will become an enforceable requirement. By then, FDA is also expected to have issued additional guidance explaining how manufacturers of single-entity or kit combination products may implement a quality system that combines elements from more than one quality standard (i.e., a streamlined quality system).

Currently, there is no final regulation or guidance describing requirements for a combination product quality system. The principles described in the proposed rule and the draft guidance are similar. They are not final but they reflect FDA's current thinking.

Combination Products Quality System Principles

When the constituent parts of a combination product are manufactured separately and remain separate, each is subject only to the quality system regulation that pertains to that type of constituent part (drug, biologic, medical device). The quality system regulation that normally applies to a drug, biologic or medical device still applies when these are part of a combination product formed through final product or investigational labeling (i.e., combination products that fit the definition of a cross-labeled combination product[3] or a combination product formed through investigational labeling[4]). Note, however, that an investigational constituent part is normally not held to the full scope of quality system requirements.

When the constituent parts of a combination product are brought together to form a single-entity or kit combination product, the constituent parts retain their regulatory status before and after they are combined. They do not lose their discrete regulatory identity as a drug, device, or biological product when they are constituent parts of a combination product. The quality system requirements that apply to each constituent part also apply to the entire combination product.

Many manufacturing facilities operate under only one type of quality system. Drug and biologic manufacturers generally follow the current Good Manufacturing Practice regulation (CGMP)[5] and medical device manufacturers usually follow the Quality System Regulation (QSR).[6] Both regulations state that should a manufacturer engage in only certain operations that are subject to the requirements of the regulation, and not in others, the manufacturer need only comply with those requirements that are applicable to the operations in which it is engaged. FDA considers the two regulations to be similar, with considerable overlap between them, and both allow flexibility in their application. Because each regulation is tailored to the characteristics of the types of products for which it was intended, it contains specific requirements that may be addressed more generally in the counterpart regulation. However, there are gaps where the regulations do not overlap.

For single-entity and kit combination products that contain both drug and device constituent parts, rather than implementing multiple (and potentially redundant) quality systems, compliance with either CGMP or the QSR, under certain conditions, will satisfy most requirements. To ensure full compliance with quality system requirements for a single-entity or kit combination product that contains drug and device constituent parts, elements of the CGMP regulation may be added to an existing QSR-based quality system, and vice versa. FDA refers to this kind of quality system as a "streamlined" system. Specifically, for a single-entity or kit combination product manufactured under a CGMP-based quality system, the additional elements from the QSR regulation that may need to be complied with are:

- 820.20 Management responsibility
- 820.30 Design controls
- 820.50 Purchasing controls

- 820.100 Corrective and preventive action
- 820.170 Installation
- 820.200 Servicing

Similarly, for a single-entity or kit combination product that contains drug and device constituent parts and is manufactured under a QSR-based quality system, certain elements of the CGMP regulation may need to be complied with:

- 211.84 Testing and approval or rejection of components, drug product containers and closures
- 211.103 Calculation of yield
- 211.132 Tamper-evident packaging for over-the-counter (OTC) human drug products
- 211.137 Expiration dating
- 211.165 Testing and release for distribution
- 211.166 Stability testing
- 211.167 Special testing requirements
- 211.170 Reserve samples

The need to fill the gaps between the CGMP and QSR will vary depending upon the manufacturing activity being performed and the nature of the combination product being manufactured. Requirements for firms that perform operations such as repackaging articles into convenience kits will generally be less demanding than requirements associated with the manufacture of complex devices such as drug-coated cardiac stents.

The QSR and CGMP require that written procedures be established and maintained to ensure that regulated products that are manufactured, processed and held meet the requirements of the applicable quality system. Accordingly, the written procedures for a streamlined quality system must ensure that the firm can demonstrate compliance with all applicable quality system requirements. FDA will consider a demonstration of compliance with the requirements of one set of regulations (e.g., CGMP), and compliance with the requirements of the specified provisions from the other quality system regulation (e.g., QSR), to be a demonstration of compliance with all requirements of the counterpart regulation.

If a constituent part of a combination product contains blood or blood components, allergenic products or other biological products regulated under the *Public Health Act*, its manufacturer will need to comply with additional quality system requirements.[7] When a human

cellular or tissue product (HCT/P) is a constituent part of a combination product, it will be regulated as a drug, device and/or biological product but additional requirements (i.e., Good Tissue Practices)[8] also apply.

When a constituent part is not manufactured in the same facility as another constituent part, the quality system under which it is manufactured must be shown to comply with all of the quality system regulations that are applicable to that constituent part. For example, a drug product manufactured in one facility would be subject to CGMP while a device manufactured in another facility would be subject to the QSR. When two or more types of constituent parts are manufactured in the same facility, a streamlined quality system approach may be taken. However, when a constituent part is produced at a facility that is separate from the manufacture of other constituent parts, manufacturing must take place in accordance with the quality system requirements that are directly applicable to that constituent part. When two or more types of constituent parts that are to be incorporated in a single entity or kit combination product arrive at the same facility, or when the manufacture of these constituent parts is proceeding at the same facility, a streamlined quality system may be utilized, except with respect to any constituent part whose manufacture does not occur in the same facility. Under these circumstances the quality system for the manufacture of that constituent part must be shown to comply with all of the quality system regulations which are applicable to that constituent part.

Discussion

There are a few differences in the principles described in the 2004 draft guidance and the 2009 proposed rule. The proposed rule expands the list of gaps between the CGMP and QSR regulations. It instructs manufacturers how to apply

the quality system requirements to combination product constituent parts when separate facilities are involved. The proposed rule also suggests that manufacturers must establish and maintain documentation demonstrating that the quality system under which combination product manufacture occurs addresses all applicable quality regulations that pertain to a particular combination product.

Conclusion

It will likely take a year or more until the combination product quality system rule is finalized and issued. Then manufacturers of combination products and combination product constituent parts will have about six months to implement changes to their quality systems in order to be fully compliant with the new regulation. Manufacturers that are developing or marketing combination products should prepare for this eventuality. First, they should become familiar with the proposed rule, assess its potential impact on their operations and identify questions that it raises or clarifications that may be needed. FDA has extended the deadline for public comments on the proposed rule from 22 December 2009 to 5 February 2010. Comments should be sent to FDA docket number 2009–N–0435.

Based on the proposed rule, manufacturers of combination products should assess the potential impact of a final rule on their manufacturing and quality systems and those of their vendors and contractors. Vendors and contractors should do the same. Risk-based gap assessments should include review of purchasing agreements and SOPs, and on-site audits. Depending upon the nature of the manufacturing operations, implementing a streamlined quality system may be appropriate. Additional SOPs and training programs may need to be established and strategies developed to demonstrate compliance with non-core quality system provisions. This will likely take a considerable amount of planning and time.

References

1. Current Good Manufacturing Practice Requirements for Combination Products (74 FR 48423)
2. *Draft Guidance for Industry: Current Good Manufacturing Practice for Combination Products* (69 FR 59239)
3. 21 CFR 3.2(3)
4. 21 CFR 3.2(4)
5. 21 CFR 210, 211
6. 21 CFR 820
7. 21 CFR 606-608
8. 21 CFR 1271

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