Navigating Packaging Challenges for Drugs and Injection Devices

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Overview

1. Packaging roles
2. Regulatory requirements
3. Regulatory challenges
   1) Design controls for combination products
   2) Minimizing medication errors
   3) New packaging technologies

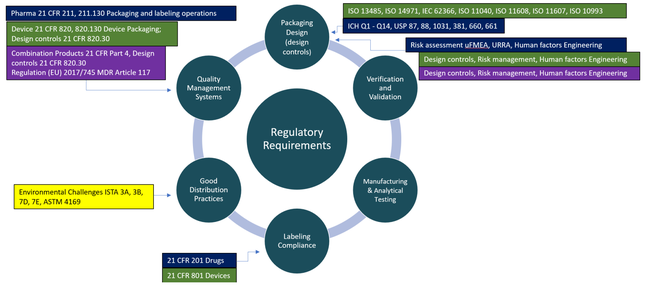
1. Role of Packaging

Protection
- Integrity, Sterile barrier system, Tamper evident
- Stability & shelf life (degradation - light, temperature, humidity, oxygen, vacuum, device functionality)
- Contamination, Mix-ups

Usability
- Safety
- User experience
- Compliance, Instructions for use

Marketing
- Dress up the products for shelves to differentiate from others
- Communicating messages
- Building a brand narrative

2. Regulatory Requirements



3.1 Challenges – Design Controls for Combination Products

FDA Guidance CGMP Requirements for Combination Products (01/2017)
Design controls and Risk management for Prefilled syringe packaging

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

Risk	*Mitigation*
Syringe filled with incorrect drug dose	In-process acceptance testing, process validation
Loss of sterility	Container-closure integrity testing, packaging validation/testing

3.1.1 Documentation Requirements

Drug User Interface Design	Design Controls for Combination Products including Packaging
Project Plan	Design & Development Plan
Drug, Pkg, Lblg, Users, Use cases, Use steps, Task analysis, Regulation, Standards	Design Input: (User needs, User requirements, SN, Standards, FDA Guidance)
Risk Assessment (prior knowledge, **use FMEA, URRA**)	Risk management (ISO 14971, Hazard Analysis, design, use, process FMEA), URRA
Packaging, labeling specs	Design Output: packaging specification, label spec, IFU
Development project Go/No Go	Design Review: review report
Usability testing, Formative Human Factor Study	Design Verification: Supplier data, document review, risk analysis, DV testing;
Human Factor Summative	Design Validation: Human Factor study, risk analysis, clinical evaluation;
Technology Transfer, Control Strategy	Design Transfer: from design to production specification, Control Strategy
Change controls (LCM)	Design Change: device constituent parts including packaging
Drug Project File + CMC + Labeling	Design History File + CMC + packaging & labeling

3.1.2 Example - Packaging Design Controls

User Needs	Design Input	Design Output	Design Verification	Design Validation	CMA CPP	Control Strategy
Device shall function after shipping	Packaging shall protect product	Pkg Drawing Spec	ISO 11608, ISTA Ship test	HFS	CMA CPP	IC, RT, ST
Label shall be intact and legible	Label presence and Legible	Label Spec	Adhesion and Rub test	HFS	CMA ICP CPP	IC, IPC, RT, ST
Enable self-injection	Easy to open carton & remove product from pkg	Pkg spec, drawing	Lab test	HFS	CMA	IC

Control Strategy: IC =Incoming Control, IPC= In-Process Control, RT = release test, ST = stability test
CMA = critical material attribute, CPP = critical process parameter, HFS = Human Factors study

3.1.3 Example - Packaging Risk Analysis

Hazard (FM)	Potential Cause	HS (Potential Failure Effect)	Harm	Risk Control
Pkg & product damaged during shipping	Carton material not strong enough to protect product from shipping	Missed dose, Delay in therapy, Loss of Sterility	Lack of therapeutic benefit, persistent lack, Infection	Pkg spec, IC
Product falls from partition cavity	Partition design not able to secure product	Missed dose, Delay in therapy	Lack of therapeutic benefit, persistent lack	Pkg spec, IC
Device cap removed from shipping	Carton design allows components to move inside pkg	Missed dose, Delay in therapy	Lack of therapeutic benefit, persistent lack	Pkg spec, IC, IFU

Note: FM = failure mode, HS = hazard situation, Pkg = packaging, spec = specification, drawing;
Risk Control Strategy: IC = Incoming Control, IPC= In-Process Control, RT = release test, ST = stability test, IFU = Instructions for use

Hazard (Use Error)	Potential Cause	HS (Potential Failure Effect)	Harm	Risk Control
Product dropped, damaged, not able to inject	User unable to remove product from pkg, damaged carton	Partial or missed dose, Delay in therapy	Lack of therapeutic benefit	Pkg design spec; IFU instructs user to properly remove product from pkg
Closure integrity Needle cover removed	User forgets the sequence	Loss of sterility, Contaminant exposure, Dried drug clogged needle	Local infection, Allergic reaction, Lack of therapeutic benefit	IFU instructs user to not remove needle cover until ready to inject

3.2 Challenge – Minimizing Medication Errors

In 2000, Institute of Medicine (IOM) "To Err Is Human"	In July 2006, IOM "Preventing Medication Errors"
• 7,000 deaths annually due to medication errors; • FDA to enforce standards for the **design of drug packaging** and labeling to maximize safety in use;	• Labeling and packaging issues caused 33% of medication errors, including 30% of fatalities; • FDA to incorporate **human factors engineering** in its review process to address issues.

Examples of known problems and medication errors due to design

- Product Strength:
  - Miscalculations or forgetting how many units have already been administered
- IV Products:
  - Fail to dilute, dilute incorrectly, wrong diluent or an incorrect amount of diluent;
  - Oral/topical drug products packaged in vial containers led to IV administration;
  - Prefilled syringe led to IV push rather than IV infusion.

3.2.1 Applying Human Factors and Usability Engineering

Medication errors can be avoided at the design stage
- Learned from past medication errors
- conducting proactive risk assessments, **FMEA and human factors or user testing.**

User interface: includes all points of interaction between product and user
- e.g. Carton, partition
  E.g. Syringe, vial, carton labels
- instructions for use, etc

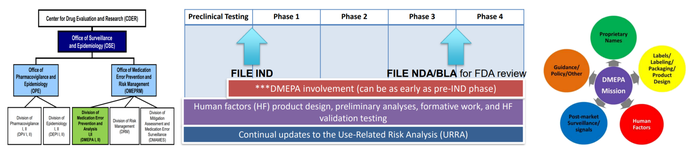
- FDA Safety Considerations for Product Design to Minimize Medication Errors (2016)
- FDA Safety Considerations for Container labels Carton Labeling Design to Minimize Medication Errors (2022)
- FDA Use Related Risk Analysis for Drugs, Biologics, Combination Products (draft 07/2024)

Reference: "URRA and HF Protocol Reviews: What to Submit for an Efficient Review" Lolita Sterrett, PharmD, Division of Medication Error Prevention and Analysis II, Office of Medication Error Prevention and Risk Management Office of Surveillance and Epidemiology CDER, US FDA SBIA's Regulatory Education for Industry (REdI) 2023 – June 6, 2023

3.2.2 Use Related Risk Analysis & Human Factor Engineering

A risk analysis tool
- Identifies use-related hazards associated with product use and the measures implemented to reduce those risks;
- supports the entire Human Factor engineering (HFE) process;
- considered as part of an overall risk management framework.

Drug Development process and Human Factors Considerations



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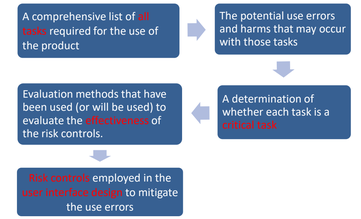
3.2.3 Example – Use Related Risk Analysis

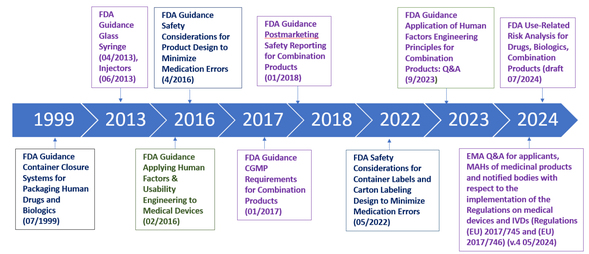
The Use-Related Risk Analysis (URRA) should include:



Task #	Use Task	Potential use error	Potential Hazard Harm Severity	Critical task	Risk mitigation measure for each use error	Evaluation method
1	Choose full dose	User takes only one vial instead of two	Full dose not delivered, underdose	y/n	IFU describes dose amount per vial on carton/vial labels	HF studies observe users, inform and optimize design of labels, confirm users can read and follow IFU
2	Prepare full dose	User forgets to dilute because the drug is already in solution	Patient receives overdose, inadvertent AE	y/n	IFU differentiates the labels between drug solution and diluent	Formative and summative HF study to observe and confirm users can read IFU and follow the process in IFU
3	Deliver dose	Nurse injects the SC drug as IV push	Patient gets overdose, inadvertent AE	y/n	Ensure clarification on syringe label for SC dose, IFU includes a picture to show SC site(s), and warning for SC delivery	HF study to observe and confirm users to inject to SC sites

The table headline is coped from Appendix URRA Table – Example format in FDA Use-Related Risk Analysis for Drugs, Biologics, Combination Products (draft 07/2024)
Note: SC = subcutaneous, IV = intravenous, AE = adverse effect, IFU = instructions for use, HF = Human Factors

3.3.1 Regulatory Evolution



3.3.2 New Packaging Technologies and Beyond