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A Risk-Based Approach to the Development of an Injectable Combination Product

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Executive Summary

Drug-device combination products (DDCPs) offer many advantages for patients but are complex and challenging to develop. This white paper examines how to establish a holistic approach to DDCP development and how to assess and manage risk throughout the development and approval process.

A Risk-Based Approach to the Development of an Injectable Combination Product

Drug-device combination products (DDCPs), such as injectables, can consist of a biological product and a device, a drug and a biological product, or a drug, device, and a biological product or simply a drug and a device. DDCPs leverage new technologies that provide many advantages for patients, such as self-administration conveniences, safety and, for payers, improved adherence.

Injectables have experienced significant market growth, with prefilled syringes representing 32 percent of the global injectables market in 2020 and an estimated compound annual growth rate of 14.1 percent reported from 2016 to 2021.[1] On-Body Delivery Systems and other injectables designed to be self-administered are driving this growth. Figure 1 shows the change in FDA approvals of DDCPs over time.

Patient preference studies have shown that the use of subcutaneous delivery alternatives (via a single-use injection device or hand-held syringe)[3] is significantly preferred over standard IV administration. In one study of 488 patients, 89 percent of patients were shown to prefer a subcutaneous system.[3] These systems help to simplify the administration aspects of drug delivery.

The complexities inherent to DDCPs, however, pose certain challenges to the development process, both from a technical perspective and a regulatory one. For example, new approaches have led to the increasing need to deliver higher-than-traditional volumes of biopharmaceutical-based products, which can have higher viscosity, increasing the delivery challenges. Because these products combine multiple chemical and physical elements, it is necessary to align the unique drug/biologic and device regulatory pathways for efficient development and effective commercialization.

This white paper will examine how to establish a holistic approach to DDCP development and how to assess and manage risk throughout the development and approval process.

FIG 1

The Increase in Combination Products Means More Opportunities for Device Innovation

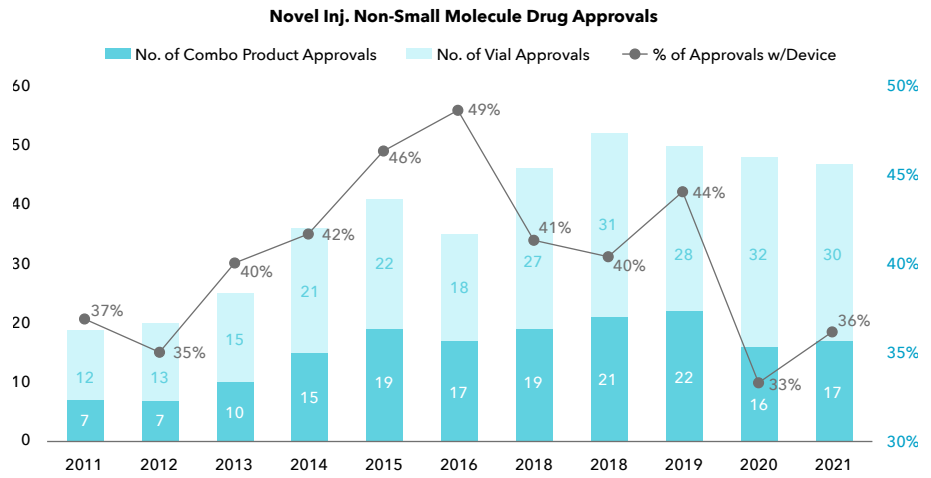

Figure 1. Source: Food and Drug Administration. Novel Drug Approvals Tracking 2022.

INTEGRATED DEVELOPMENT – A HOLISTIC APPROACH

When developing injectable combination products, it is essential to integrate the development of the drug and the device as much as possible. This means bringing together the science of the drug and the engineering of the device from the start.

paradigm, together with device design controls, are the foundation of DDCP development. The QbD principles are intended to ensure efficient drug development and the manufacturing of a device that protects product quality and performs to specifications. In turn, one needs to investigate the safety

FIG 2

Drug-device Integrated Development

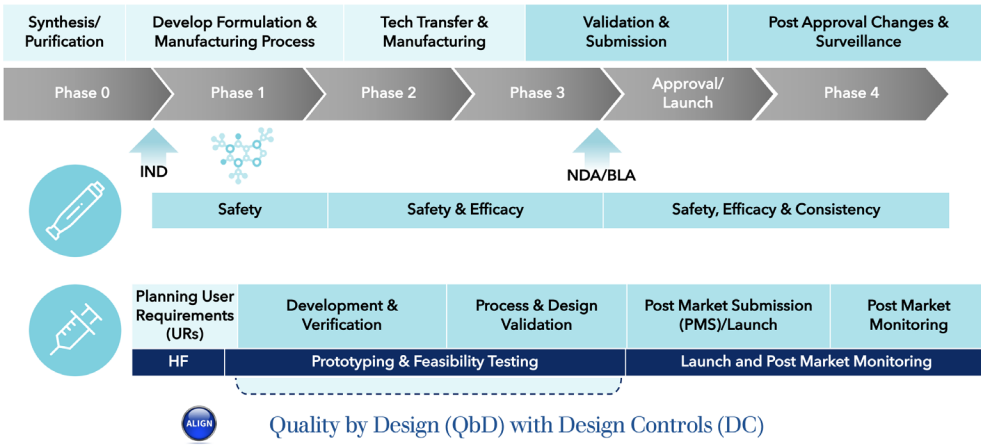

Figure 2 shows a strategy for integrating drug-device development, meeting the requirements for establishing safety, efficacy, and consistency, and how this approach aligns aspects of Quality by Design (QbD) and Design Controls, as defined by the United States Food and Drug Administration (FDA). Introduced by the FDA in 2000, QbD is a systematic approach to drug development with the goal of building quality into the product with the patient in mind. The drug and biologic QbD

and compatibility of the device with the drug product and the patient. This can be accomplished by understanding and providing various supporting data, and must:

- Consider all materials in contact with the drug and patient
- Demonstrate physical and chemical compatibility with both:
  - *Studies that assess chemical characteristics, such as extractables and leachables*
  - *Interaction studies that access physical properties, such as surface absorption and system performance*

Human Factors Considerations

DDCPs are unique. Their safety profile and product efficacy depend on user interaction. Therefore, human factors are essential to development. Human factor considerations may include:

- Patient population, who are the potential users?
- Adherence or safety and effectiveness to administer the drug
- Is it emergency vs routine use?
- Is it in a clinic vs homecare?
- Aesthetics and usability: is packaging a factor in access?

Quality System Alignment

Developers should aim to address the drug regulations and device regulations together from the beginning of development. For example, in the US, FDA drug regulations are in the Code of Federal Regulations (CFR) Parts 210/211, and the device regulations are in the CFR, Parts 800-898 (Subchapter H). However, other global authorities have similar but different combination product requirements; understanding these expectations and aligning early with your device partners is vital.

In addition, it's important to understand the relationship between the materials and the components into which they are formed, and then the complete system that these components create. The final system and materials must be appropriate for the specific intended application.

CONSIDERATION IN THE DEVELOPMENT PROCESS

Start with the final product in mind. Consider the example of a prefilled syringe in an auto-injector. In this case, the developer is bringing together the target product profile for the drug and the user requirements for the device to create the combined delivery system. Figure 3 illustrates the requirements and considerations for this type of system, including aspects of the drug and the delivery system and the ability of the system to perform appropriately.

FIG 3

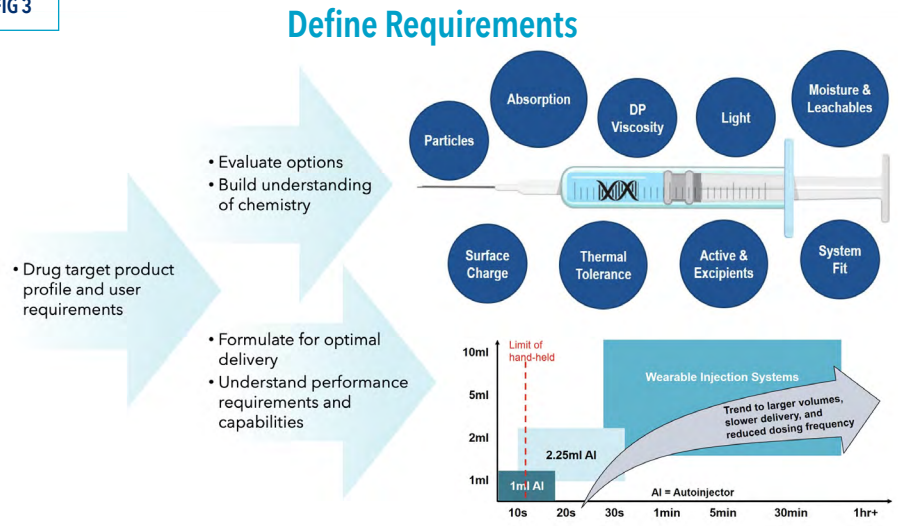

Figure 3. Source: DeGrazio, F. (2019, April). Enablement of Patient Centric Solutions Through Integrating Drug – Device Development [Conference presentation]. 4th PQRI/FDA Conference on Advancing Product Quality, Drug Development and Manufacturing, Rockville, MD. https://pqri.org/4th-pqri-fda-conference-on-advancing-product-quality-posters/

Managing Risk During DDCP Development

To mitigate risks, it is important to first understand the potential risks associated with each individual component. In the example of a prefilled syringe in an auto-injector, the following risk factors to maintain consistent glide force need to be considered: the environment, the plungers, the syringe barrel, the auto-injector sub-assembly, the chemistry of the drug and the fill-finish process. As shown in Figure 4, an Ishikawa diagram illustrates the potential factors that could affect glide force.

The use of this Ishikawa hazard assessment diagram, along with a thorough understanding of the materials and attributes of each component in the system, can help identify the causes and effects of potential risks. This knowledge supports product risk assessments and drives mitigation efforts. Product risk assessment, in turn, identifies potential hazards of the product that could harm the patient.

FIG 4

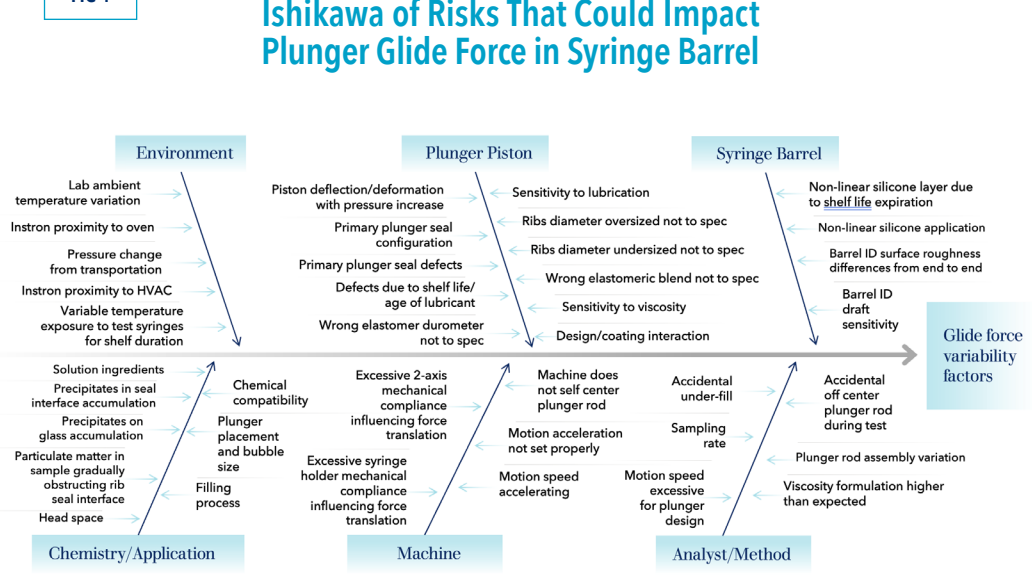

Figure 4. Source: DeGrazio, F., & Paskiet, D. (2020). Injectable Combination Product Development: Facilitating Risk-Based Assessments for Efficiency and Patient Centric Outcomes. Journal of Pharmaceutical Sciences, 109(7), 2101–2115. https://doi.org/10.1016/j.xphs.2020.03.020

Identifying the Critical Quality Attributes (CQA)

Every drug and therapeutic application has unique requirements for the delivery device. For example, a manual, prefilled syringe application with a rigid needle shield could be compared to an auto-injector application. The removal force needed to access the product, whether through a rigid needle shield or the cap on an auto-injector, is just one of the critical factors that should be considered.

A risk assessment is also necessary to examine the performance

of the product and the effect on the product's CQAs. For example, this would determine whether a product delivers the drug in the appropriate time frame. For a prefilled syringe/ auto-injector to deliver a dose within one to two seconds at the appropriate depth, a number of risk factors must be examined. This includes considering risk and variation in injection volume, speed and depth, and plunger force and friction. These factors and their associated effects and consequences, in case of failure that impacts the quality of the drug product, provide a perspective on the overall risk.

Identifying Essential Performance Requirements (EPRs)

EPRs are performance attributes responsible for the clinical performance of the device at the point of use. That is, EPRs represent what is most important for clinical relevance – assuring that the medication is safe and stable. EPRs are a subset of all design inputs. Figure 5 illustrates attributes that may or may not be considered EPRs.

In the example of a prefilled syringe in an auto-injector, essential functions for effective dose delivery include dose volume, dose time and needle extension. Essential functions for safety are needle cover removal force and sharps protection.

Defining Established Conditions

Established conditions[4] form part of the product's regulatory application, and they are legally binding from the FDA's perspective. They include the product's EPR and other information, such as manufacturing sites and processes. Any changes to established conditions must be submitted to the FDA.

FIG 5

What About the Following as EPRs?

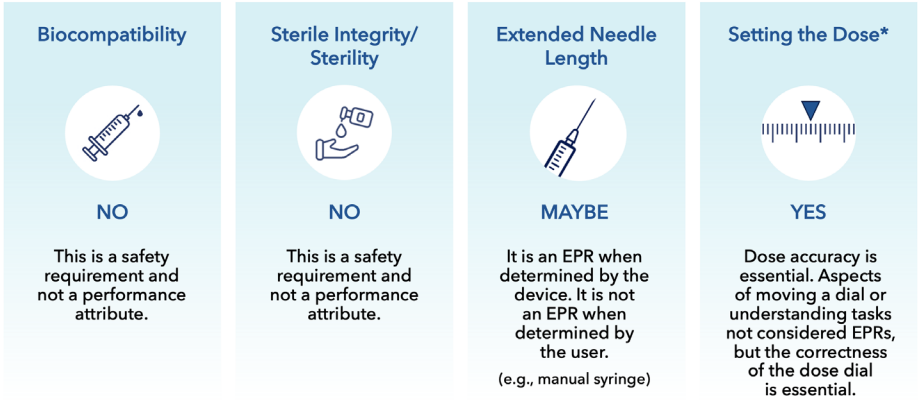

Figure 5. Source: Essential Performance Requirements. (2019, September 13). [Conference Presentation]. Xavier Health Combination Products Meeting.

Testing Strategy

The development process includes human factor testing, as well as establishing and executing a testing strategy. Comprehensive risk assessments drive the testing strategy. This information will inform the development process and increase understanding of the product.

Required testing of DDCPs go beyond the baseline of compendia – i.e., USP <381>, <382> or <660>, <788> as examples. Additional testing may include assessments related to fill-finish, environmental conditioning, and shipping simulation.

Fill-finish tests are important to establish:

- Deliverable volume
- Head space and plunger placement
- Septum/stopper crimping quality
- Tip cap placement and security
- Particle contamination

Environmental conditioning and shipping simulation tests establish:

- Transit distribution cycles and storage
- Performance over time
- Altitude (vacuum/ pressure) simulation

Other examples of testing specific to auto-injector performance may include:

- Force to remove safety cap
- Needle shield removal force
- Activation force of trigger button
- Injection time
- Weight of the drug volume
- Effective length of the needle

Verification vs Validation

Design verification evaluates whether the output meets the input. Design validation examines whether the specifications meet the user needs and intended use(s).

Documents associated with verification and validation include:

- Design verification and validation protocols
- Design verification and validation reports
- Design verification and validation summary report
- Design verification and validation phase review

Control Strategy

The control strategy[4] assures process performance and product quality through understanding and controlling the product and process.

The control strategy includes but is not limited to:

- Material attributes
- Manufacturing process design
- Operations controls – understanding of critical process parameters
- In-process controls
- Product specs/quality control release testing

The development program informs the control strategy. Implementing the control strategy throughout the process is critically important and related documents are included in a product's application. A robust control strategy ensures the final combination product meets acceptable performance levels.

A Feedback-Driven Approach to Risk Assessment

The development process does not flow completely in one direction (see Figure 6). Rather, it is an iterative process, with feedback loops informing adjustments during the lifecycle. New information is generated during the process that can improve and optimize the product to avoid future problems.

Risk assessment is at the center of this process. The steps along the way – from merging the aspects of drug and delivery, acquiring data that are going to meet the evolving global expectations, testing and evaluations – will ultimately provide a realistic picture and rationale for your product.

The eventual "line of sight" technical package that is produced supports not only the choices leading from development to commercialization, but also supports the regulatory approval process.

FIG 6

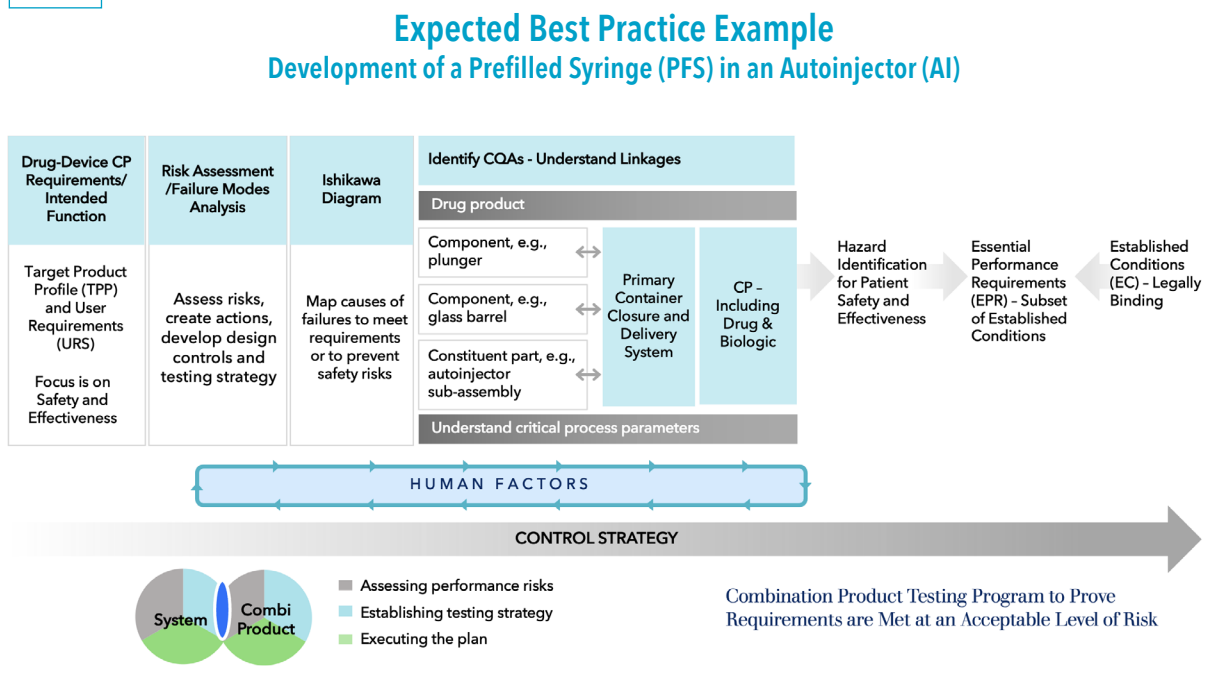

Figure 6. Source: DeGrazio, F., & Paskiet, D. (2020). Injectable Combination Product Development: Facilitating Risk-Based Assessments for Efficiency and Patient Centric Outcomes. Journal of Pharmaceutical Sciences, 109(7), 2101–2115. https://doi.org/10.1016/j.xphs.2020.03.020

WEST FOR DDCP DEVELOPMENT

As the DDCP market expands and brings increased convenience and reduced medical costs to patients, it will be important for drug manufacturers who are preparing to be part of this growth to navigate risk assessment and testing during product development. Doing so efficiently will be critical to competing in the market. As outlined in this white paper, risk assessment and testing during DDCP development build complexities into the process.

West is well-prepared to help companies navigate DDCP development. Among our integrated services and solutions, we offer in-depth knowledge and expertise in designing combination products and packaging components. We also have an extensive understanding of the regulatory expectations and guidance on acquiring appropriate data during drug and device development and testing. We understand how to design an efficient DDCP development process while meeting regulatory requirements.

Our team of specialists works with companies to develop an overall strategy appropriate for their product and helps them with a variety of integrated solutions. We use our extensive knowledge of and experience with the unique challenges of DDCP development to help our customers move products to market faster and more efficiently to improve patient health.

If you would like to learn more about how West is working alongside our customers to Simplify the Journey™ to DDCP development, please contact us or visit our Integrated Solutions Program page on our website.

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