COMBINATION PRODUCTS SUMMIT

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Combination Products Risk Management Workshop

Exercise Material

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AFDO RAPS HEALTHCARE PRODUCTS COLLABORATIVE

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This exercise workbook is intended to be a helpful resource and reflects the expertise of the author.

It is not legal nor regulatory advice.

Key Definitions

- **Safety**: Freedom from unacceptable risk.
- **Risk**: Probability of occurrence of harm x severity of that harm.
- **Harm**: Injury or damage to the health of people, property or the environment, including physical or mental injury, and that which occurs due to loss of product quality or availability.
- **Hazard**: Potential Source of Harm (Consider design, use, and processing root causes; Consider normal conditions, fault conditions, previous hazards, specific sequence(s) of events)
- **Hazardous Situation**: Exposure to Potential Source of Harm.

Harm Severity Categorization for Exercise:

Example

Harm Severity	Code	Definition
Critical	S4	Imminent risk of death, serious injury or serious illness to more than one individual, requiring prompt medical attention (public health threat) Imminent risk of death or fetal harm Life-threatening illness or injury, which if untreated, would be fatal
Serious	S3	Permanent (irreversible) deterioration in the state of health Severe toxicological or immunological response requiring hospitalization, but not life-threatening Clinically significant intervention and/or extended treatment time required
Minor	S2	Temporary (reversible) deterioration in the state of health Minor impact on disease progression/ minimal toxicological or immunological response, e.g., minor infection Mild injury, illness or impairment that can be treated with minimal intervention or just monitoring Local or non-invasive intervention required
Negligible	S1	Injury or illness that is transient and requires no intervention: asymptomatic or mild symptoms No adverse medical event Inconvenience or temporary discomfort Annoyance or dissatisfaction with product quality

Neadle, Susan. *The Combination Products Handbook: A Practical Guide for Combination Products and Other Combined Use Systems*. Taylor & Francis/ CRC Press, 2023.

- *Defined by Organization.*
- *Clinician involvement in assessing harms and their severities is essential.*
- *Harm categorization is a critical reference post market for vigilance and reporting.*

Example Hazard Categories

Device Hazard	Drug/Biologic Hazards	Production Hazards
Electrical	Purity	Incapable processes
Mechanical	Excipients	Inaccurate procedure
Thermal	Content Uniformity	Operator non-compliance
Biocompatibility	Sterilization	Cleaning
Usability	Stability	Labeling
Electromechanical		Test Methods
Software		
Interactive Hazards between the Device and Drug / Biologic		

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Example Hazards

- User interface design inadequacy (e.g.,
  - Illegible/unintelligible labeling
  - Training problem
  - Unclear measurement units
  - Use error, e.g., handling, sharps exposure)
- Biocompatibility
- Biological Agents
- Chemical Agents
- E&L
- Particulates
- Allogenic Substances (e.g., latex, plasticizers)
- Immunological Agents
- Drug-device interaction/degradation
- Inherent product design issue (e.g., blunt needle or defective component)
- Ingestion of small parts
- Mechanical Functionality problem
- Computer Software problem
- Cybersecurity issue
- Shipping problem (e.g., temperature or humidity)
- Packaging problem
- Manufacturing problem

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Example Hazardous Situations

- Dose Completion: Overdose, Underdose/ Intermittent dose, Missed dose
- Delay to treatment/therapy due to device performance
- Use of Placebo
- Exposure to contaminated device
- Injection of sub-visible or visible particulates
- Misdiagnosis
- Device revision or replacement
- Device reprogramming
- Delay to diagnosis as a consequence of device performance
- Booster dose missed
- Contraindicated product administered
- Counterfeit product administered
- Discontinued product administered
- Drug administered in wrong device
- Drug dose titration not performed
- Duplicate therapy error
- Expired product administered
- Failure to suspend medication
- Inappropriate schedule of product administration
- Incorrect drug administration rate
- Incorrect drug administration duration
- Incorrect product formulation administered
- Incorrect route of product administration
- Lack of administration site rotation
- Product administered in wrong person
- Product administered to patient of wrong age
- Single component of two-component product administered

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Example Probability of Occurrence of Harm Levels

Level	Common Term	Qualitative Description (e.g., Time-based) Typically occurs, or occurs on average within the time frames displayed	Examples of Quantitative Probability Range
O-4	Frequent	<Monthly	$\geq 10^{-3}$
O-3	Probable	>Monthly but ≤ Yearly	$\geq 10^{-5}$ and $< 10^{-3}$
O-2	Occasional	>Yearly but ≤ 5 years	$\geq 10^{-6}$ and $< 10^{-5}$
O-1	Remote	>5 years	$< 10^{-6}$

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Example Risk Acceptability Matrix

			Severity of Harm (S)			
			Negligible	Minor	Serious	Critical
			S-1	S-2	S-3	S-4
Probability of Occurrence of Harm	Frequent	O-4	Moderate Risk	Unacceptable Risk	Unacceptable Risk	Unacceptable Risk
	Probable	O-3	Broadly Acceptable Risk	Moderate Risk	Unacceptable Risk	Unacceptable Risk
	Occasional	O-2	Broadly Acceptable Risk	Broadly Acceptable Risk	Moderate Risk	Unacceptable Risk
	Remote	O-1	Broadly Acceptable Risk	Broadly Acceptable Risk	Broadly Acceptable Risk	Moderate Risk

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Example Risk Estimation Example

Failure Mode	Source Document(s)	Hazard	Hazardous Situation	Harm	Severity	P1	P2	Probability of Occurrence of Harm	Risk Level
User selects expired / non-sterile / previously used needle	Use FMEA Preliminary Hazard Analysis	Biological Agents	Administration of biological agent into the patient.	Death.	Catastrophic	Low	Extremely Unlikely	Improbable	Marginal
				Systemic infection (sepsis), permanent impairment or life-threatening/irreversible injury.	Critical	Low	Extremely Unlikely	Improbable	Marginal
				Localized infection, abscess, systemic effects, requiring medical/surgical intervention.	Serious	Low	Unlikely	Improbable	Low
				Localised infection, not requiring medical intervention.	Minor	Low	Possible	Remote	Low

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Detectability is not included in Hazard/Harm Analysis

Scenario

- A drug manufacturer (Manufacturer A) plans to sell a Crohn's disease drug in a prefilled syringe presentation.
- Manufacturer A already has marketing approval for the drug product and intends to apply for marketing approval for the prefilled syringe presentation. No changes to the drug formulation will be made.
- Manufacturer A will buy off-the-shelf syringe components from a supplier (Manufacturer B) who also manufactures finished syringes using the same components.
- Manufacturer A will assemble the syringe components, prefill the syringe at a facility it operates, and then package, label, and distribute the prefilled syringe from this facility. Manufacturer A's facility has an existing drug CGMP operating system.

Design Input/User Needs	*Design Output*
Required minimum/maximum dose delivery for drug	Drawing/specification for syringe dimensions, markings, etc.
Drug viscosity and desired/required delivery rate	Drawing/specification for needle bore, glide force, etc.
Expected use condition (e.g., expected user experience/education level)	Content and reading level for the prefilled syringe's labeling
Maximum and minimum allowable temperature for prefilled syringe	Packaging/labeling specifications for the prefilled syringe
No degradation of drug or syringe over the expected shelf-life as a result of contact with one another	Specifications for drug-contacting syringe materials
Expected shipping method and appropriate storage conditions	Design drawings/specifications for primary and secondary packaging, labeling for acceptable storage conditions
Drug delivery method (e.g., needle or needleless delivery)	Drawing/specification for needle and/or other associated syringe components

Scenario

Manufacturer A should identify risks associated with the prefilled syringe design, its manufacturing processes, and intended uses, and also reduce or mitigate any unacceptable risk(s

Risk	*Mitigation*
Syringe filled with incorrect drug dose	In-process acceptance testing, process validation
Loss of sterility	Container-closure integrity testing, packaging validation/testing
Drug contamination from materials of syringe construction	Purchasing controls (including receiving acceptance activities for components received from syringe component manufacturer), in-process and finished product testing to ensure no introduction of contaminants during manufacture and over the product shelf-life
Syringe failure during use	Design verification testing on syringe, purchasing controls over syringe component manufacturer(s)

List Potential Hazards for PFS

(Drug-agnostic and drug-dependent, chronic-care for Crohn's disease)

Hazard ID	Hazards

List Potential Hazardous Situations for the PFS (Drug-agnostic and drug-dependent, e.g., emergency use vs chronic)

Hazard ID	Hazards	Hazardous Situations

List Potential Harms for the PFS

(Drug-agnostic and drug-dependent, (Drug-agnostic and drug-dependent, e.g., emergency use vs chronic))

Hazard ID	Hazards	Hazardous Situations	Potential Harms

List Severities of Potential Harm for the PFS

Hazard ID	Hazards	Hazardous Situations	Potential Harms	Severity Rating

List Severities of Potential Harm for PFS

Hazard ID	Hazards	P1	Hazardous Situations	P2	Potential Harms	Severity Rating

Risk Analysis for PFS

Hazard ID	Hazards	P1	Hazardous Situations	P2	Potential Harms	Severity Rating	Risk Acceptability

Risk Analysis for PFS

Hazard ID	Hazards	P1	Hazardous Situations	P2	Potential Harms	Severity Rating	Risk Acceptability	Mitigation