Combination Products 2.0: Applying the New FDA Regulations

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Combination products, those that contain medical devices embedded with pharmaceutical or biologic components, have become a large and growing segment of the medical device market. Some analysts estimate they represent over 30% of all new product submissions to the FDA. This article reviews testing and FDA compliance concerns with them.

Over the last 10 years, FDA regulatory centers have struggled with the changes and challenges that combination products present. For manufacturers too, the convergence of drugs/biologics and devices has created a host of regulatory issues, along with many exciting opportunities.

The FDA issued an informational compliance document in 2004. This didn't provide much guidance for practitioners in terms of regulatory methodology and lacked information on what parts of the USP and ISO documents would be required for combination products. In 2007, Microtest Labs authored a paper on the subject, "Combination Products: Navigating Two FDA Quality Systems," that addressed these difficulties.

To make matters even more complex, human tissue and cellular products (HCT/Ps) are being incorporated into combination products, raising a host of new challenges for testing, sterilization, and contamination avoidance.

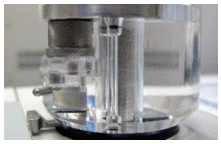
Over the past 12 months, however, the FDA has addressed the dichotomy of dual quality systems by developing streamlined regulations for Good Manufacturing Compliance.

The New Regulations

In September 2009, the FDA published proposed Good Manufacturing Practices (GMP) for combination products in the Federal Register, giving the industry three months to comment. Entitled "21 CFR Part 4—Current Good Manufacturing Practice Requirements for Combination Products," it revised the regulations by establishing different categories of products. These included single-entity products (such as a drug-eluting stent) and co-packaged products (such as a packaged syringe and pharmaceutical). The rules also distinguished between a drug with a device, a biologic with a device, and a device with an HCT/P. These new requirements streamlined the previous regulations and provided the industry with enough information for compliance.

The new rules guide the manufacturer into one of two approaches, depending upon the characteristics of the product:

- If pharmaceuticals or biologics are primarily being produced, the manufacturer must start with the quality foundation of the drug GMPs. Then it follows specific Quality System Regulations (QSRs) to cover the medical device requirements.
- If the majority of a facility manufactures medical devices, and it is producing a combination product, the manufacturer would start with a quality foundation of medical device QSRs and then overlay some of the drug GMPs to cover the pharmaceutical requirements.



A particle size distribution analyzer used to test powders in a combination product

Principal Mode of Action
Initially, a company developing a combination product must determine its principal mode of action (PMOA)—device or drug. A product's PMOA is determined by the FDA's Office of Combination Products (OCP) by submitting a Request for Designation (RFD). The PMOA dictates whether the foundational quality framework will use medical device QSRs or drug GMPs.

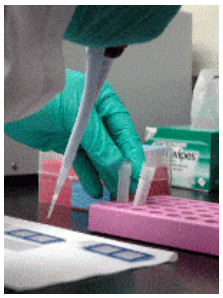
Following FDA approval, manufacturing must be scaled up for commercial production. A fully compliant quality system, including the necessary testing programs, must be developed as part of this effort. (The expertise of an experienced life science testing firm can be invaluable during this process.)

If the PMOA is a medical device, the QSRs would be used as the foundation framework. If it contains a drug, the manufacturer must overlay the drug GMPs for finished pharmaceuticals (21 CFR Part 210-211). Testing requirements would include stability, batch control, pH, color and appearance, particulates, concentrations, and label claims. If the device contains a biologic, the manufacturer must overlay the biologic GMPs (21 CFR Part 600 – 680). In addition, stress testing

should be done on the finished product.

On the other hand, if the PMOA is a drug product, the company would use the drug GMPs (21 CFR Part 210-211) as the foundational quality framework, and also show compliance with elements of the medical device QSRs.

Stem Cells & Human Tissue
There is much confusion in the market on whether the inclusion of stem cells and human tissue in transplants constitutes a combination product. The FDA is struggling to regulate tissue products for several reasons. They incorporate emerging technologies, are generally used in hospitals more than commercial settings, and are introduced to patients in ways that present new quality issues.



Technician testing combination products for stability

The new 21 CFR Part 4 regulations define the requirements for HCT/P quality systems and Good Tissue Practices in Part 1271. They state that “an HCT/P that is combined with another article (other than water, crystalloids, or a sterilizing, preserving, or storage agent) does not meet the criteria for regulation solely under Section 361 of the PHS Act, but rather would be regulated under the PHS Act and/or the act as a drug, device, and/or biological product.”

This definition includes bone, skin, ligaments, tendons, duramatter, heart valves, hemopoetic stem cells, progenitor stem cells, dried cord blood, and semen that are combined with a device.

The new regulations are focused on the source of HCT/P material. In general, the FDA is concerned about stopping the spread of communicable disease and protecting people from getting sick. But sterilization issues in tissue products can be challenging from a validation stand point. There is still much work to be done in blending Good Tissue Practices with drug GMPs and testing regimens.

Testing and Validation
As the new regulations are promulgated, testing will present combination products manufacturers with many challenges. Companies must adjust their GMP and QSR programs to incorporate the correct testing regimen that ensures their products are

safe and efficacious.

Sterilization is a key test for every combination product and is part of the design review required under the new GMP regulations. Manufacturers must consider sterilization and contamination issues up front during the design phase of product development. Sterilizing the product using a medical device sterilization procedure is acceptable. These procedures are outlined in the ISO documents, specifically 11135 and 11137. Most drug manufacturers use steam or filter sterilization methods on their products. Others use radiation processing for powders. Some companies employing ethylene oxide gas for sterilization have experienced FDA issues. The FDA's stand on drug products sterilized by EO gas is complicated by EO residual compounds.

Combination products are also susceptible to degradation, loss of efficacy, and stability issues. A robust quality system must include testing for drug, biologic, and HTC/P stability using established guidelines.

There continues to be confusion regarding testing requirements for human cellular and tissue-based products. For example, bone and tissue banks are not FDA regulated. They are not required to test for sterility of products or to validate the process.

Part 1271 includes defining the testing requirements for this new class of combination products. Since HCT/P products must be manufactured in clean, sterile environments, they require testing for viruses (animal or human), bacteria/fungi, or mycoplasma. For example, bovine/porcine-based material must be rigorously tested for viruses and other diseases. The FDA is voicing concerns about stability and contamination control. These issues can be highly detrimental and may result in product recalls or manufacturing facility closures. As a result, it is strongly recommended that a percentage of harvested tissue used in a combination product go through a sterility testing process. It is imperative that independent labs follow USP/FDA regulations for testing these products.

When developing their quality systems, combination products manufacturers should work hand-in-hand with testing laboratories to develop validated procedures that will fulfill all anticipated testing requirements. This partnership can be highly effective in identifying potential contaminants (viral, microbial, and non-microbial) and opportunities for reduced cycle time and costs. A strong relationship will ensure that all information required by the FDA is captured and that the manufacturer's products are safe and efficacious.

During manufacturing scale-up, the engineering studies must be designed to ensure the process follows correct procedures and that products meet required performance standards. The FDA requires the validation of process and raw materials testing. A high degree of statistical confidence is required to ensure the combination product will be manufactured consistently and meet finished product specifications. The validation program should also include Process Analytical Technology and Design of Experiment programs. The FDA wants to see these methodologies included in all pharmaceutical manufacturing processes.

Case in Point: Drug-Eluting Stents

To help illustrate how the new regulations are applied, a drug-eluting stent will be used as an example. In this case, the stent is the primary therapeutic agent. The drug is a therapeutic coating to prevent scarring. The reviewing agency for the product would be the Center for Device Evaluation in Radiological Health and the PMOA is a medical device.

According to the proposed rules, the manufacturer would be required to have a robust quality foundation that complies with QSR Section 820. This ensures that the quality system is maintaining good control over the design and manufacture of the product. But 21 CFR Part 4 also stipulates that when introducing the pharmaceutical in the device, the following sections of the drug GMPs must be satisfied:

- Section 211.84: Testing and approval or rejection of components, drug product containers, and closures
- Section 211.103: Calculation of yield
- Section 211.137: Expiration dating
- Section 211.165: Testing and release for distribution
- Section 211.166: Stability testing (including forced degradation studies)
- Section 211.167: Special testing requirements
- Section 211.170: Reserve samples

Conclusion

With the proposed 21 CFR Part 4 document published and the comment period closed, the FDA is now reviewing public and industry input. Final action is scheduled for August 2011. The rule is to become law 180 days later, which is anticipated to be around February 2012. Once 21 CFR Part 4 gets promulgated, manufacturers will be held accountable for compliance and the FDA will use it as a legal document for enforcement.

This new streamlined approach for regulating combination products is a big step forward for the practitioner. It applies parts of both the QSR and GMP quality systems in a way that makes sense for the unique characteristics of each combination product. 21 CFR Part 4 closes the gaps in the 2004 guidelines and succinctly clarifies the process for establishing quality systems that ensure compliance and patient health and safety.

Reliable testing procedures will be critical in complying with these new requirements. Pharmaceutical testing laboratories can play an important role in guiding combination product developers on their quality system journey. Testing laboratories that also offer contract manufacturing services, such as Microtest Labs, are particularly adept at understanding the new regulations and requirements. With the capability to test and process biologics, drugs, medical devices, and tissue products, these firms can provide expertise that will lower costs and accelerate the introduction of a combination product to market.

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Captions

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Links:
[1] http://www.microtestlabs.com
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