Quality by Design and Design Control Roadmap for Combination Products

West®
By your side
for a healthier world™

Quality by Design and Design Control Roadmap for Combination Products

Ana Ladino

West Pharmaceutical Services, Inc.

ABSTRACT

Quality by Design (QbD) principles help to facilitate design of products and processes that maximize the product's efficacy and safety profile, while enhancing product manufacturability. Its systematic framework begins with predefined objectives, and emphasizes product and process understanding. It really enables manufacturers to focus on what matters the most, Quality should be built in the design, it cannot be tested into products. A proposed roadmap to utilize QbD principles in conjunction with design control requirements (21 CFR 820.30 and ISO 13485) for design and manufacture of drug-device combination products based on sound science and risk management is presented.

QbD and design control requirements start and end with the patient in mind. They provide principles to define the quality target product profile (QTPP), user needs/design inputs, identify the potential critical quality attributes (CQAs) and use risk assessment tools to determine the link between them. The end goal is to develop safe, high-quality products to improve the wellbeing of patients. The proposed roadmap uses drug and device regulatory guidelines and best practices that complement each other to address the complex and evolving combination product development process from concept to commercialization.

QbD AND DESIGN CONTROLS

Essentially, GMPs for drugs and biologics including human cell/tissue products advocate the Quality by Design (QbD) framework that encompasses International Council on Harmonization (ICH) pharmaceutical development, risk management, and pharmaceutical quality systems (PQS) guidelines while devices follow design controls under the quality system requirements (QSR). Design controls are a set of interrelated procedures to be incorporated into the design and development process. The QSR has been harmonized with the international quality management system standard, International Organization for Standardization (ISO) 13485 for medical devices and recognizes ISO 14971 for risk management.

QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." (Ref: ICH Q8 R2, 2009). The QbD/design control strategy should place the patient at the center of its universe to provide safe and effective combination products to the communities and loved ones that we support to improve their health conditions.

The QbD/design control framework should successfully connect risk assessment, design space and control strategy in order to understand the link between the QTPP, user needs, critical quality attributes (CQAs), design inputs, and critical process parameters (CPP) and control them. Figure 1 below describes the road map between the QbD requirements aligned with design controls.

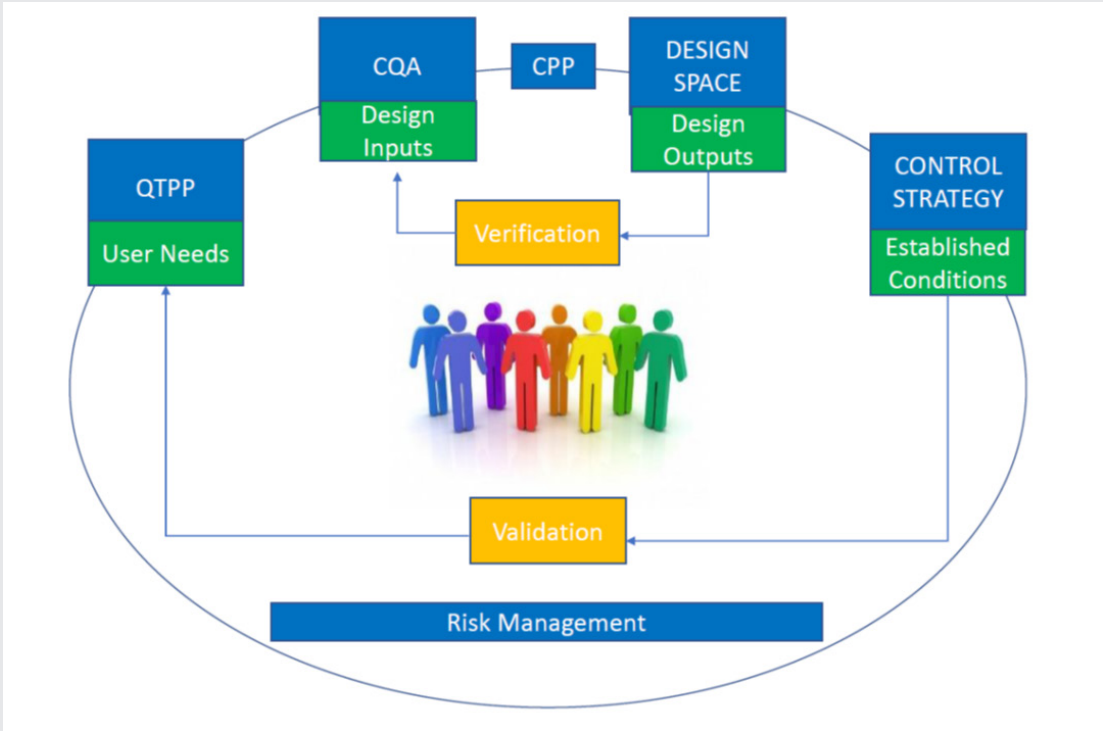

FIGURE 1: QbD and Design Controls Roadmap

It is important to design a product to meet the required claims and be developed based on principles of QbD and design controls. The QTPP and design inputs must be clearly defined to establish meaningful specifications to meet claims based on clinical performance. In addition to properly identifying CQAs, CPP, and design space, ICH Q8 (R2) defines it as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval, control strategy. ICH Q10 describes control strategy as a planned set of controls, derived from current product and process understanding that assures process performance and product quality and the established conditions, Established conditions (ECs) for combination product manufacture and control are legally binding information in the technical dossier or market application. Agreement on ECs and the ability to proactively maintain should help provide a focus on the most critical changes that have the highest opportunity to impact product quality.

The drug product quality and deliverability are essential elements of a combination product development process and the user interface (UI) central to the design of a drug-device combination product. The design of the delivery device relies on human factors (HF) data in many cases to guide reduction of risk for medication errors. The principles of Quality Risk Management described in ICH Q916(p9) will empower proper scientific evidence to support combination product approvals. Although pharmaceutical and device quality systems are distinct, the basic risk concepts are the same. Different systems should not lend themselves to duplicative efforts to meet regulatory requirements. Table 1 below provides a summary of the QbD and design control holistic development.

TABLE 1: Integrated Holistic Development

Drug Development QbD	Device Development – Design Controls
Quality System Framework: ICH Q10 Pharmaceutical Quality System, 21 CFR 211 (Drugs), 21 CFR 600 (Biologics)	21 CFR 820 Quality System Regulations and ISO 13485 Combination Product (CP) :21 CFR Part 4 Final cGMP Rule – Streamline Approach
Development Process: ICH Q8 Pharmaceutical Development	21 CFR 820.30 Design Controls and ISO 13485 (7.3) Design and Development
Risk Evaluation: ICH Q9 Quality Risk Management	ISO 14971 Risk Management – Devices
Master Project Plan	Design and Development plan 21 CFR 820.30(b) ISO 13485 (7.3.2) Design and Development Planning
Voice of the Customer (VOC)/ Target Product Profile (TPP), Technical Requirements, QTPP, CQA	User Needs, Essential Performance Requirements Design Input 21 CFR 820.30 (c), ISO 13485 (7.3.3) Design and Development Inputs
Specifications, Drawings, MBR	Design Outputs 21 CFR 820.30(d) ISO 13485 (7.3.4) Design and Development Output
CMC stage gate reviews	Design Reviews 21 CFR 820.30(e), ISO 13485 (7.3.5) Design and Development Review
Characterization/Suitability	Design Verification 21 CFR 820.30(f), ISO 13485 (7.3.6) Design and Development Verification
Clinical Studies	Design Validation 21 CFR 820.30(g), ISO 13485 (7.3.7) Design and Development Validation
Tech Transfer/MRB	Design Transfer 21 CFR 820.30(h), ISO 13485 (7.3.8) Design and Development Transfer
Change Control	Design Change Control 21 CFR 820.30(i), ISO 13485 (7.3.9) Control of Design and Development Changes
Product Dossier, Dev reports, Drug Development Project Files	Design History File 21 CFR 820.30(j), ISO 13485 (7.3.10) Design and Development Files
Master Batch Records	Device Master Record 21 CFR 820.181
Guidance on Medication Errors	Human Factors IEC 62366-1 Usability Engineering

CASE STUDY: Development Activities for A Drug - Autoinjector Combination Product

This case example is intended to illustrate the impact device components can have on the deliverability of the drug product in relation to patient convenience and comfort. Due to the expansive nature of integrated drug- development, only a few activities are represented. Five of the process steps designated in Figure 2 Expected Practice for Development of a PFS in an AI, are further described for increased understanding.

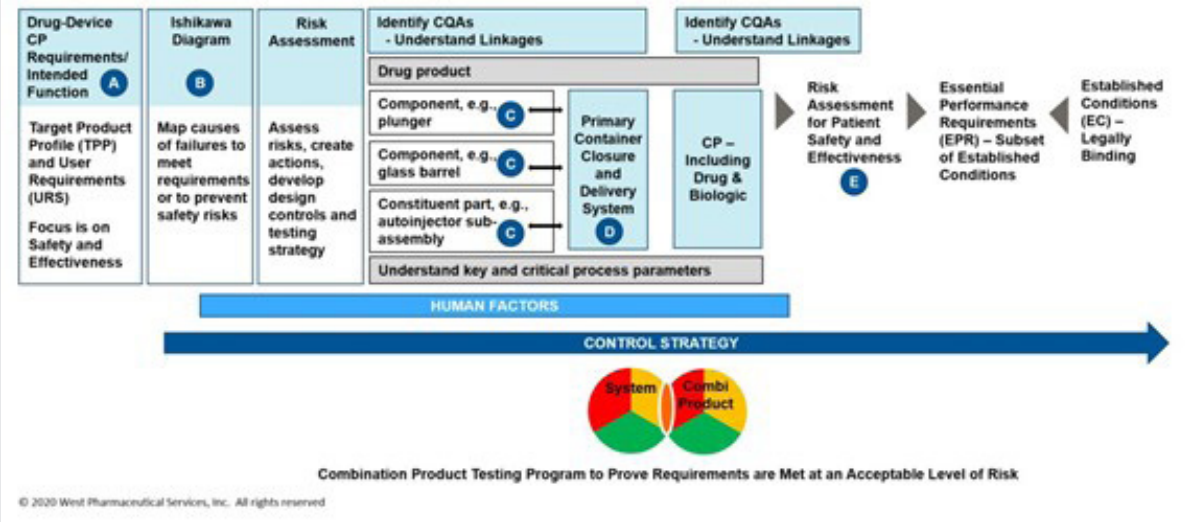

FIGURE 2: Expected Practice for Development of a PFS in an AI

A. Combination Product Requirements: TPP/URS: Development of a drug-device CP starts by defining the end target.

B. Ishikawa Diagram: Map Causes of Failures: Helps identify potential causes of failures in meeting requirements. Figure 3 provides an example of potential risks that can impact the plunger component used in the prefilled syringe that is then assembled into the autoinjector delivery system.

C. Identifying CQAs: Understand Component Linkages to Delivery System: There are many factors related to the syringe that should be characterized. Factors to highlight that could have a direct impact on the example of dose delivery time would be: Glide force, Dead space and Injection force necessary to depress the plunger and eject content

D. Example Data: Interaction of Individual Components on System EPRs: Figure 4 provides an example of how an individual component can have an impact on a function such as delivery time. This chart shows average delivery time of three viscosity solutions over multiple timepoints. The PFS and AI system characterization will guide appropriate combination of components to meet the desired user requirement.

E. Risk Assessment: Patient Safety and Therapeutic Effectiveness: Once the PFS/AI system has been characterized, including special focus on where the components and systems may impact each other, the understanding of risks with the specific drug product must be understood. One common best practice for this is to complete a failure modes and effects analysis for each CQA. For sumatriptan succinate autoinjector case study,80 the key functional attributes for this combination product are identified as: Needle gauge and length, Needle penetration depth, Dispensing time, Dispensed volume and Injection force

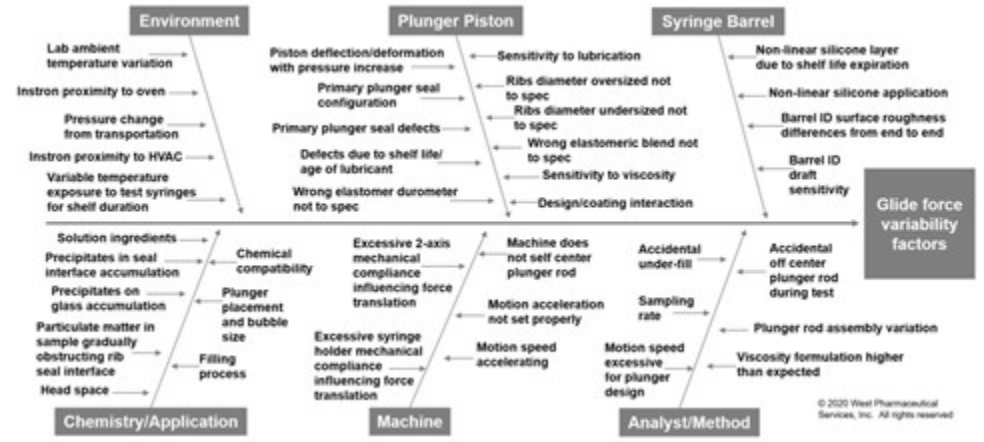

FIGURE 3: Ishikawa Diagram of Risks that Could Impact Plunger Glide Force in Syringe Barrel

Function/URS	Potential Failure Mode(s)	Potential Effect(s) of Failure	S E V	Potential Cause(s)/ Mechanism(s) of Failure	O C C	Current Design Controls	D E T	R P N	Risk Rank	Recommended Action(s)
Within 1.0-2.0 Seconds Deliver 0.9mL +/- 0.1mL Subcutaneously 5mm +/- 1.0mm	Injection Volume too Low <4.5mL	Under Dose	4	Spring Constant vs Plunger Friction Load	3	Low Plunger Force	4	48	Med	Prove spring constant, and total friction forces.
		No Dose	5	Spring Constant vs Plunger Friction Load	3	Spring Constant and Tolerance	4	60	High	Model force required with viscosity range and needle bore tolerance
	Injection Volume too High >5.5mL	Over Dose	4	Excessive fill volume and low headspace	4	Fill Volume and Tolerance	4	64	High	Determine headspace requirement and confirm fill volume tolerace
	Injection Speed too Fast <1.0 Sec	Excessive Pain - premature removal low dose	3	Spring Constant vs System Friction Load vs Drug Viscosity Imbalance	3	Drug Viscosity Proven and Controled	4	36	Med	Determine pain threshold vs injection rate
		Leak at Injection Site / Low Dose	4	Spring Constant vs System Friction Load vs Drug Viscosity Imbalance	3	Spring Constant and Tolerance	4	48	Med	Determine minimum injection depth vs leak
	Injection Speed too Slow >2.0 Sec	Low Dose - Premature Removal	4	Plunger Friction vs Injection Site Backpressure Imbalance	3	Spring Constant and Tolerance	4	48	Med	Human factors: model injection time vs user error
	Injection Depth too Deep >6mm	Intramuscular Injection - poor Pharmacokinetics	4	Lower Injector Housing Stop too Deep or Needle Length	1	Stop Feature Dimension and Tolerance	5	20	Low	Confirm syringe lower stop position and needle length tolerance
	Inection depth too high <4mm	Intradermal Injection - poor Pharmacokinetics	4	Lower Injector Housing Stop too Shallow or Needle Length	1	Stop Feature Dimension and Tolerance	5	20	Low	Confirm syringe lower stop position and needle length tolerance

FIGURE 4: FMEA for Delivery Time of PFS/AI Combination Product

CONCLUSION

A holistic assessment of the product design should begin with the patient and be inclusive of drug-device compatibility and functionality. Cutting edge and novel technologies for advancing patient care are frequently designated as combination products, and the issues related to the drug-device and constituent parts compatibility may not be readily apparent during development. Risk management is common to both QbD and design controls and is fundamental to achieving patient centered outcomes. Critical thinking and open dialogue with a broad range of stakeholders should be part of project planning to facilitate appropriate study designs. Quality should be built into every facet of the pharmaceutical lifecycle to enable quality clinical trials and patient adherence. QbD and design control principles help develop safe, high-quality products to help improve the well-being of patients.

REFERENCE

1. *Journal of Pharmaceutical Sciences, Injectable Combination Product Development: Facilitating Risk-Based Assessments for Efficiency and Patient Centric Outcomes*

ACKNOWLEDGMENTS

Fran DeGrazio, Chief Scientific Officer, West Pharmaceutical Services, Diane Paskiet, Director, Scientific Affairs