Innovative medical device manufacturers have discovered that the benefits of combining a drug, biologic or tissue with their device to create a new product may improve clinical outcomes for patients and provide a distinct competitive advantage. Unexpected regulatory compliance issues, however, and the technical challenges of combination products can confound plans, resulting in delays and unexpected costs. To avoid missteps during combination product development, medical device firms new to developing combination products should be aware of these three common misconceptions.

1. The Legacy Device

The first common misconception of medical device developers is the belief that “grandfathering” of legacy combination products is an accepted policy at FDA. A legacy device is one that incorporated a drug before the combination product regulations went into effect, and was reviewed and approved by the Centers for Devices and Radiological Health (CDRH) without any other agency consultation. After years on the market, inevitably, at least one of the constituent parts of the combination product needs to be changed. Many medical device manufacturers have mistakenly assumed that since the legacy product was initially reviewed only by CDRH in the past, the revised product will have the same review process. This is not true. In fact, CDRH will consult with other agencies to ensure that issues associated with the other constituent parts are appropriately reviewed by relevant agencies e.g., the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). The market authorization requirements from these allied FDA agencies can be a costly (time and money) surprise to device manufacturers.

2. The Me-Too Approach

A second misconception held by many medical device manufacturers is that an iterative change to combination products can be adequately supported by leveraging information from the predecessor product and that minimal new data is needed; the “me-too” approach. For example, the manufacturer of an...

What is a Combination Product?

A combination product is composed of any combination of a drug/device, biologic/device, drug/biologic or a drug/device/biologic. The FDA’s final rule for combination products describes an approach to GMP compliance that uses existing regulations. The existing regulations include devices, drug, biologic products and human cellular/tissue-based products, (each defined as ‘constituents’). The possible configurations can be two (2) or more regulated constituents physically, chemically or otherwise combined, mixed or produced as a single entity. Developing the actual combination product is a huge effort in itself. Designing, manufacturing and maintaining the product under a ‘combination product’ quality system is an equally challenging endeavor. The FDA provides a menu of opportunities to assure that each constituent part is compliant with the appropriate QSR or GMP system. It’s important to note that the Office of Combination Products facilitates interactions between CDRH, CDER and CBER, however this office does not grant market approvals.

EXAMPLES OF COMBINATION PRODUCTS

Drug Delivery
- Implantable drug pumps
- Transdermal Patches
- Metered dose Inhalers
- Antimicrobial urinary catheters
- Eye drops for glaucoma

Orthopedic and Dental
- Antibiotic Bone cements
- Woundcare
- Antimicrobial dressings
- Steroid-containing Creams
- Antimicrobial impregnated Sutures

Vascular
- Drug coated balloon catheters
- Coated vascular prostheses

1 21 CFR 4, 21 CFR 803, 806, and 820, 3 21 CFR 210 and 211, 4 21 CFR 600-680, 5 21 CFR 1271
injection pen that is cross-labeled with a prefilled syringe changes the instructions for use to deliver the drug in the syringe at a faster rate than is prescribed by the prefilled syringe manufacturer. The injection pen manufacturer believes that new safety/efficacy data is not needed because the drug is not actually changing. In fact, every use of every drug constituent of a combination device is considered a new product; every dosage change to the drug constituent of a combination product is considered a new product; every change in container-closure to a combination product is considered a new product. Changes to either constituent may require studies to demonstrate safety and effectiveness because FDA may consider a changed combination product as a new product. The medical device industry needs to educate itself to better interpret and understand the implications and consequences of 21CFR4.

3. Underestimation of Expertise and Time Required

Finally, some device manufactures undervalue the expertise and time needed to technically support the drug constituent of a new combination product. As an example, the team developing a drug-eluting stent is composed of only device-trained engineers. This is an oversight that can have serious consequences. Every product development team needs to employ chemists or biochemists with a thorough understanding in analytical methods used to measure the drug characteristics, and an ability to design experiments that provide objective evidence that the drug constituent remains active throughout processing. For example, the chemists have the expertise to design drug product formulations, demonstrate controlled release of drug from the device matrix, and assess any other device/drug interactions of a drug coated stent that could adversely affect the quality of the product, such as drug inactivation by device contact or flaking off of drug coatings after implantation. Understanding the basic science of these types of issues is not usually within the purview of design engineers.

Developing combination products requires expertise from both the engineers and pharmaceutical scientists in order to develop a combination product with safety and effectiveness data supported by compelling scientific evidence.

Conclusion

Combination products offer medical device developers exciting and challenging opportunities. Device manufacturers need to enter into this new paradigm with eyes wide open, understanding the nuances and embracing the requirements of this medical product category. Misinterpretation of the regulation, agency expectation and technical issues can lead to unexpect-

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