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Design control considerations for biologic-device combination products

Dave Anderson, Roger Liu, J. Anand Subramony, Jon Cammack *

AstraZeneca/MedImmune, One MedImmune Way, Gaithersburg, MD 20878, United States

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ABSTRACT

Combination products are therapeutic and diagnostic medical products that combine drugs, devices, and/or biological products with one another. Historically, biologics development involved identifying efficacious doses administered to patients intravenously or perhaps by a syringe. Until fairly recently, there has been limited focus on developing an accompanying medical device, such as a prefilled syringe or auto-injector, to enable easy and more efficient delivery. For the last several years, and looking forward, where there may be little to distinguish biologics medicines with relatively similar efficacy profiles, the biotechnology market is beginning to differentiate products by patient-focused, biologic-device based combination products. As innovative as biologic-device combination products are, they can pose considerable development, regulatory, and commercialization challenges due to unique physicochemical properties and special clinical considerations (e.g., dosing volumes, frequency, co-medications, etc.) of the biologic medicine.

A biologic-device combination product is a marriage between two partners with "cultural differences," so to speak. There are clear differences in the development, review, and commercialization processes of the biologic and the device. When these two cultures come together in a combination product, developers and reviewers must find ways to address the design controls and risk management processes of both the biologic and device, and knit them into a single entity with supporting product approval documentation.

Moreover, digital medicine and connected health trends are pushing the boundaries of combination product development and regulations even further. Despite an admirable cooperation between industry and FDA in recent years, unique product configurations and design features have resulted in review challenges. These challenges have prompted agency reviewers to modernize consultation processes, while at the same time, promoting development of innovative, safe and effective combination products. It remains the manufacturer's responsibility to comply with the relevant requirements and regulations, and develop good business practices that clearly describe how these practices comply with FDA's final rule (21 CFR Part 4) and aligns with the company's already established quality system.

Contents

1. Blending two different cultures

Combination products in general are defined and classified by their primary mode of action (PMOA). The PMOA in a biologic combination product derives from the biologic medicine, with the device enabling delivery in ways that are ever more focused on ease and efficiency from a patient perspective. Biologics development has traditionally attempted to rapidly identify a promising new molecule or mechanism of action, accelerate the molecule through pre-clinical trials governed by GLP regulations, and ramp up manufacturing to make enough GMP-produced medicine that is then used to support clinical trials

* Corresponding author.
E-mail address: cammackj@medimmune.com (J. Cammack).

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governed by GCP regulations. For biologics, outcomes in early clinical work largely define how the final commercial product will be prescribed and used. Where there has been a desire to couple the biologic medicine with a delivery device, the approach in early development has been to use a simple delivery means, such as vial and syringe, until a dose and frequency is identified. Then, after these clinical administration parameters have been established, manufacturers develop approaches to combine the medicine with a medical device uniquely suited to the biologics physicochemical properties and clinical administration requirements that satisfy patient and end user needs.

Medical device development, however, has occurred using a different paradigm: namely, identifying the needs of an end user or users (i.e., clinician and/or patient), and then designing and manufacturing the device to meet those specific design and performance requirements. This development process is regulated by Design Controls (21 CFR 820.30 and ISO 13485) and traditionally has been described through the "waterfall model".[1] Accordingly, when a biologic developer wants to combine its medicine with a specific delivery device (e.g., a syringe, auto-injectors, wearable patches, micro-needles, etc.), design control regulations now applicable for these kinds of medical products must be considered.

When FDA issued its Current Good Manufacturing Practices (CGMP)[2] regulation for combination products in 2013, biologic manufacturers were tasked with design control elements that historically were absent in their product development (but as described above, had been present for many years in device development). FDA has said that constituent parts of a combination product retain their regulatory status (as a biologic or device, for example) after they are combined. Accordingly, the CGMP requirements that apply to each of the constituent parts continue to apply when they are combined to make combination products.

2. Design controls focus on end users

Adapting a biologic to a combination product with a delivery device requires a focus on users of the product. However, user focus is often complex with regard to understanding all "end users". Depending on the commercial potential for the biologic, users can vary from pharmacists to health care practitioners (HCPs) to patients themselves. Establishing user requirements can prove difficult with the variation in users; HCPs are often experienced in giving injections and handling temperature sensitive products, though conversely, end-user patients can be naïve when handling needles and possibly unaware of the temperature sensitivity of a biologic. Identifying the target user profile and carrying out human factor studies with the user population is an important step in developing instructions-for-use that ensure safe and appropriate usage. Additionally, a biologic manufacturer may consider multiple devices to satisfy multiple sets of user needs. In using multiple devices, complex supply chain requirements of multiple devices require special attention. Also of note, a manufacturer must account for the cost of goods and resources needed to conduct the activities that demonstrate compliance to the development regulations for each biologic-device combination.

Traditional development of a biologic has been an iterative process of trying things that worked in the past, testing and analyzing the results, and selecting the most favorable option(s) to move forward. With the publication of ICH Q8, an alternative approach – Quality by Design (QbD) – was introduced and refocuses development on the end result – specifically, "working backwards" to plan targeted development activities. The QbD approach often defines Critical Quality Attributes (CQA) of the drug product through risk assessment (based on ICH Q9 methodologies), such as protein aggregates. This development approach allows process developers to focus their research and process refinement on manufacturing steps that might result in, or increase, such protein aggregates. Integrating the necessary analyses for the biologic development with the device and combination product development steps continues to be complex process, although greater clarity has emerged in recent years, as discussed in the risk management section below.

3. Specific design control considerations

Development of a biologic-device combination product starts with the end user, and cascades desired attributes through inputs to a design process. For example, an end user may need to inject a solution that minimizes the amount of biologic-related particles, or self-inject medicine with minimal or no supervision. The design process is often iterative, refining specifics (e.g., silicone oil amounts on the inside of a prefilled syringe) based on lab tests. Once design is complete, a set of design outputs is then tested against the input criteria and the product is ultimately validated against the original user needs. The design process often employs risk assessment methodologies laid out in ISO 14971.[3]

Design control activities (and related documentation) for a combination product that incorporates a well characterized biologic into, for example, a conventional prefilled syringe will involve different considerations than development of a combination product that incorporates a novel biologic or novel formulation to be used with a unique delivery system.

An overview of design controls are provided below, and are a system of well-defined and ordered steps:

- As indicated, design development first needs to be planned, and the plan documented.
- Design Inputs include the needs of the users and the intended use of the combination product that are translated into measurable attributes, a requirements document, and risk analysis.
- Necessary Design Outputs (specifications, labeling, drawings, procedures, and risk controls) are produced as a result of the design and development activities.
- As Design Outputs are finalized, Design Verification ensures that the requirements of the design are adequately addressed.
- Pursuant to design verification, Design Transfer ensures that the Design Outputs (i.e., final device and process specifications) are transferred to manufacturing, service, post-launch monitoring systems, and suppliers.
- Traditionally, after transfer has occurred from design to manufacturing, product equivalent units are built for Design Verification (bench-top and animal testing) and Design Validation (human or simulated use) testing.

Design Verification and Validation (V&V) ensures user needs and intended uses have been met by the product design and, like Design Controls, V&V is an additional system of well-defined and ordered requirements and steps. Appropriate statistical sample sizes must be factored into the design of Design Verification, Validation and Process Validation studies. Valid Statistical Techniques rely on stable manufacturing processes and normality assumption. Design Validation should follow completion of successful design verification.

There are special considerations included in the Design Verification phase:

- Stability: Process Validation requirements should be addressed *prior to* producing stability units.
- Expiration dating: careful consideration should be given to the start of expiration dating studies given the combination product type. For example, a pre-filled syringe may require both component and finished product expiry dating when multiple sites are involved in

[1] Design Control Guidance for Medical Device Manufacturers. FDA, March 11, 1997.
[2] Effective July 22, 2013 (21 CFR Part 4).
[3] EN ISO 14971:2012 Application of risk Management to Medical Devices.