Combination Products
Risk Management and Control Strategies

Susan Neadle
Sr. Director, Global Value Chain Quality Design
Head, J&J Combination Products CoP
Johnson & Johnson
sneadle1@its.jnj.com

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Agenda

- Container Closure or Combination Product?
- Evolving Global Regulations
- Control Strategies to Safeguard Patients
  - Typical Integrated Development Process
  - CtQ Cascade and Control Strategy
  - Product Risk Management Integration
  - Combination Products Risk Considerations
- Combination Products Control Strategies
- Summary

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Container Closure vs Combination Product

The United States FDA distinguishes between mere drug **containers and closures** versus containers and closures that are also **devices**.

Drug **container-closure**:
Vial **contains and protects** the drug

Subject to drug cGMPs as a container or closure

Combination Product (Single Entity):
Syringe serves both as
a drug **container-closure AND as a device** which delivers the dose

Subject to drug cGMPs as a container or closure AND to the device Quality System Regulations

Combination Product (Co-pack):
Vial = **container-closure**
+
Piston syringe= **delivery device**

Subject to drug cGMPs as a container or closure AND to the device Quality System Regulations

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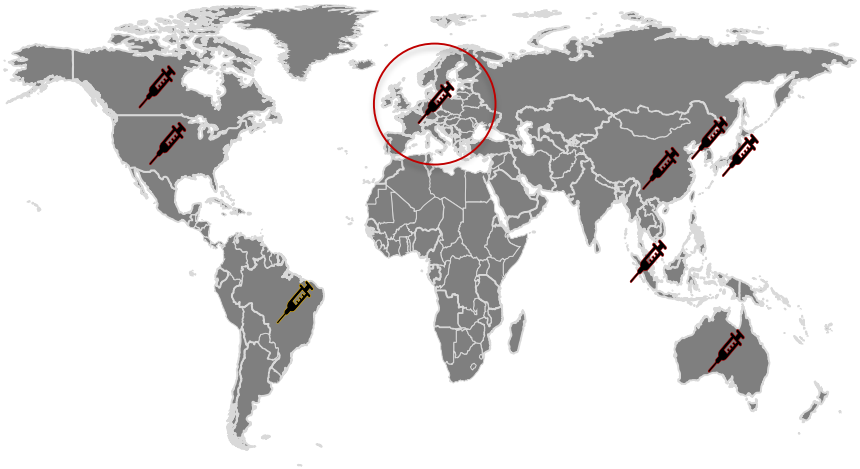
Evolving Global Regulations

Focus is on successful practices and control strategies throughout the product lifecycle to ensure risk is commensurate with patient needs.

- 21st Century Cures
  - *Alternative or Streamlined Mechanisms for cGMPs for CPs*
  - *Process for Interacting with FDA on CP cGMPs*
- US Part 4
- EU MDR Article 117
- Product Designation & Submissions
- Inter-Center Coordination
- Human Factors/ Medication Errors Reduction
- Digital Health/ SaMD
- ICH Q9 and ISO 14971
- Stability
- Reliability
- Comparability
- Post Marketing Safety Reporting
- Post Market Modifications



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Evolving Global Regulations

- Combination product regulations are relatively recent, and specific regulations only exist in certain markets

- **Primary Mode of Action** and **type of Combination Product** (e.g., single entity, co-pack, or cross-label "set") largely drives regulations, submissions procedures, pathway to market and post marketing safety reporting in most markets.

PRIMARY MODE OF ACTION:

"…the single mode of action of a combination product that provides the most important therapeutic action … The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects…" (21 CFR Part 3.2(m)

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Control Strategies to Safeguard Patients

- **Cornerstones**
  - Combination Product Integrated Development

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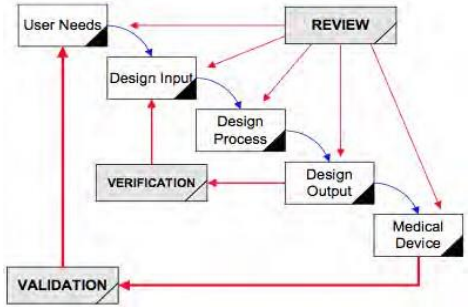
DESIGN CONTROLS



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RISK MANAGEMENT

  - Risk Management:
    - Essential Performance Requirements/Critical Control Points
    - Human Factors
    - Reliability
    - Change Controls
    - Purchasing Controls

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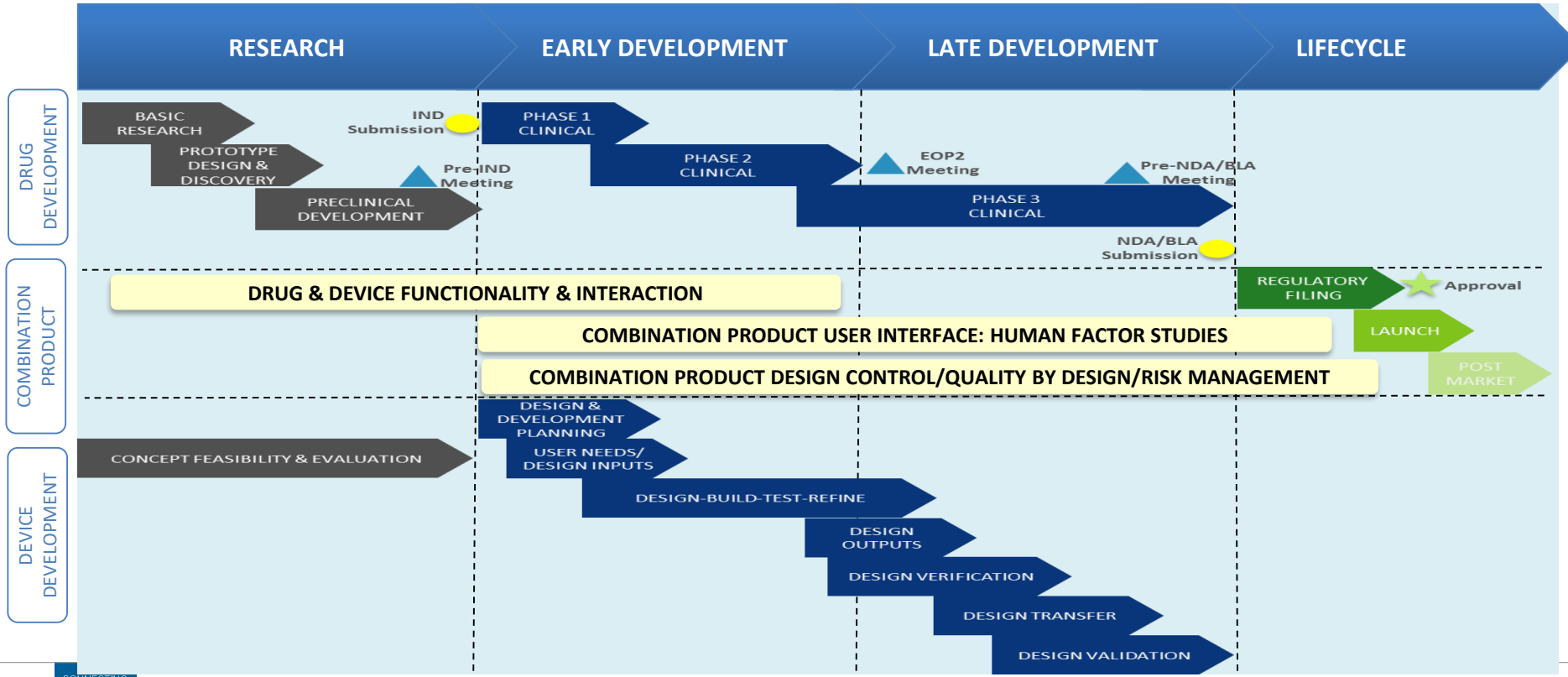
Typical Integrated Development Process

PRO-ACTIVE RISK MANAGEMENT UNDERPINNING



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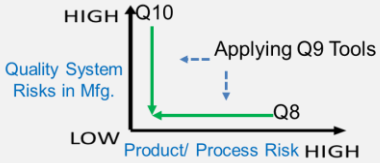
Combination Products Integrated Development

Part 4, and evolving Global CP Regulations

- ICH Q8: Pharmaceutical Development
- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality Systems
- Safety Considerations for Product Design to Minimize Medication Errors Guidance for Industry
- Post Marketing Surveillance & Safety Reporting



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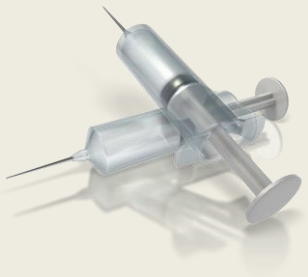

- 21 CFR 820: QSRs (Design Controls, Change Control, Purchasing Controls)
- ISO 13485: QMS
- ISO 14971: Risk Management
- Post Marketing Surveillance & Safety Reporting
- IEC 62366-1: Usability Engineering
- FDA Draft Guidance Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Proactive and Active…

RISK ASSESSMENT **RISK CONTROL** **RISK REVIEW** **QUALITY RISK/BENEFIT ANALYSIS**

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CtQ Cascade and Controls Strategy

For Constituent parts, their interactions, and the Combination Product as a whole.

User Needs and Requirements

Product Requirements/Intended Functions (CtQs and CQAs)

- Focus on both **SAFE** and **EFFECTIVE** use of the combination product
- Essential for the proper functioning of the device, the drug, and the combination product
- **Essential Requirements**: Subset of Intended Functions needed to achieve freedom from unacceptable harm and/or for acceptable delivery of the dose

CtQ: Critical-to-Quality; CQA: Critical Quality Attribute

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CtQ Cascade and Controls Strategy

For Constituent parts, their interactions, and the Combination Product as a whole.

CtQ: Critical-to-Quality; CQA: Critical Quality Attribute; CPP: Critical Process Parameter; CMA: Critical Material Attribute; EPR: Essential Performance Requirement

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Product Risk Management

Risk Management is the process of…

- Identifying hazards
- Evaluating associated risks
- Mitigating/controlling the risks
- Monitoring the effectiveness of the controls

- Neadle, Susan (editors: Bills, E. and Mastrangelo, S.) (2016). “Risk Management Considerations and Strategies in Product Development” in Lifecycle Risk Management for Healthcare Products: From Research Through Disposal. Davis Healthcare International Publishers.

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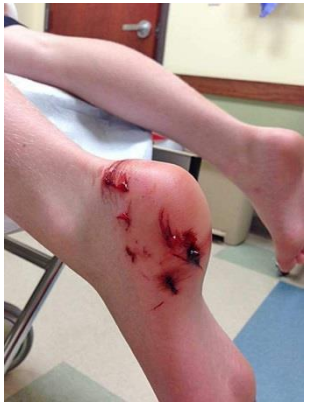
Hazard, Hazardous Situation, Harm

Hazard

Hazardous Situation



Harm

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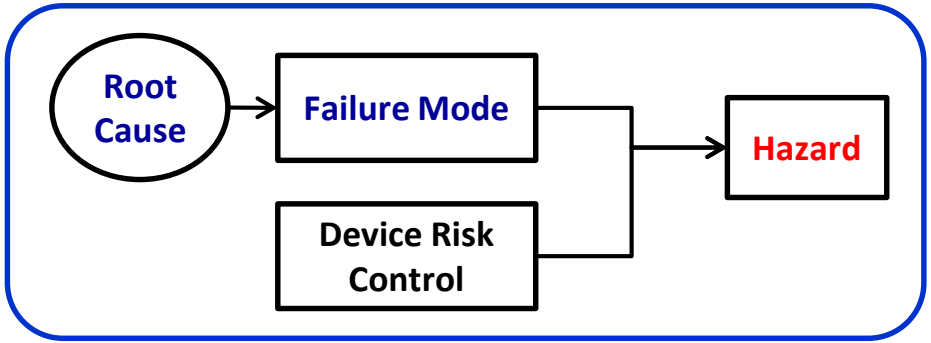
Product Risk Management Integration

Failure Analysis

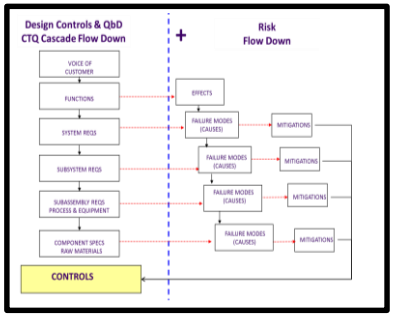


Failure Mode & Effects Analysis (FMEA)

- Identifies failure modes their causes/effects and supports PRA to drive mitigation efforts
- Bottom-up analysis that is focused on identifying the causes and establishing risk control measures
- FM are typically local to the process or component (fails to meet spec, lack of function, defect, etc.)
- Probability of the root cause leading to failure mode and hazard

CtQ Cascade: Control Strategies Foundation

(design, process, use, etc.)



Generic example – typical tables for each FMEA type can run 10-20 pages

ISO 14971 Based	IFU Task/ Design feature/ Assembly Step	Hazard Types	Harm to patient with a deviation	Severity for each Harm	Probability or frequency	Detectability pFMEA only	Risk Score	Mitigations	Severity	Probability or frequency	Detectability pFMEA only	Post Mitigation Risk Score
User FMEA	IFU steps	Needle stick – re-cap needle (multiple)	Cross infection (multiple)	High	Medium	NA	High	Design; IFU warning	High	Low	NA	e.g., ALAP
Design FMEA	Design Feature	Needle stick – mis-fire	Cross infection	High	Medium	NA	High	Safety interlock	High	Low	NA	e.g., Tolerable
Process FMEA	Assembly step	Missed dose / mis-assembly	Lack of drug effect	Medium	Medium	Medium	Medium	Vision detection	Medium	Very low	Very high	e.g., Acceptable

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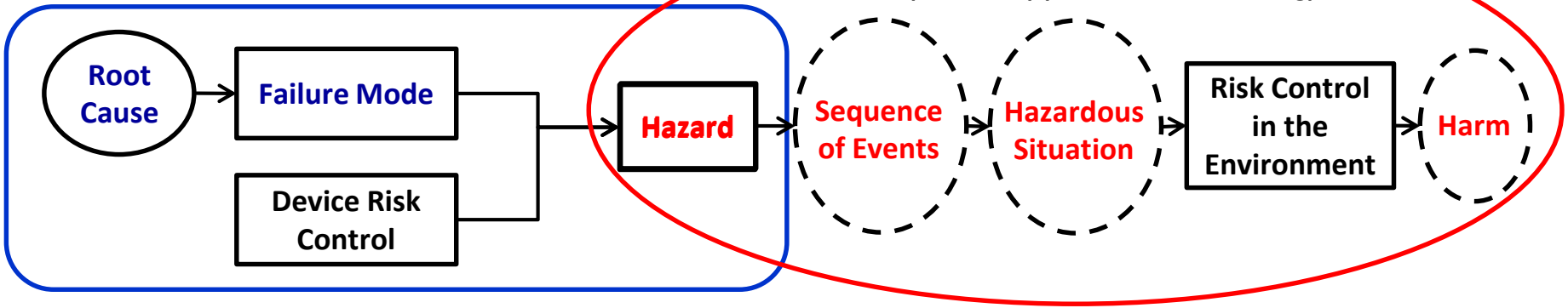
Product Risk Management Integration

Failure Analysis

(design, process, use, etc.)

Risk Analysis

(what happens in use setting)



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Product Risk Assessment (PRA)

- Identifies potential hazards of the PRODUCT (drug + device) that could harm the patient
- Top-down analysis that focuses on interactions and/or sequence of events that lead to Harm
- Probability of the Harm to the User

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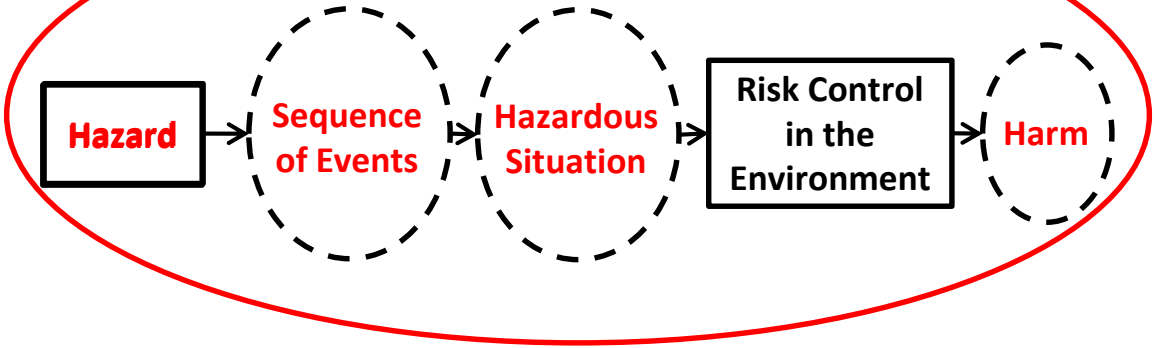
Product Risk Management Integration

Risk Analysis

(what happens in use setting)



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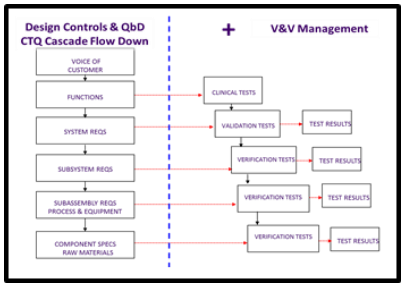
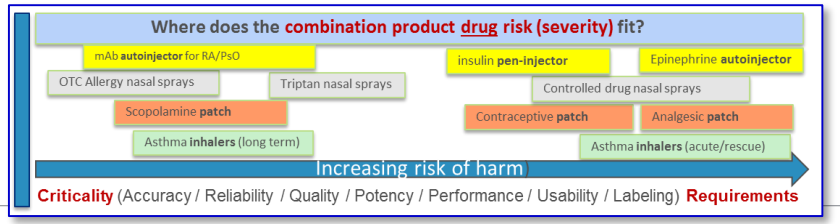
CtQ Cascade: Control Strategies Foundation

- Formative & Summative Human Factors/ Usability Engineering
- Clinical Studies
- Design Validation
- *Linkage to Post Marketing Safety Reporting*





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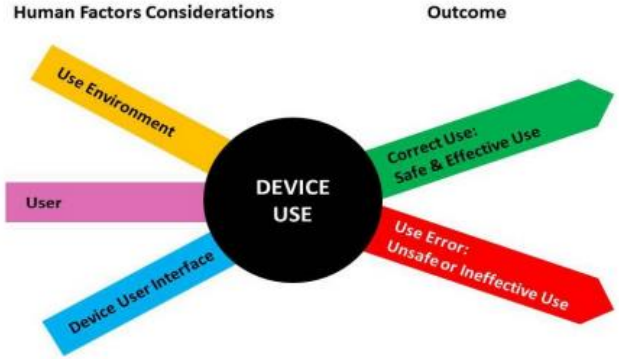
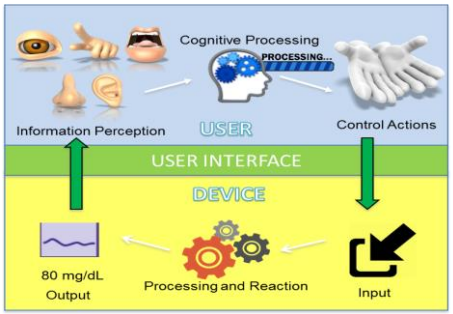
Product Risk Management Integration

Hazards and Harms Analysis and Risk Evaluation: Who is the User?





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- FDA Guidance: Applying Human Factors and Usability Engineering to Medical Devices(2/16)
- FDA Draft Guidance Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (2/16)
- Safety Considerations for Product Design to Minimize Medication Errors Guidance for Industry (4/16)

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Combination Products Risk Considerations

Drug Considerations:

- **Formulation** (Identity, strength, quality, purity, potency, viscosity, particle size, etc.)
- Change in **intended use** that may impact safety and efficacy
- Physical discomfort associated with **drug administration**
  - E.g., due to injection force required, volume or pH of drug, or time required to administer the drug
- **Dose accuracy**: Over dose, under dose, wrong dose related adverse events

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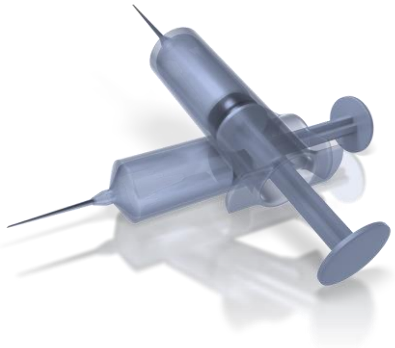
Combination Products Risk Considerations

Device Considerations:



- **Product differentiation**
- **Technological characteristics/ configuration for intended route of administration**, e.g., needle extension (protrusion into subcutaneous or intramuscular biospace)
- Clear **units of measure**
- Clarity of **dose completion**
- **Drug delivery activation**, e.g., spring compression force required, impacting injection force and/or injection time (*rheumatoid arthritis patient?)*
- **Assembly lines** for production scale up

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Combination Products Risk Considerations

Use Environment Considerations:

- **Storage** (e.g., refrigeration, away from children, shelf-life, use away from home)
- **Human Factors:**
  - **Who is the user?** Pediatric? Elderly? Caregiver? Training adequacy?
  - What is the **complexity of the environment?** User stress levels and distractions? At home?
  - What is the **user interface? Clear Labeling**, e.g., Instructions for Use (IFU)
  - What is the **consequence for user error?**
  - What are the **physical/sensory requirements?** Self-injection?
  - What are the **cognitive requirements?**
  - What are the **user habits and expectations?** Adherence to **dose regimen** that is not daily (e.g., weekly? Bi-weekly? Monthly?)

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Combination Products Control Strategies

- Focus on both **SAFE** and **EFFECTIVE** use for the proper functioning of the **device**, the **drug**, and the **combination product**

Essential	Functions and components that have potential to harm the patient or affect the mechanics of the clinical performance of the product
Non-Essential	Remaining functions and components that are not considered to be essential

- Risk-based evaluation and application of routine controls
- Emphasize greater controls on essential functions and the aspects of the components which contribute to essential performance

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Combination Products Control Strategies

- Cascade controls for EACH Essential Performance Requirement

Purchasing/ Supplier Controls

- Material Specs
- Supplier Specs
- Supplier Quality Agreements
- Component manufacturer controls
- In-process controls
- Release testing

Mfg Control Plans

- Incoming inspection & release procedures
- Incoming Specifications
- Deviation Disposition
- Statistical Justification(s)

EM Controls

- External Manufacturer Controls
- In-process controls
- Release testing

Packaging & Labeling Controls

- Control of packaging and labeling of materials across component and suppliers

Incoming Controls

- Incoming inspection & release procedures
- Incoming Specifications
- Deviation Disposition
- Statistical Justification(s)

Final Testing and Release Controls

- Incoming inspection & release procedures
- Incoming Specifications
- Deviation Disposition
- Statistical Justification(s)

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Summary

- Focus on both **SAFE** and **EFFECTIVE** use of the combination product
  - Essentials for the proper functioning of the device, the drug, AND the combination product
- Control strategies supported by product and process understanding, and robust definition of CTQ characteristics
  - Science- and risk-based
  - Supported by strong quality system
- Systematic, integrated approach, aligned with QbD and Design Controls can be applied for combination products

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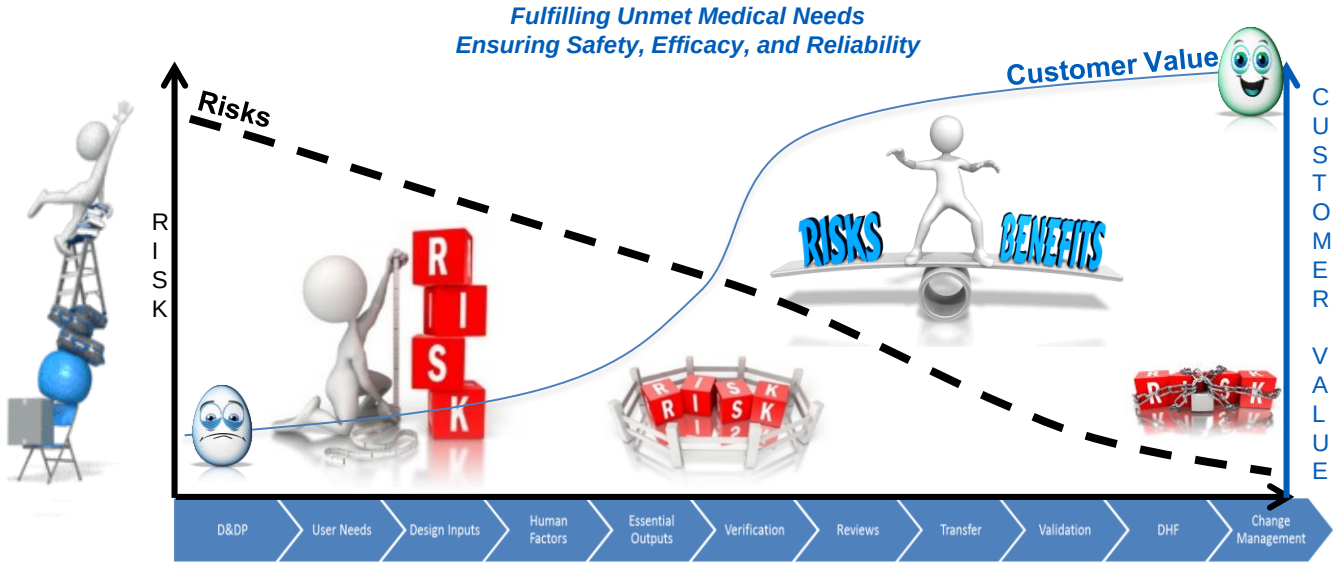
Summary: Final Control Strategy

- Impact of Systematic Integration of Risk Management Strategies throughout Development

Systematic integration of risk management strategies throughout development proactively reduces risks while simultaneously creating value for the Customer.



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Contact: sneadle1@its.jnj.com
susan_neadle@comcast.net

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