HEALTH

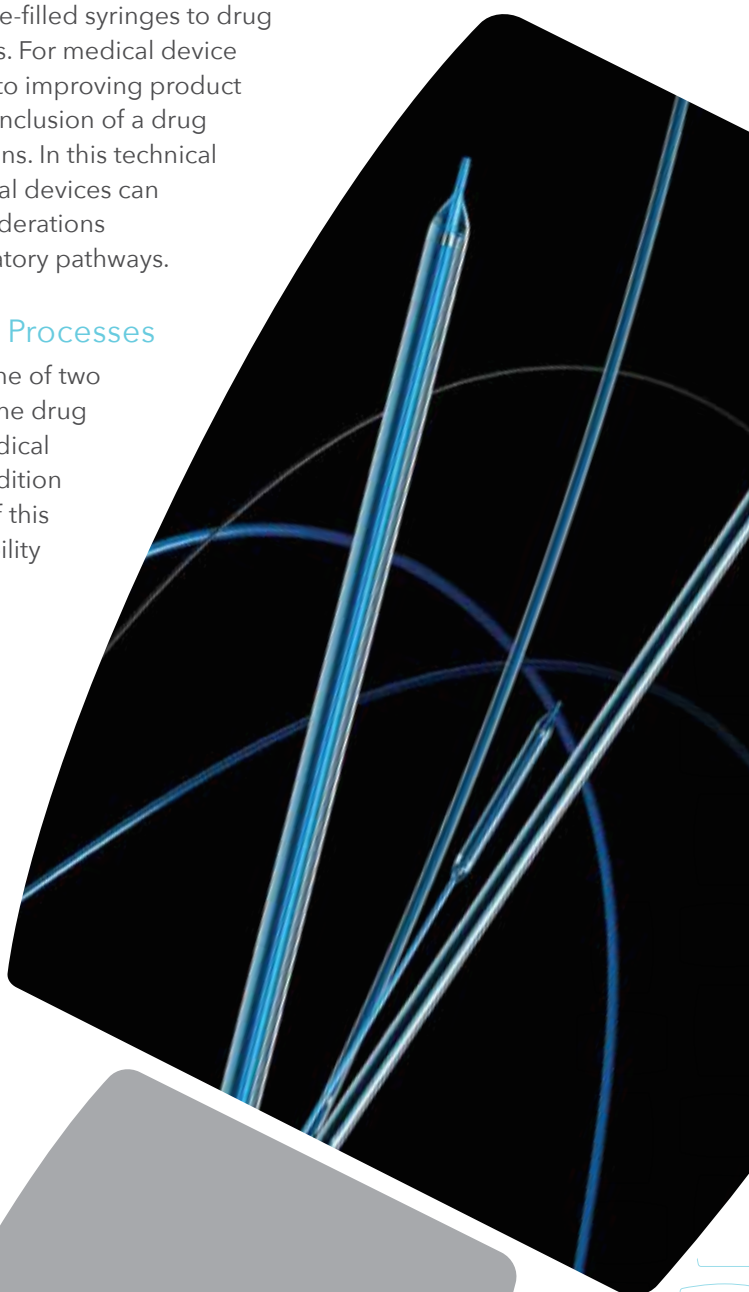
Combination Products for Medical Device Developers

Introduction

Combination products are defined in 21 CFR 3.2(e) as therapeutic and diagnostic products comprising two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity. This broad definition includes products ranging from pre-filled syringes to drug coated implants. In this brief, the focus is on implanted devices. For medical device companies, combination products provide an attractive route to improving product performance or extending a product's lifecycle. However, the inclusion of a drug also introduces new development and regulatory considerations. In this technical brief, we focus on how the addition of drugs to existing medical devices can enhance their performance. We will also explore the key considerations associated with combination product development and regulatory pathways.

Types of Combination Products and Production Processes

Broadly speaking, drugs and implants are used together for one of two reasons: 1. the device acts as a vehicle to deliver a drug or 2. the drug is included to enhance the performance of the device. For medical device developers, the most relevant examples involve the addition of a drug to an existing medical device. The classic example of this is a drug-eluting stent, in which a drug enhances the stent's ability to maintain a clear blood vessel by inhibiting cell proliferation. Antimicrobial catheters, steroid-coated pacemaker leads, and antibiotic bone cements are also examples of traditional medical devices that are enhanced by the inclusion of a drug. Polymer selection is a critical component of medical device development, and the same guidelines apply when choosing a polymer for a combination product. The biocompatibility of a selected polymer is evaluated according to ISO 10993 and USP <1031> tests, designed to document that the final product is safe for its intended use, location, and duration. Combination product developers should ensure that their chosen polymer(s), as with any key component, will be available in the grade necessary for an implant and that the manufacturer can provide the needed documentation and support.



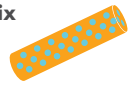
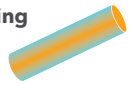
Types of Combination Products and Production Processes (continued)

The drugs incorporated with devices may be either impregnated or surface-coated. Many common medical device polymers have been combined with drugs through hot-melt extrusion (HME), a process familiar to the medical device industry. Common polymers used in HME include polyolefins, polyesters (especially those based on lactic acid, glycolic acid, and caprolactone), polyurethanes, and ethylene-co-vinyl acetate polymers. Silicone rubber can also be combined with drugs through reactive injection molding. In cases where temperature sensitivity is an issue, drug loading may be accomplished with the use of solvents.

Drug-eluting devices can take several forms, namely **matrix, coating, and reservoir (Figure 1)**. In the case of matrix-type products, the drug is uniformly dispersed throughout the polymer. Drug release from matrix-type products typically follows first-order kinetics **(Figure 2)**, often with an initial burst of drug and a release rate that decreases over time. In cases where a device is hollow or surface protection is critical, a drug-containing coating can be applied. These coatings can be made from biodurable or biodegradable materials and may demonstrate a wide range of release rates depending on the coating composition, thickness, and surrounding environment. The final type of combination product, reservoir-type, is less commonly utilized for modifying medical devices. An example of a medical device utilizing a reservoir is the drug-filled stent. These are metallic stents that have laser-drilled holes to allow drug to continuously elute out of the device, preventing restenosis of a vessel. Reservoir designs are appealing because they can achieve steady drug release over time, also known as zero order release. For medical devices, the burst release of a zero-order matrix-type product may be desirable to help fight an initial infection risk or inflammatory response. Whatever the goal of a combination product, the drug incorporation method and material selection can be optimized by experienced developers to achieve the desired drug release rate.

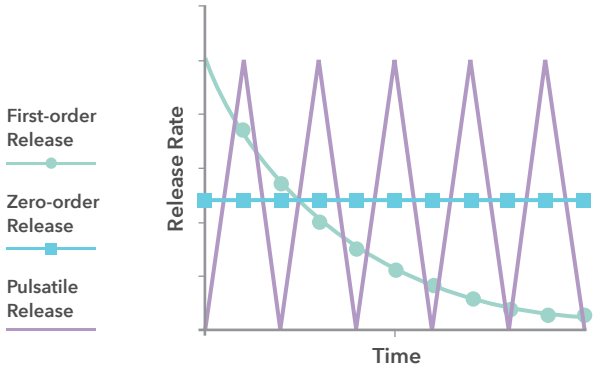
LUBRIZOL LIFE SCIENCE

Figure 1: Various Combination Device Configurations

API / Polymer	Description	Example
Matrix 	Drug uniformly dispersed throughout polymer	Antibiotic bone cement
Coating 	Drug-containing layer applied to the surface	Drug-eluting coronary balloon
Reservoir 	Drug core surrounded by polymer shell	Drug-filled stent

Lubrizol Life Science

Figure 2: Various Types of Drug Release Profiles

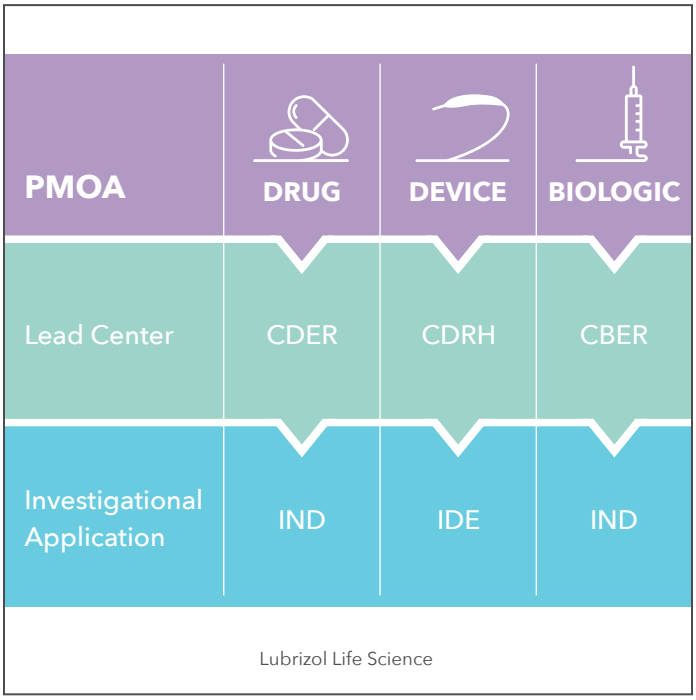


Lubrizol Life Science

Phases of Combination Product Development

Successful combination product development requires an understanding of the design process for both medical devices and drug products. Most medical device companies have expertise in areas such as prototyping, design controls, human factors analysis, and verification/validation protocols. Where they may lack knowledge is in the formulation development, pre-clinical/clinical testing, and safety and compliance studies that accompany drug products. Any successful combination product development requires a grasp of both pathways and the challenges that may arise from either **(Figure 3)**. As the FDA says in their Combination Products Guidance, "When combining products such as drugs or biologics and devices that are customarily delivered using different regulatory paradigms, certain critical development issues, such as the interaction of the drug/biologic and device constituents, may not be readily apparent." Medical device developers must be willing to seek out expertise in the drug/biologic space (and vice versa) to address the considerations for combination products, some of which will be explored in the following paragraphs.

Figure 3: Combination Product Production Process



Drug/Device Compatibility: Medical device developers are no strangers to evaluating devices for safety and efficacy through laboratory and clinical studies. However, the introduction of a drug to a medical device adds complexity to the development process. Device developers routinely evaluate biocompatibility between polymers and the body. With a combination product, they must also ensure drug stability, including compatibility between the polymer and the drug. This requires the development of additional analytical methods to assess drug content, state, and uniformity within a device or coating. Formulation studies explore the best route for adding a drug (impregnation, filling, or coating), the necessary level of drug to achieve therapeutic effect, and ways of stabilizing a formulation for processing or storage. For example, since device manufacturing through HME or injection molding often involves elevated temperatures, the thermal stability of the drug in the polymer is of interest and must be determined early on.

Drug Release: Medical devices undergo leachables and extractables testing to ensure devices are not releasing harmful agents in the body. But when a drug is introduced, additional drug release studies must be performed as well. To determine *in vitro* drug release kinetics, a combination product is immersed in a fluid designed to simulate in-vivo conditions, such as body temperature or environmental pH. The fluid can either be replaced periodically to maintain sink conditions (i.e. daily) or circulated around/through the device (i.e. flow-through apparatus). The amount of drug released from the device is determined by regularly sampling the medium and analyzing for drug content, usually by HPLC. *In vivo* release kinetics are similarly determined by measuring levels of the drug in tissue or biological fluid over a chosen period.

Stability/Safety: While medical devices must be evaluated for structural and chemical stability, combination products require additional stability studies typically used for drug products. Using ICH guidelines, combination products are stored at controlled temperature and humidity (preferably in the primary packaging chosen for the product), removed at set timepoints, and measured for specific properties. Typically, the drug and related substances are assayed to ensure no degradation. Drug release, physical properties, and appearance are also measured. For GLP toxicology and GMP human clinical trials, a stability study would be conducted using devices made for the study to demonstrate that all devices had comparable properties no matter what point in the study they were used.

The Regulatory Pathway for Combination Products

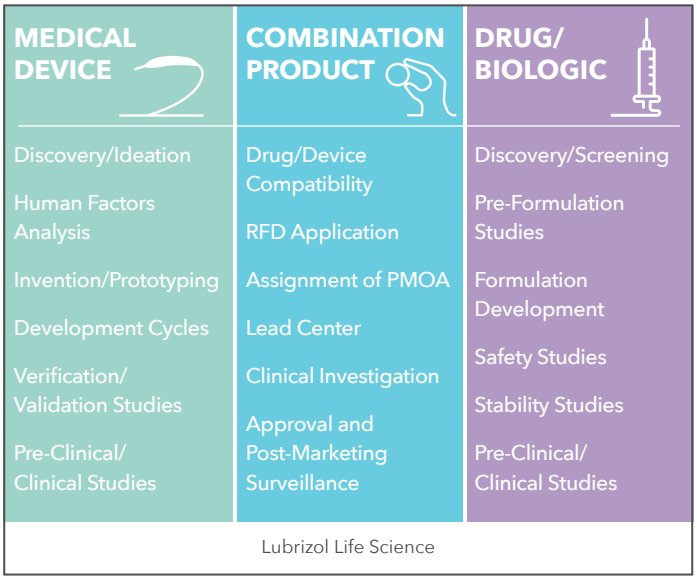
Because of the complex nature of combination products, the FDA Office of Combination Products (OCP) was created to handle their regulatory filings and approval process. The OCP helps determine the regulatory pathway for combination products, ultimately deciding who will be evaluating the product and what the application process looks like. After formulation and pre-clinical testing of a combination product is complete, the device developer submits a Request for Designation (RFD) to the OCP. The RFD is a document that outlines key product characteristics including composition, pre-clinical study results, and proposed indications. However, the most critical piece of the RFD is the identification of the **primary mode of action (PMOA)**. The PMOA is used by the OCP to classify combination products and assign the appropriate lead review center for the approval process. There are three review centers with different specialties—drugs (CDER), devices (CDRH), and biologics (CBER). Based on the PMOA in the RFD as well as their own review process, the OCP assigns a lead review center that oversees the regulatory pathway and determines the type of investigational application that is required **(Figure 4)**. In cases where the PMOA is unclear

The Regulatory Pathway for Combination Products (continued)

or a device has no clear precedent, the OCP uses an algorithm to determine the PMOA. The algorithm first takes into consideration consistency—assigning the lead center based on previous rulings with similar safety/efficacy considerations. If this does not apply, then the primary safety/effectiveness questions are determined and the lead center with the most expertise in that area is assigned.

If the OCP classifies a combination product as a medical device, the device developer gets to operate within the familiar investigational device exemption (IDE) framework. However, classification as a drug or biologic requires additional expertise in the investigational new drug application (IND) process, including management of phase I-III clinical trials. Regardless of which lead center is assigned, all three centers are likely to be involved in the approval process through consultations and/or collaborations. Combination product developers should expect to come under scrutiny from multiple FDA agencies as they proceed through the product approval process.

Figure 4: Combination Product Approval Process



Conclusion

The addition of a drug to a medical device can greatly enhance the safety and efficacy of products, providing differentiated product performance. A wide range of combination products have been commercialized and continue to be developed as medical device companies seek ways to improve their product lines. Combination products present unique development and regulatory challenges, from determining how to incorporate a drug into a device to interacting with the Office of Combination Products. Any successful combination product development requires an understanding of both the drug and device sides of the equation. Using an experienced development partner can mitigate much of the risk by closing knowledge gaps and shortening the time between developmental inflection points.

As a growing number of medical devices make the leap to combination products, the benefits of drug inclusion become more apparent. Drugs have allowed devices to last longer in the body, perform therapeutic actions more effectively, and mitigate unwanted effects. As long as drugs continue to improve the safety and efficacy of both existing and novel medical devices, combination products will remain an area of significant growth.

References

1. SO 10993-1, 3rd Edition 2003-08-01 *"Biological Evaluation of Medical Devices"- Part 1: Evaluation and Testing*

2. http://www.fda.gov/CombinationProducts/AboutCombinationProducts/

3. https://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm

LUBRIZOL LIFE SCIENCE
9911 Brecksville Road
Cleveland, OH 44141-3201 USA

For more information, visit lubrizolcdmo.com
or call us toll free at +1 610-861-4701