Device Development for Pharmaceutical and Biologic Combo Products

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Combination products are defined as therapeutics combining two or more products (drug/device, biologics/device, biologics/drugs or drug/device/biologics), regulated and sold as a single unit. As these pharmaceutical and biological therapies and treatments have evolved, so has the need to develop appropriate delivery mechanisms for these applications. When developing a combination product, there are many things that need to be considered – the critical relationships between device development and the pharmaceutical or biologic, early establishment of regulatory and clinical strategies, understanding 'user' needs, determining product requirements, as well as, device manufacturing variation.

Development Strategy and Scaling

Engaging in an efficient combo product development process begins with understanding your regulatory and clinical strategies. Creating these strategies, as early as possible, will help ensure the device development is well aligned with the pharmaceutical (drug) or biologic development and applicable regulatory requirements. In addition, having these strategies in place will reduce time to market.

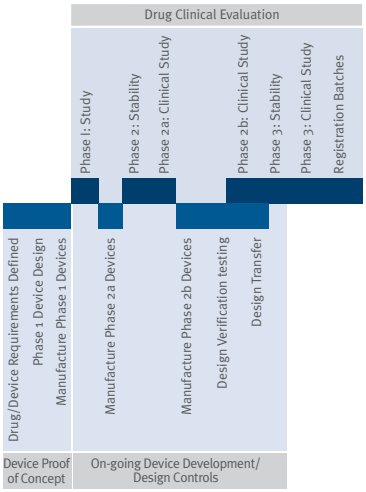
An integrated regulatory/clinical strategy between the client and CMO/supplier contributes significantly to de-risking the product in the early stage of development. In addition, having such a strategy reduces the number of questions that come back from the reviewing agency.

Regulatory Strategy

In combination products, regulatory submission involves not only fulfilling drug/biologic requirements, but also a scaled version of the device-design history file. The depth and breadth of device development documentation can vary significantly based on the lead regulatory agency reviewing the documentation (device – CDRH, drug – CDER, or biologic – CBER); the agency is assigned based on the product's primary mode of action (PMOA). Although there could be multiple modes of action, designating the one with the simplest form of intended use as the PMOA is the key to submission expediency. Accordingly, there are two questions to consider when developing a combination product.

What is the PMOA of a combination product?

The PMOA is the main therapeutic component in a combination product that zeroes in on the product's intended use. For example, in a drug eluting stent used for opening diseased arteries, the PMOA is the device's ability to open the artery. The drug provides a secondary PMOA of preventing restenosis and inflammation as an "aid." In this example, the product will most likely be submitted through the FDA's Center for Devices and Radiological Health (CDRH) which approves and clears medical devices. Conversely, if the PMOA is considered linked to a drug component of a drug/device product, for example, the Center for Drug Evaluation and Research (CDER) – which normally processes new drug applications – would be the lead FDA center. The assigned reviewing agency may or may not be the actual agency involved in cGMP/PAI inspections for the registered facilities. It is important to know, however, that the lead agency will usually outsource review of the other constituent part to its counterpart(s).



The clinical strategy helps establish the relationship between device development and clinical milestones.

Lastly, it is incumbent upon the sponsor to define the PMOA. Should a company struggle with determining the PMOA, they may choose to submit a request for designation (RFD), which enables the FDA to give a binding ruling. If the PMOA is not clear, then the agency will use an established algorithm to categorize the device for PMOA.

What marketing submissions and applications will be required for a combination product?
Depending on the PMOA and the lead FDA center, a manufacturer may be required to undergo clinical trials using one or more of the following – investigational device exemption (IDE) for a device, and investigational new drug (IND) or new drug application (NDA) for a drug. Determining the submission pathway is essential to understanding the clinical trial strategy. Consequently, that knowledge will be important in identifying the device development schedule and level of product robustness necessary to be met before submission can occur.

Clinical Strategy

The clinical strategy helps establish critical milestones for device development. Critical milestones may include things such as when feasibility prototypes or breadboard-level electronics and software development are needed. Those milestones continue all the way through the process to when design verification testing should be completed and commercial equivalent product needs to be available. Early clinical studies, for example, may be conducted with prototype devices that produce the essential core device technology, but do not require the device to be in its final commercial configuration. There is, however, a point at which the device needs to be "production-like" and manufactured under full cGMPs, verified against the design input requirements and validated to show it meets its intended use and needs. That's when, again, it can be very valuable to have an integrated regulatory/clinical strategy between the client and CMO/supplier.

It is imperative the device development team understand the critical drug development milestones so that adequate resources are applied and it can be determined if the device will achieve the performance and repeatability levels needed to conduct effective drug development. Understanding the clinical schedule early in the process helps to ensure the most efficient device development approach is considered by scaling the development strategy appropriately.

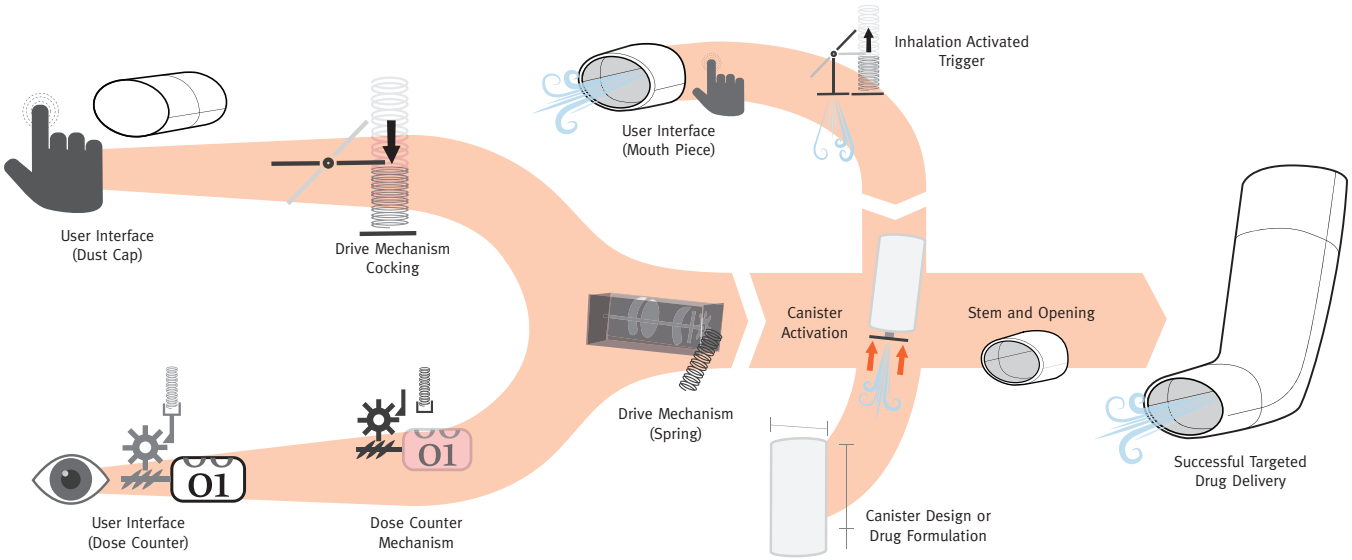
It's also important to consider where the studies will take place. For instance, it tends to be easier to enroll patients and less expensive to conduct studies outside of the U.S. However, the FDA may be less apt to accept the clinical data from such studies due to confidence with the sponsor's clinical data study plan, and data integrity itself. With the release of the 2015 guidance on this topic, though, firms now have clearer guidelines and a better path to acceptance.

Understanding Product Needs

Defining the needs of the user, business, or stakeholder is fundamental to developing a product that will be successful. To satisfy both user and stakeholder needs, the product must be:

- Useful – meet a specific need
- Usable – easy to understand and manipulate
- Desirable – appealing to the intended user so it will be adopted into their daily use
- Manufacturable – the process output is true to the actual value or target desired, but is also repeatable

An integrated product development process that combines human-centered design principles with a solid design for manufacturing philosophy dramatically improves the probability of success and speed to market. Also, appropriate levels of design research are needed in order to fully understand user needs.



To ensure a combination product will perform as intended, the multiple subsystems need to be well defined and understood.

Product Requirements

The user and stakeholder needs identified during device development are then translated into design input requirements (product requirements) – written to an engineering level of detail – and ultimately into manufacturing specifications. Combination products, by nature, consist of multiple subsystems that need to be well defined and understood to ensure the product will perform as intended. When software and electronics are an integral part of the drug delivery device, an additional layer of development complexity exists. While some requirements can be looked at independently, a set of requirements needs to be developed for the integration of the drug and device together with additional emphasis on the ways each constituent part can adversely affect the other.

Once the Target Product Profile (TPP) of the drug substance has been established, relating this to the materials science aspects of device development is key for things such as stability, toxicity, and ADME studies. One potential way of defining this relationship more clearly is in the early stages of development, through the use of Quality By Design (QbD). QbD (drug standpoint), and proof of concept (device) are not mutually exclusive. Through the development of a design space, QbD helps establish the target product profile (TPP) of the drug substance. But the design space for the TPP could be impacted by the properties of materials (drug delivery device) where product contact is made. This potential interaction over time (stability) can possibly alter the efficacy of the drug, sterility, etc., which in turn lowers the efficaciousness and effectiveness of the drug product for therapeutic effect.

Drug Performance

Requirements that focus on the drug alone typically describe how the molecule and formulation need to be configured such that the drug will have its desired affect once it is interacting with the patient. Those requirements often include pharmokinetics, pharmodyanmics and other pharmacological performance definitions.

Device Performance

Device-specific requirements typically describe how the device will interact with the user and how the drug will be readied for delivery. It is worth noting that human factors engineering, design research and industrial design (collectively known as human-centered design) all have a significant role in establishing these device requirements. How the device is used is critical to ensuring the drug is delivered as intended. Any combination product should be easy to use, and during the development process, the appropriate levels of user risk should be assessed. Formal usability studies conducted early in the development process should inform the device design as much as the technical performance studies.

Integration of the Drug and Device

Developing the requirements for where the device impacts drug performance is the most challenging part of this process. A strong partnership between the drug development and device development teams is essential to success, along with an understanding of what each group needs, which often means some level of bilateral education. Device development companies need to understand the mechanics of drug dispersion (e.g. aerosol, transdermal, subcutaneous) so they can identify key device features that may impact drug delivery. Similarly, drug development companies need to understand the nature of device manufacturing and variation as well as pay close attention to the material selection as it could impact drug delivery and drug performance.

Both groups need to also understand the iterative nature of device development and clinical nature of drug development, so that these critical interfaces can be identified, quantified and stabilized as early as possible in order to generate robust clinical data. The following are examples of different drug and device interfaces and how requirements may be generated by both groups.

Container Closure System

Devices are often considered a part of or the entirety of a container closure system (CCS). Per FDA Guidance for Industry-Container Closure Systems for Packaging Human Drugs and Biologics, "A container closure system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product." This critical distinction is important as the vials, ampules, bottles or molded components that a company may use to house a drug must be tested in conjunction with the drug and be considered a "whole" throughout the product development process.

Drug product integrity and effectiveness are additional important aspects for why CCSs need to be thoroughly tested against edge-of-failure conditions. Any potential breach of a CCS for a sterile product, parenteral, or injectable could introduce byproducts, toxins, impurities, or other foreign materials that could impact the drug product stability profile. In turn, the drug product could be less effective for the targeted disease state, adverse reactions could manifest due to the foreign materials or degraded product, or a combination of these two could happen. The CCS must be designed to allow for the integrity of the product all the way through the supply chain until the end of expiration.

A liquid vial and plunger in a spring-loaded syringe is a classic example of how the container closure system can impact product performance. The drug development team may specify the vial that will be used and how much time is allowed to deliver the drug, while the device development team must characterize the amount of force needed to push the plunger to extrude the drug through a needle of a certain diameter in a set amount of time.

Another example is a blister strip for a dry powder inhaler (DPI). The drug development team may specify the materials to be used in the blister strip as well as the bond strength and thickness of the layers, while the device development team must characterize the peeling geometry, angle, force and rate needed to ensure that the blister strip is peeled appropriately on each dose.

Formulation

The drug formulation may impact how the drug moves, interacts with, and is delivered through the device. Some formulations may be sensitive to molecular shearing and require slow, laminar delivery through the device, while other formulations (especially inhalers) may have high static charges that attract to plastic, requiring device materials that dissipate static electricity. In addition, some formulations need to be developed with the intent of the device and sterilization method in mind. Some substances, especially peptides, are extremely heat labile, where protein molecules can break apart, degrade, or get altered into a new form with high impurity profiles that can become toxic if administered.

Device

The device itself can have a significant impact on product performance. Consider first that the device is the primary user interface and so, in effect, controls the user portion of

how the drug is delivered. Again, the impact of human factors engineering and industrial design should heavily influence this portion of device development. Secondly, the device is the means by which the drug is pressed, extruded, inhaled or otherwise, "delivered" to the patient. Requirements that establish the position of the drug – prior to delivery, the delivery path, the method of delivery activation – all impact how much (volume) and at what rate (time) the drug enters the patient.

Device Manufacturing Variation

It is common knowledge that device A is not the same as device B when viewed on a micro-scale. This is where specifications come into play. A device will be manufactured to specifications that most commonly control the size of a feature and/or its position relative to another feature. This is very important to understand, especially when coming from a pharmaceutical or biological background. Since a device is made up of multiple components, each of which has multiple features and every feature requiring some level of manufacturing tolerance, there is a lot of room for device performance variation.

Specifications are derived from requirements, however, specifications are not requirements themselves. If the requirement of a spring-loaded syringe is to deliver the drug within 1-2 seconds of actuation, the device team must create manufacturing specifications and tolerances that will create this result.

In the following example, the drug viscosity needs a specification in order for this system to meet the requirement. Similarly, different features of this simple springloaded syringe have specifications and tolerances applied to them in order to meet this requirement.

- Syringe inner diameter: 1.00 mm +/-0.05 mm
- Plunger outer diameter: 1.10 mm +/- 0.05 mm
- Needle inner diameter: 0.3 mm +/-0.01 mm
- Drug viscosity: XXXX +/- XXXX
- Spring rate: XXXX +/- XXXX

The manufacturer of the syringe is responsible for ensuring the syringes meet the specification of 1.00 mm +/-0.05 mm. The plunger manufacturer is responsible for ensuring the plunger meets the 1.10 mm +/- 0.05 mm specification, and so on.

Similarly, when software and electronics are involved, complex algorithms may be developed early on to perform a function using one, two, or three prototype devices. But during development, the software and electronics team need to understand the manufacturer's tolerances for sensors, processors and the like, as well as for any molded or fabricated components. Software development may require ongoing development as additional units are produced and additional component variation begins to enter the picture.

It's important not to overlook the regulatory expectations regarding configuration management for medical devices with software platforms. Configuration management ensures that as-built configurations conform to their documented requirements and are

built to the correct versions of those documents. A configuration management capability model should be established from the early stages of device development through to the end of life.

The Right Tolerances for Different Features

This is where design for manufacturing comes into play. Early involvement from the manufacturing partner during the design process, or partnering with a device development company that truly understands manufacturing, ensures early concepts aren't reliant on component features that can't be produced in higher volumes. When making a single component or a low volume of components, often smaller tolerances can be achieved. However, in higher volumes, more variation is inserted into the manufacturing process, including but not limited to, multiple cavities for tools, different operators, and multiple assembly lines.

Characterization Testing

At this point, process optimization begins prior to transfer. Once the initial specifications and tolerances have been established (with manufacturing input), parts can be prototyped at their specification limits in order to determine if these tolerances are appropriate. This is often referred to as characterization testing, where performance is being characterized against a range of feature sizes. This testing helps provide confidence that the manufacturing specifications and tolerances will result in a product that will meet requirements when manufactured at commercial volumes. Prototyping features at their size limits also allows for refinement of software and complex algorithms that may be either interfacing with the user or responsible for controlling some aspect of drug delivery.

Integrating characterization testing into the development process is key to understanding drug and device interactions that will to be observed in full-scale manufacturing. As part of the process, this activity can be planned for and executed as part of the strategy rather than reacting to and trying to troubleshoot errors and defects once component variation starts to enter the process.

Summary

There are many things to consider when developing a combination product. But there is greater opportunity for success with early design involvement and careful consideration of the knowledge needs of everyone involved. Before you begin development of your combination product, consider the following:

- Early establishment of the regulatory and clinical strategy will help ensure device development is scaled appropriately to meet regulatory requirements and is in-line with the clinical milestones.
- User and stakeholder needs are the foundation of product development and will help to ensure the right product is developed.
- Product requirements ensure the product was built right and need to be determined for:

  - Drug performance
  - Device performance
  - Drug/device integration performance
- Container closure system
- Formulation
- Device
- Device manufacturing variation needs to be understood and designed for. Characterization testing should be conducted to understand the impact of manufacturing specifications and tolerances on product performance.

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