Risk Management Considerations for Drug-Device Combination Products

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Risk Management in Combination Products

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The Case for Risk Management

Continuous and early application of risk management principles are crucial during development to ensure combination product meets desired intended use with required reliability performance

- Focused, cross-functional and integrated approach will increase product understanding
- Reduces design and/or manufacturing changes later in development and/or post design freeze that incur unwanted delays and cost
- Reduces potential for costly control strategies being introduced at last minute due to non-integrated approach to risk controls
- Decreases complaints and adverse events from product performance and/or usability issues

Risk Management for Combination Products: What & Why

Risk Management

- is an holistic and continuous evaluation of your products' risk profile underpinning all elements of device development from concept to lifecycle management

- is part of an overall Design Control process used as the framework for all device development:
  - Design Control (21CFR820.30) is a proactive process based on engineering and quality principles that enables manufacturers to ensure their device meets the intended user needs, intended uses, and specified design requirements.

- requires continuous, proactive application within an established framework (Risk Management Plan) to enable assessment of residual risk

- *ISO 14971… Application of risk management to medical devices* …. specifies a process for a manufacturer to identify the hazards associated with medical devices….to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls.

Risk Management for Combination Products: What & Why

- Consideration too late in the program means combination product performance may not be fully understood (& controlled)
  - ➢ Potential impact to safe and effective use by end user/ patient
  - ➢ Can lead to rework in development, or post market complaints & recalls
  - ➢ Costly and timely
- Is often considered in isolation during specific elements of a development program
  - an FMEA activity (FMEA ≠ Risk Management), or
  - late in development as an 'after-thought'

- *Historically*: Patients are not using the device properly (like we designed it☺)

✓ *Reality:* design a reliable product for intuitive, safe & effective use

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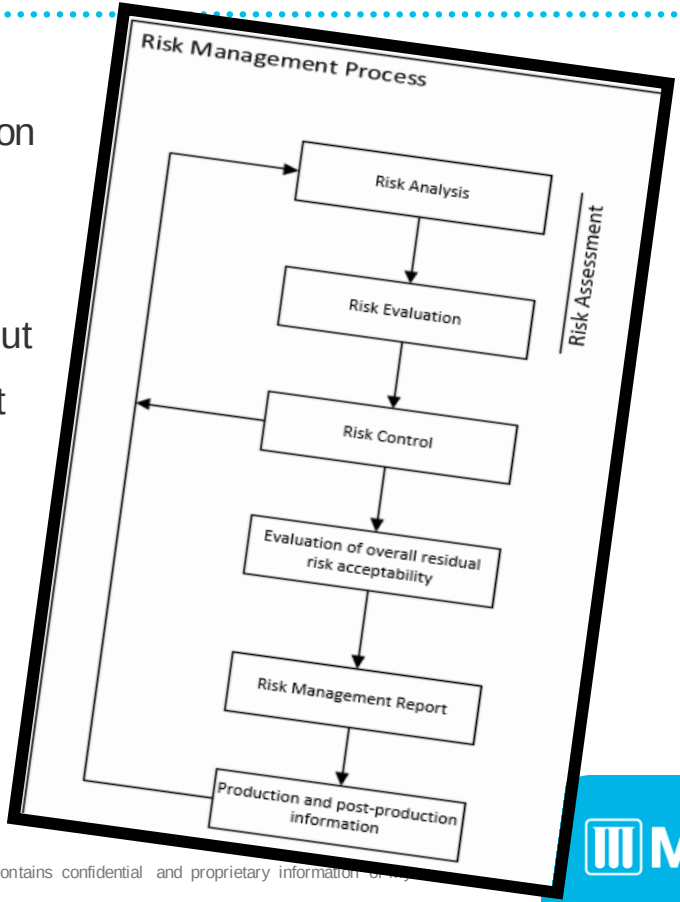
Risk Management for Combination Products: What & Why

- Device program starts with understanding safety, clinical and drug performance needs, and consideration of the RLD delivery system

- ISO 14971 provides a framework for how to think about risk and capture risks as you go through development

- Enables assessment of medical benefits vs any residual risks, and vs the RLD.



Risk Management Process

Design, User, Process

Develop a cohesive, integrated plan at the start of device development program

- Identify potential hazards
- Define how they could manifest to end user: harm, usability, performance
- Understand severity of safety & clinical/medical implications of potential hazard realisation: under/ over/ no dose, needle stick
- Estimate the risk profile: identify unacceptable risks
    - Understand device function & intent, knowledge & issues with similar & marketed products
- Eliminate potential hazards through design changes
- Define what can be controlled during manufacture – detectability
    - Introduce controls, monitor effectiveness
    - Clarity in labelling: IFU & information for safety
    - Specific considerations for generic products vs RLD labelling

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Risk Management Process

- Define the outstanding / residual risks once all controls in place
- Does the device meets its intended use & need as it relates to your product vs the RLD:
  - ➢ Safe and effective use – what data do you need to generate vs the RLD
  - ➢ Reliability specification
- Additional considerations for generic CPs
  - Are there new risks introduced with your CP vs the RLD – are they acceptable vs the risk profile of the product
    - Use Comparative Analysis methodology early on to proactively understand & assess any such differences
    - Does the outcome of Comparative Analysis drive a need for additional information/data to support Design Validation
- Does the benefit of the device/CP outweigh any residual risks?

Risk Management during Design Phase

Risks should be considered during all aspects of development:

- Design intent
- Concept development & Prototyping
- Usability – ergonomic design and proposed labelling
- Use of statistical modelling to predict failure rates
- Device characterisation, performance & engineering assessment vs target reliability
- Continuous engineering verification during development - use appropriate sample sizes to ensure product performance understanding
- Test device to point of failure or at a minimum understand performance capability well outside parameters of use

Risk Management during Design Phase

- Test mis-use scenarios sufficiently – test ‘real-life’!
- Understand and interlink design capability and performance assessments
- Understand influence of drug product properties on device
- Understand impact of device on drug properties
- Interlinkage of drug primary container to device performance
- Design For Manufacture (DFM) critical before design freeze – device tooling and assembly processes must be scaleable & robust with critical controls maintained
- FMEA ≠ RM! Don’t use FMEA as the only tool; consider Fault Tree Analysis (FTA), apply proper root cause analysis during characterisation and usability assessments

❖ *Don’t be afraid to fail early on – better than after verification, validation and on-market!*

Risk Management: Confirmation of effective Risk Controls

Confirmation of device robustness & reliability for intended use

- Data from qualification of device manufacturing processes
- Complaints assessment during any clinical / PKPD studies
- Design verification program
- If required, comparative use / validation human factor studies, inc IFU & labelling
- In-vivo studies may be required based on nature of product: often reflected in the BE guidance: at-home / actual use studies
- Device performance data from registration / exhibit batch release and stability studies

Risk Management input to Control Strategy

Control Strategy is one output of a Risk Management program

- Supplier controls for incoming resins
- Moulded components: IPCs, critical dimensions, extractables
- Assembly processes (sub & final): in-line vision & measurement systems
- In process testing, QC release
- Incorporation of identified essential performance requirements

Have all outstanding risks been controlled during manufacture to ensure device is consistently safe and effective for its intended use?

Could scientific research into risk analysis methodologies and approaches be conducted to drive engineering and scientific understanding, consistency in approach and ultimately lead to increase in accessibility of robust generic drug-device combination products?


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