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Proactive Risk Management as the Integrating Backbone of Combination Product Development

A practical approach to managing technical, organizational and regulatory complexity in Combination Product development through iterative risk management.

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Abstract

Combination Products (CPs) are becoming increasingly important within the pharmaceutical industry due to their potential to improve patient compliance, reduce use-related errors and enhance therapeutic effectiveness. However, integrating a medicinal product and a medical device into a single therapeutic system introduces significant technical, organizational and regulatory complexity.

This white paper presents a practical methodological framework for managing Combination Product development through iterative and proactive risk management. The proposed approach integrates pharmaceutical development, device engineering, usability engineering and regulatory expectations within a single risk-based decision-making framework.

Using the example of a pen injector system combined with a drug solution cartridge, the paper illustrates how task analysis, usability engineering, design controls and risk management can interact dynamically throughout the development lifecycle. Particular attention is given to the role of risk management in guiding design inputs, verification and validation activities, human factors studies and residual risk evaluation.

The paper ultimately positions risk management not merely as a compliance activity, but as the integrating backbone enabling consistent, efficient and robust Combination Product development.

Executive summary

The increasing diffusion of Combination Products is driving pharmaceutical companies to integrate competencies traditionally associated with medicinal products and medical devices.
This integration creates several challenges:

- alignment of drug and device development timelines;
- integration of different regulatory frameworks;
- incorporation of usability engineering and human factors principles;
- management of organizational and cultural differences between pharmaceutical and device teams;
- development of consistent verification and validation strategies.

Traditional linear development approaches are often insufficient to manage this complexity effectively.
This white paper proposes an alternative methodological perspective in which iterative and proactive risk management acts as the central integrating framework connecting:

- product requirements;
- task analysis;
- usability engineering;
- design controls;
- verification and validation activities;
- labeling strategy;
- regulatory submission readiness.

Using a pen injector Combination Product as a practical example, the paper demonstrates how iterative risk assessment can progressively refine development decisions while maintaining traceability and consistency across the project lifecycle.
The proposed framework supports:

- improved development consistency;
- earlier identification of critical issues;

- better integration between drug and device development;
- risk-based prioritization of activities;
- stronger regulatory robustness.
- Ultimately, the paper argues that proactive risk management should be considered a strategic development methodology rather than a stand-alone compliance exercise.

Key takeaways

Core message	Key takeaway
Integration of disciplines	Combination Product development requires the integration of pharmaceutical, device and usability engineering disciplines.
Risk management as backbone	Risk management should act as the integrating backbone of the entire development lifecycle.
Iterative task analysis and risk assessment	Iterative task analysis and risk assessment improve consistency between design inputs, usability engineering and verification activities.
Early integration of human factors	Human factors and usability engineering should be integrated early during development rather than treated as late-stage validation activities.
Risk-based prioritization	Risk-based decision-making can support prioritization of verification, validation and labeling activities.
Structured integration of standards and principles	Structured integration between ISO 14971, ISO 62366-1, Design Controls and QbD principles strengthens development robustness.
Reduction of risk and complexity	A proactive methodological framework helps reduce product risk, regulatory uncertainty and project complexity.
Organizational and cultural integration	Combination Product development is not only a technical challenge, but also an organizational and cultural integration challenge.

1. Introduction

This white paper is intended for pharmaceutical companies currently developing, or planning to develop, Combination Products (CPs), a category of products that is becoming increasingly important across multiple therapeutic areas.

After a brief overview of the regulatory landscape in the key markets (US and EU) and of the strategic drivers leading pharmaceutical companies to invest in these products, the paper focuses on the operational and methodological aspects of CP development.

More specifically, this paper aims to provide R&D Managers and Project Managers with a practical methodological framework for addressing the technical, organizational and cultural challenges associated with integrating a drug product and a medical device into a single therapeutic system. These challenges can be effectively managed through a structured, iterative and risk-based approach.

The example presented in this paper refers to a CP consisting of a pen injector and a drug solution contained in a cartridge. However, the same methodological approach can also be applied to other categories of CPs, including DPIs, pMDIs, prefilled syringes, infusion pumps and similar systems.

Developing a CP requires integrating different engineering cultures, regulatory frameworks and development methodologies. In this context, risk management should not be considered a stand-alone compliance activity, but

rather the integrating backbone guiding design decisions, usability engineering, verification and validation activities throughout the entire development lifecycle.

A structured risk-based framework contributes to reducing product risk, improving quality, safety and efficacy, and increasing development consistency. In addition, it helps reduce project and submission risks by minimizing requests for information from Health Authorities.

For the US market, the term "Combination Product" is defined in 21 CFR 3.2(e), while in the EU the corresponding concept is generally referred to as a Drug-Device Combination under Medical Device Regulation (EU MDR 2017/745), including Article 117 requirements.

In the context of this paper, the term Combination Product (CP) refers to a system combining a medicinal product and a medical device, where the medicinal product provides the therapeutic primary mode of action (PMOA).

For the Marketing Authorization Holder (MAH), the decision to develop and commercialize a CP represents not only a technological solution, but also a strategic business decision. Combining a drug with a delivery system may improve patient compliance, reduce use-related errors, address unmet medical needs, strengthen market differentiation and increase the overall value of the medicinal product.

Additional strategic considerations include the opportunity to develop either a custom CP or a family of products based on the same delivery platform technology. Such a platform may either be developed from scratch or adapted from commercially available off-the-shelf solutions offered by established device suppliers.

Regardless of the strategic drivers supporting these decisions, CP implementation represents a significant organizational and cultural challenge for the future MAH.

The compatibility and combined performance of both the drug product and the delivery device are critical to patient safety and product quality. However, during early development phases, when formulation characteristics and dosage strengths are not yet finalized, defining device requirements and selecting the appropriate regulatory and clinical strategy can be particularly challenging.

Consequently, successful CP development requires managing multiple technical, regulatory and organizational complexities.

2. Integration Challenges in Combination Product Development

R&D functions, particularly Drug Development, Regulatory Affairs, Clinical Development and Quality Assurance, are required to integrate methodologies, terminology and development approaches traditionally associated with the medical device field.

These activities must be properly embedded within the pharmaceutical stage-gate development model, from Phase 1 clinical development through commercialization, in order to minimize delays, inconsistencies and requests for information during interactions with Health Authorities.

A prerequisite for successful development is the ability to ensure CP safety and efficacy while simultaneously controlling project timelines, development costs and regulatory complexity.

Typical challenges associated with CP development include:

- Synchronizing drug and device development timelines
- Integrating regulatory and quality system requirements applicable to combination products
- Managing cultural differences between pharmaceutical and medical device development teams
- Integrating Design Controls within the broader Quality by Design (QbD) framework

- Defining clinical strategy and design input requirements early in development
- Incorporating usability engineering into product development activities
- Implementing proactive and iterative risk management throughout development and lifecycle management

The complexity of these challenges depends on the specific project context. Nevertheless, methodology and structured decision-making remain essential elements for reducing both product and project risk.

Within this framework, two concepts become central:

- Integration
- Risk-based decision making

These principles are fully aligned with the expectations described in the ICH quality guidelines.

Iterative and proactive risk management can provide critical input to multiple development activities, including:

- identification of design and labeling requirements;
- prioritization of critical user interfaces and user tasks;
- definition of verification and validation strategies;
- planning of usability and human factors activities;
- evaluation of residual risk acceptability.

Risk management therefore becomes the common methodological framework connecting pharmaceutical development, device engineering, usability engineering and regulatory strategy.

3. Example Scenario: Pen Injector Combination Product

To illustrate a practical implementation approach, this paper considers the case of an MAH planning to commercialize a CP in both the US and EU markets.

The CP consists of:

- a drug solution contained in a glass cartridge;
- a reusable pen injector used for dose dialing and dose delivery;
- a disposable needle already available on the market.

In this example, the MAH selects an off-the-shelf pen injector platform that must be customized to support a different intended use compared to the one originally validated and commercialized by the device manufacturer.

Although the device supplier performs the engineering development activities associated with the pen injector, the MAH retains ultimate responsibility for the safety, performance and regulatory compliance of the CP.

For this reason, the MAH remains responsible for:

- the overall risk management process according to ISO 14971;
- the usability engineering process according to ISO 62366-1;
- the integration of device and drug development activities.

To support development activities and manage the increasing amount of project information, the MAH adopts a visual knowledge management approach integrating task analysis, risk management and development traceability within a common framework.

3.1 Initial Task Analysis

Since the engineering details of the pen injector remain under the supplier's responsibility, the MAH initially focuses on the user interface and on the interactions between user and device.

The first step consists of performing a task analysis based on the Use Specification document, which represents the first formal deliverable of the usability engineering process.

When administering a dose, the user is generally required to:

- remove the pen cap;
- load the cartridge containing the drug solution;
- attach the needle;
- prime the system;
- dial the prescribed dose;
- start the injection by pressing the activation button.

For simplicity, this example focuses only on a subset of these activities. The objective is not to provide a complete risk analysis example, but rather to demonstrate how iterative risk management can guide development decisions while maintaining consistency throughout the project lifecycle.

The task analysis is performed using a structured functional mapping methodology commonly adopted in complex industrial environments to describe user interactions, process functions, controls and system interfaces.

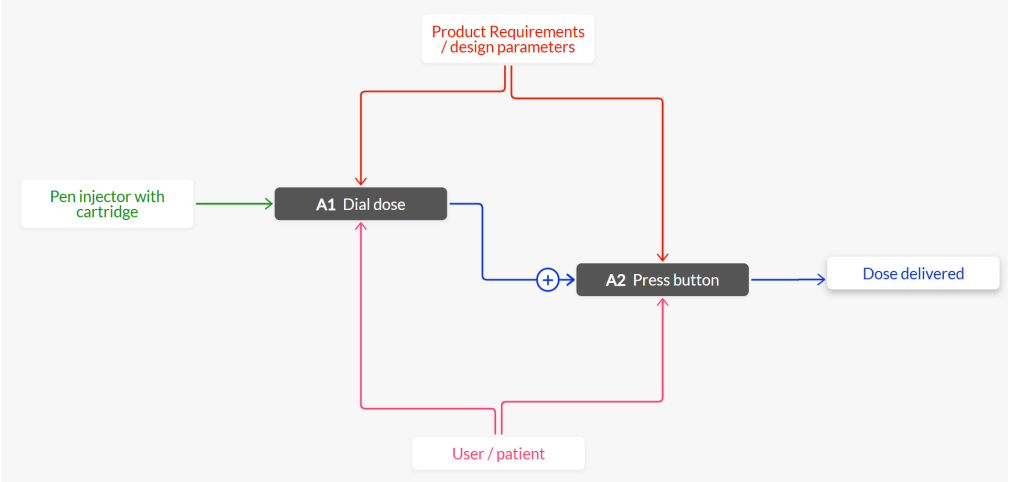
Within this type of functional mapping framework:

- boxes represent user tasks or system functions;
- green arrows represent Inputs (I), namely data or objects transformed by the function;
- blue arrows represent Outputs (O), namely results generated by the function;
- red arrows represent Controls (C), namely rules, constraints or conditions governing the function;
- pink arrows represent Mechanisms (M), namely resources used to perform the function.

The mapping structure can be progressively decomposed into lower-level sub-functions to increase the level of detail during development.

Dedicated visual knowledge management tools can support both the creation and the iterative management of the task analysis, while also improving traceability and consistency across development activities.

The picture below shows the tasks the user has to do when administering a dose.



3.2 Initial Risk Assessment

Once the first version of the task analysis becomes available, the MAH performs the initial risk assessment using a risk analysis structure aligned with ISO 14971:2019.

In this scenario, use-related errors occurring during dose dialing may lead to underdosing and consequently to lack of therapeutic efficacy.

During the first iteration of the risk assessment, the MAH and the pen injector supplier identify the need to implement a design risk control measure (RCM): a visual display window providing real-time feedback during dose setting.

User Task	Hazardous situation	Use Error (Cause)	P1	P2	P	Harm	SEV	Risk level Before	Risk Mitigations	Category	RCM implementation and verification	P1	P2	P	SEV	Risk level After	Residual Risk Acceptability
Dial dose	User injects a lower dose	User does not dial properly the prescribed dose	10^3	1	P3	No therapeutic effect	S4	H	RCM 01: Visual indication during dose setting	Design	\	\	\	\	\	\	Final risk level will be confirmed at later stage
...	...	...															

This feature is consistent with principles already described in ISO 11608-1:2022, which applies to needle-based injection systems.

In this example, the risk assessment directly informs the design input process by triggering an update of the Product Requirements document.

For example:

No.	Requirement	Reference
PRS_XXX	The dose indication in the Display Window shall be designed in a way so that it shows the actual mechanical dose setting	RCM 01

At the same time, the task analysis is updated accordingly.

The second iteration of the risk assessment introduces additional controls and constraints into the analysis, including:

- device torque force;
- activation force;
- user capability;
- display window visibility;
- IFU instructions.

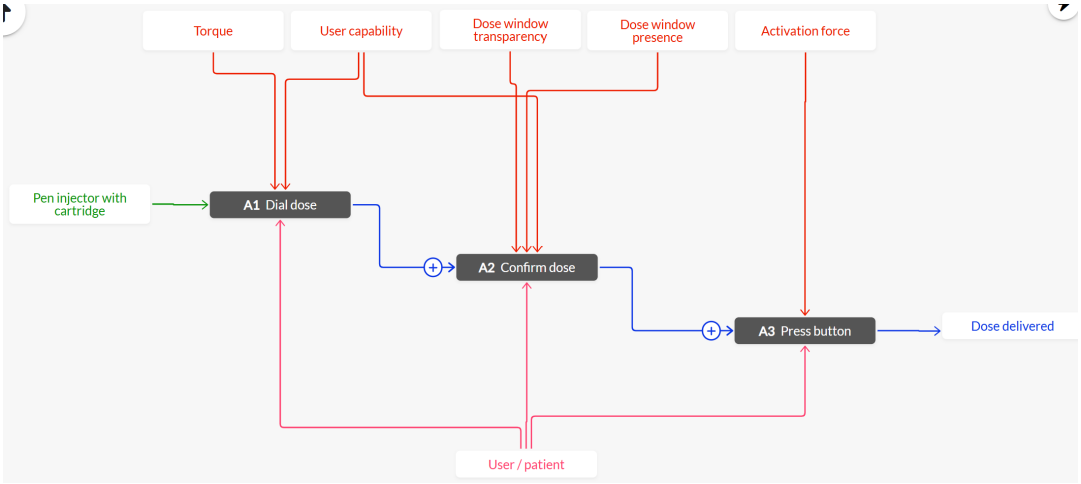
These controls may themselves become potential root causes of hazardous situations.

For example:

- excessive dialing torque may negatively affect the “Dial dose” task;

- excessive activation force may negatively affect the “Press button” task.
- The iterative approach progressively expands the understanding of the interaction between:
- user;
- device;
- environment;
- labeling;
- product requirements.

This iterative logic represents one of the main methodological advantages of integrating functional mapping, task analysis and risk management within a unified visual knowledge management framework.



User Task	Hazardous situation	Use Error (Cause)	P1	P2	P	Harm	SEV	Risk level Before	Risk Mitigations	Category	RCM implementation and verification	P1	P2	P	SEV	Risk level After	Residual Risk Acceptability
Dial dose	User injects a lower dose	User does not dial properly the prescribed dose	10^3	1	P3	No therapeutic effect	S4	H	RCM 01: Visual indication during dose setting	Design	\	\	\	\	\	\	Final risk level will be confirmed at later stage
Dial dose	User injects a lower dose	High pen torque force required	10^2	1	P3	No therapeutic effect	S4	H	RCM 02: to verify the torque force for dose dial	Verification	\	\	\	\	\	\	Final risk level will be confirmed at later stage
Dial dose	User injects a lower dose	User does know how to dial the dose	10^2	1	P3	No therapeutic effect	S4	H	RCM 03: to describe in the IFU how to dial the dose	Labelling	\	\	\	\	\	\	Final risk level will be confirmed at later stage
Dial dose	User injects a lower dose	User not able to dial the dose	10^3	1	P3	No therapeutic effect	S4	H	RCM 04: to validate user is able to dial the dose	Validation	\	\	\	\	\	\	Final risk level will be confirmed at later stage
...	...	...															

3.3 Risk Control Measures and Development Integration

The second iteration of the risk assessment may also identify labeling-related risk control measures.

For example, the Instructions for Use (IFU) may include specific guidance explaining how to correctly rotate the dose knob during dose setting.

The IFU therefore becomes an additional control element within the task analysis.

User Task	Hazardous situation	Use Error (Cause)	P1	P2	P	Harm	SEV	Risk level Before	Risk Mitigations	Category	RCM implementation and verification	P1	P2	P	SEV	Risk level After	Residual Risk Acceptability
Dial dose	User injects a lower dose	User does not dial properly the prescribed dose	10^3	1	P3	No therapeutic effect	S4	H	RCM 01: Visual indication during dose setting	Design	Visual display component; Summative HF Report	10^6	1	P1	S4	L	The risk is considered acceptable and represents the current state of the art.
Dial dose	User injects a lower dose	High pen torque force required	10^2	1	P3	No therapeutic effect	S4	H	RCM 02: to verify the torque force for dose dial	Verification	Design Verification Report	10^5	1	P2	S4	M	The residual risk is considered to be at an acceptable level.
Dial dose	User injects a lower dose	User does know how to dial the dose	10^2	1	P3	No therapeutic effect	S4	H	RCM 03: to describe in the IFU how to dial the dose	Labelling	IFU; Summative HF Report	10^5	1	P2	S4	M	The residual risk is considered to be at an acceptable level.
Dial dose	User injects a lower dose	User not able to dial the dose	10^3	1	P3	No therapeutic effect	S4	H	RCM 04: to validate user is able to dial the dose	Validation	Summative HF Report	10^6	1	P1	S4	L	The residual risk is considered to be at an acceptable level.

Development iterations continue until the MAH concludes that no additional design or labeling risk control measures are required.

At this stage, the project can transition toward design verification and validation activities.

Once again, risk management acts as the integrating framework supporting decision-making.

More specifically, the risk assessment provides input to:

- design verification planning;
- usability engineering activities;
- human factors simulations;
- validation strategy.

4. Risk-Based Verification and Validation

Unless otherwise specified by applicable standards or guidance documents, the MAH may adopt a risk-based approach to define the extent of verification activities.

For example, the extent of testing or the rationale supporting sample size selection may be adjusted according to the associated risk level, provided that the approach is scientifically justified and formally documented within the Pharmaceutical Quality System.

In the present example, verification testing is performed to confirm that the dialing torque remains within predefined acceptance criteria.

Similarly, the same risk-based logic can support the development of the Summative Human Factors (HF) Study protocol.

According to FDA guidance documents, user tasks associated with high-severity harms are considered "critical tasks." Consequently, these tasks require increased attention during simulated-use activities and data evaluation.

Risk management may also support optimization of the IFU layout itself.

Warnings and instructions associated with high-severity hazards should receive greater visibility and emphasis to reduce the probability of use-related errors.

5. Final Risk Evaluation and Residual Risk Assessment

Once verification and validation activities are completed, the MAH collects and reviews all available evidence within the final iteration of the risk assessment.

This final review allows:

- evaluation of individual residual risks;
- confirmation of risk control measure effectiveness;
- assessment of overall residual risk acceptability compared with the expected clinical benefits of the CP.

At this stage, the iterative process initiated during early development converges into a consolidated body of evidence supporting:

- product safety;
- product performance;
- usability;
- regulatory submission.

6. Conclusions

Combination Product development is intrinsically complex from operational, organizational and technical perspectives.

In addition, pharmaceutical and medical device development are traditionally driven by different perspectives:

- pharmaceutical development primarily focuses on disease treatment and therapeutic efficacy;
- medical device development primarily focuses on user interaction and device performance.

Successfully integrating these perspectives requires a structured methodological framework capable of maintaining consistency across the entire development lifecycle.

This paper illustrates how iterative and proactive risk management can become the integrating backbone of CP development by connecting:

- design inputs;
- usability engineering;
- verification and validation activities;

- labeling strategy;
- regulatory expectations.

When properly implemented, this approach helps organizations:

- reduce product risk;
- improve quality, safety and efficacy;
- strengthen development consistency;
- reduce regulatory uncertainty;
- minimize project and submission risks.

Beyond regulatory compliance, proactive risk management therefore becomes a strategic tool for managing complexity and enabling robust Combination Product development.

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