REGULATORY FOCUS

Changes Coming to FDA Quality System Requirements for Prefilled Injection Devices

By Michael Gross, PhD, RAC

This article reviews the current state of the development of quality system requirements for combination products, in particular prefilled drug delivery devices. As part of a series on US Food and Drug Administration (FDA) regulation of combination products,[1-9] it discusses industry's response to FDA's proposed rule on quality systems for combination products and how manufacturers of combination products should prepare for compliance with the anticipated final rule and related guidance.

On 23 September 2009, FDA proposed *Current Good Manufacturing Practice Requirements for Combination Products*.[10] Once this regulation is finalized, it will be codified as 21 CFR 4, Sub-part A.

The rule is expected to require combination product manufacturers to comply with both Current Good Manufacturing Practice regulations for drugs and biologics (21 CFR 210, 211 (CGMP)) and the Quality System Regulation for medical devices (21 CFR 820 (QSR)), during and after formation of a combination product. This has significant implications for pharmaceutical and medical device manufacturers that produce medicated devices, prefilled drug delivery devices and their components.

Comments on the proposed rule submitted by combination product manufacturers and their representatives mainly focused on how, where and when FDA expects the QSR and CGMP regulations to be applied during the combination product lifecycle.

FDA has indicated publication of the final rule will occur during the first half of 2012. Typically, there is a transition period before FDA requires compliance with a final rule.

Once this period is over, pharmaceutical and medical device manufacturers producing medicated devices, prefilled injection devices and/or their components, or filling prefilled syringes or assembling drug delivery devices should be in compliance with the new regulation. Failure to comply will be a violation of the *Federal Food, Drug, and Cosmetic Act*.

Quality System Requirements for Drugs, Biologics, Medical Devices and Combination Products

According to FDA's combination product definitions in the *Product Jurisdiction Regulation*,[11] prefilled drug delivery devices such as prefilled syringes, auto-injectors and pens containing drugs or biologics are combination products. Some manufacturers prefer to consider syringe components as components of a pharmaceutical container closure or primary parenteral packaging system.

While the syringe constituent part of a prefilled syringe is a container closure system, syringe components, once assembled, form a syringe, which is a medical device. Filling a medical device with a drug formulation creates a combination product.

FDA has the authority to apply drug, biologic and medical device regulations to any product composed of a drug or biologic and medical device constituent parts. Thus, FDA can require medical device, drug or biologic manufacturers of combination products and/or their constituent parts to comply with applicable requirements of the both QSR and the CGMP regulations.

According to the proposed quality system rule for combination products, when the constituent parts of a combination product are manufactured separately and remain separate, each is subject only to the regulation that pertains to that type of constituent part. When the constituent parts of a combination product are combined to form a single-entity combination product, or are co-packaged to form a kit combination product, the constituent parts retain their regulatory status both before and after they are combined. When the constituent parts are combined or co-packaged, quality system requirements that apply separately to each constituent part also apply to the entire combination product.

FDA considers the QSR and CGMP regulations to be similar and overlapping. Each regulation is designed to fit the characteristics of the products it regulates.

The proposed quality system rule for combination products suggests specific requirements of one regulation can be satisfied, perhaps with some fine tuning, by complying with a general requirement of the counterpart regulation. For manufacturers of single-entity and kit combination products containing drug (or biologic) and device constituent parts, rather than implementing multiple and potentially redundant quality systems, the proposed rule allows compliance with either the CGMP or the QSR to satisfy most requirements.

There are gaps where the regulations do not overlap. To ensure full compliance with quality system requirements for single-entity or kit combination product development and manufacture involving drug (or biologic) and device constituent parts, missing QSR elements may be added to an existing CGMP-based quality system (and vice versa in the case of a medicated device developed under a QSR-based quality system) to form a "streamlined" (i.e., hybrid) quality system.

The proposed rule identifies six gaps between a CGMP-based quality system and the QSR: management responsibility, corrective and preventive actions, design controls, purchasing controls, installation and servicing.

Installation and servicing usually do not usually apply to drug delivery systems. With some fine tuning, the management responsibility and corrective and preventative action requirements of the QSR can be satisfied by conformance to the ICH Q10 guideline that defines CGMP best practices. This leaves design controls and purchasing controls as truly unique elements of the QSR, for which there are no counterparts in the CGMP regulation.

Design controls are interrelated practices and procedures intended to control medical device design development throughout the product lifecycle. They are first applied during establishment of the initial device design requirements specification.

The QSR requires established and maintained formal procedures defining the design planning process activities and responsibilities. Procedures also are required to assure design inputs appropriately satisfy performance specifications and user needs and design outputs allow adequate evaluation of conformance with design inputs.

Design reviews must be conducted by appropriately structured multidisciplinary teams at appropriate times throughout design development. Design verification testing procedures must be established and maintained to determine whether the design output satisfies the design input requirements.

Procedures must be established and maintained for validating production units under use conditions to demonstrate that the product's intended use and user needs are

satisfied. Design changes and manufacturing transfer from prototypes to production and beyond are also controlled through design control procedures.

Finally, all records needed to demonstrate that the product was developed in accordance with the design plan are archived in a Design History File, which differs from a Pharmaceutical Development Report.

Purchasing controls are a set of interrelated practices intended to ensure purchased products, components and services conform to specifications; and selected suppliers, contractors and consultants are qualified; their performance is periodically assessed; and appropriate quality controls are established and maintained based on supplier performance.

Purchasing controls can be viewed as a design control system for purchasing. Both follow the same basic principles, methodically establishing input requirements and verifying performance outputs.

Vendor selection must be based on an evaluation of their ability to meet specified requirements (viz., design input) and appropriate controls (viz., design verification) must be established on the basis of this evaluation (viz., design output). Records of acceptable suppliers must be established and maintained (viz., Design History File).

Communication of requirements, including quality requirements, must be documented (viz., Design History File). Purchasing documents should include, where possible, an agreement that the vendor will notify the device manufacturer of changes to the product, processes or services to enable the impact of the change on overall product quality to be evaluated (viz., design changes).

Typically, pharmaceutical manufacturers establish quality systems that comply with the CGMP regulation, and medical device manufacturers establish quality systems that comply with the QSR. Medical device manufacturers may obtain certification of conformance to the international quality system standard for medical devices, ISO 13485 (Medical Devices—Quality management Systems—Requirements for Regulatory Purposes).

Medical device manufacturers that consider their drug delivery products to be pharmaceutical packaging system components may obtain certification of their quality system's conformance to the international standard ISO 15378 (Primary Packaging Materials for Medicinal Products—Particular Requirements for the Application of ISO 9001:2000). It remains to be seen, once the final rule is in place, whether FDA will consider conformance to these standards to be sufficient for vendor compliance with quality system regulatory requirements for combination products, device constituents and component parts.

Development Partner, Vendor and Contractor Compliance

The manufacturer of a combination product has the overarching responsibility for assuring compliance with relevant quality system regulations. Any development partner, vendor or contract manufacturer that joins the drug and device constituent parts of a combination product will need to be in compliance with more than one quality regulation.

If a combination product manufacturer is not involved in establishing or changing an existing design specification for a drug delivery device or does not change the intended use of an existing medical device constituent part of a combination product, it must assure that its co-development partner, vendor and/or contractor, at minimum, is compliant with applicable elements of the QSR.

If a pharmaceutical company chooses to either outsource device development or allow a development partner, vendor or contractor to modify an existing device to meet specified requirements, or if the pharmaceutical manufacturer is involved in establishing device design requirements, it will need to be effectively involved in the device design control process and its quality system procedures should reflect this.

Industry Concerns

Pharmaceutical and medical device companies expressed their concerns about the proposed rule by providing comments directly to FDA or through their trade or professional associations. Some of the key issues raised in these comments concern FDA's expectations on the applicability of the QSR to component manufacturers of combination product device constituent parts.

Clarification also was requested on how FDA expects combination product manufacturers to apply device quality system requirements to combination product constituent parts before and after arrival at the manufacturing facility where the combination product is formed. Pharmaceutical companies manufacturing prefilled drug delivery systems that consider prefillable syringe components to be pharmaceutical packaging or container closure systems subject only to CGMP regulations have sought clarification from FDA on the need to apply design controls to their pharmaceutical formulation and packaging development activities.

Others have sought clarification of what FDA expects combination product manufacturers to do to document the compliance of a "streamlined quality system" to 21 CFR 4, Sub-part A. Pharmaceutical and medical device manufacturers also would like to understand how FDA will apply these new quality system requirements to legacy products. These and other issues are expected to be addressed in the final rule and preamble and in anticipated guidance documents.

Conclusion and Recommendations

Manufacturers of prefilled drug delivery devices and their components need to begin preparing for compliance with the coming quality system regulation for combination products. Combination product and constituent part developers, manufacturers and their development partners, vendors and/or contractors should assess, and where necessary enhance, their quality systems and those of their development partners, vendors and contractors to assure they will be in full compliance with the new quality system requirements.

Implementing changes to an existing quality system requires planning, time and expertise. Quality system gap assessments should evaluate existing quality systems in the context of the combination products and/or constituent parts being developed and manufactured. These assessments should include a review of purchasing agreements, quality policy and procedures.

To fill the gaps, supplemental standard operating procedures (SOPs) and quality policy elements will need to be established. Which gaps need to be filled will depend on the development and manufacturing activities performed and the nature of the combination product. Manufacturers of prefilled drug delivery systems that engage in even the best CGMP industry practice still will need to incorporate additional elements of the QSR that are unique to medical device quality system practice into existing quality policies and SOPs.

Development partners, manufacturers and/or vendors of device constituent parts whose quality systems conform to only the ISO 13485 or ISO 15378 standards may need to enhance their quality systems by adding, as appropriate, additional QSR elements.

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