Applying Human Factors Engineering to Drug Development

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North Carolina Regulatory Affairs Forum Monthly Seminar Series

Oct 26, 2023

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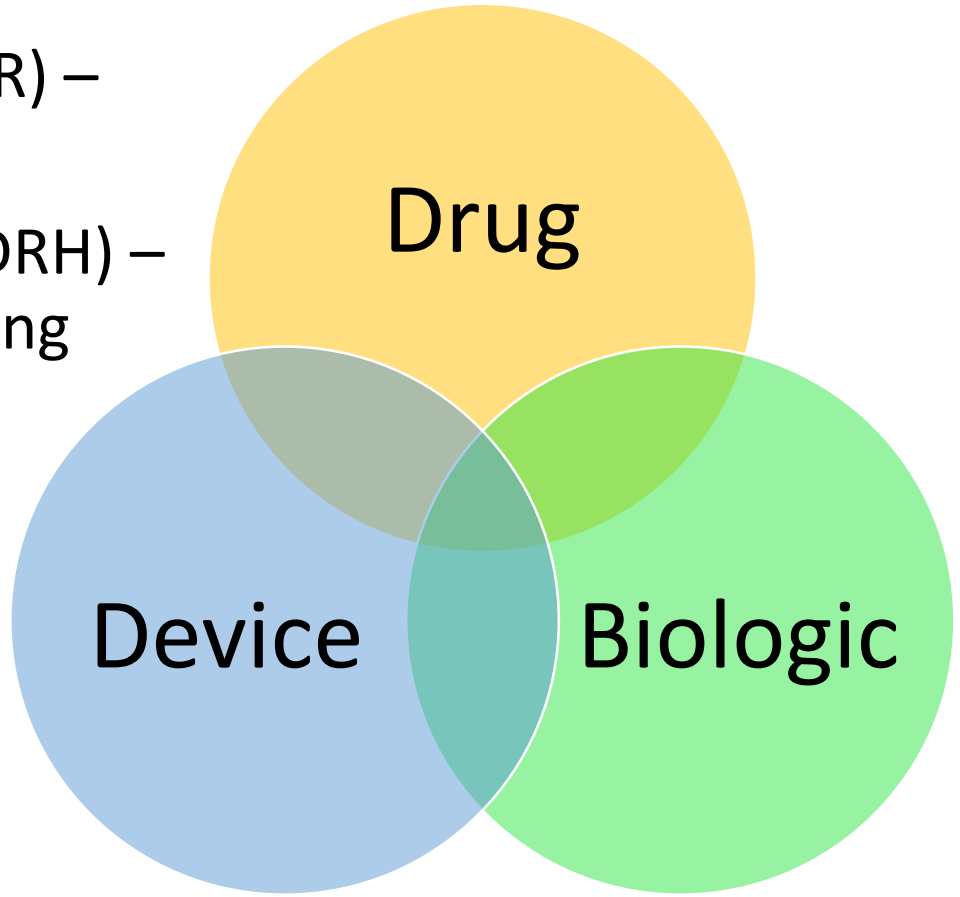
Agenda

1. FDA Overview
    a. Product Review Centers
    b. Combination Products
2. Human Factors Engineering (HFE)
    a. Considerations
    b. Key terms & definitions
    c. Risk Management in HFE & Combination Product Development
    d. Process (IEC-62366, FDA Guidance docs)
3. Regulatory Review

FDA Organization – CDER, CBER, and CDRH

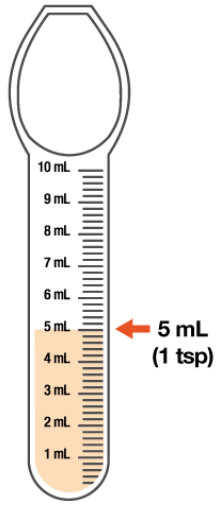
- Center for Biologics Evaluation and Research (CBER) – regulates biological products for human use
- Center for Drug Evaluation and Research (CDER) – regulates drug products
- Center for Devices and Radiological Health (CDRH) – regulates medical devices and radiation-emitting products

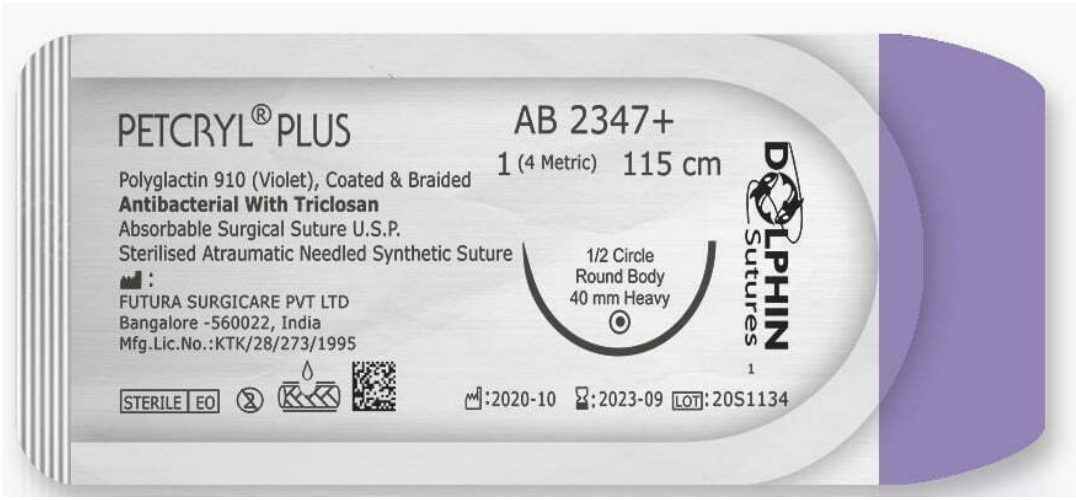
- What about combination products?
  - Drug-device, drug-biologic, device-biologic



Drug-Device Combination Products - Examples

- Co-packaged kit: drug vial packaged with devices for administration, like a liquid oral medication packaged with a dose-dispenser
- Prefilled drug delivery device: autoinjectors (Epipen), nasal sprays (Flonase), pre-filled syringe (insulin pen)
- Device coated/impregnated with drug: drug-eluting stent, antimicrobial-coated sutures, transdermal patch





Regulation of Drug-Device Combination Products

- Who regulates – CDRH or CDER/CBER? Which Agency Center has primary jurisdiction for the product?
- Lead Center is determined based on primary mode of action (PMOA)
  - PMOA: “the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product”
- If the PMOA is unclear, Sponsors can contact the Office of Combination Products to discuss if the product is drug- or device-led (ie, which constituent holds the PMOA)
- Lead Center will consult with other involved Center(s) during review

Regulation of Drug-Device Combination Products

- Device-led combination products
  - Drug-eluting stents – FDA has determined that these products' primary mode of action is to physically maintain the vessel. The drug component has a secondary role in augmenting the safety and/or efficacy of the stent.
  - Clinical investigations under IDE instead of IND
  - Marketed under a PMA or 510(k)
- Drug-led or Biologic-led combination product
  - Products where the device works to administer the drug (inhalers, injectors, transdermal patches)
  - Clinical investigations conducted under an IND
  - Marketed under an NDA or BLA

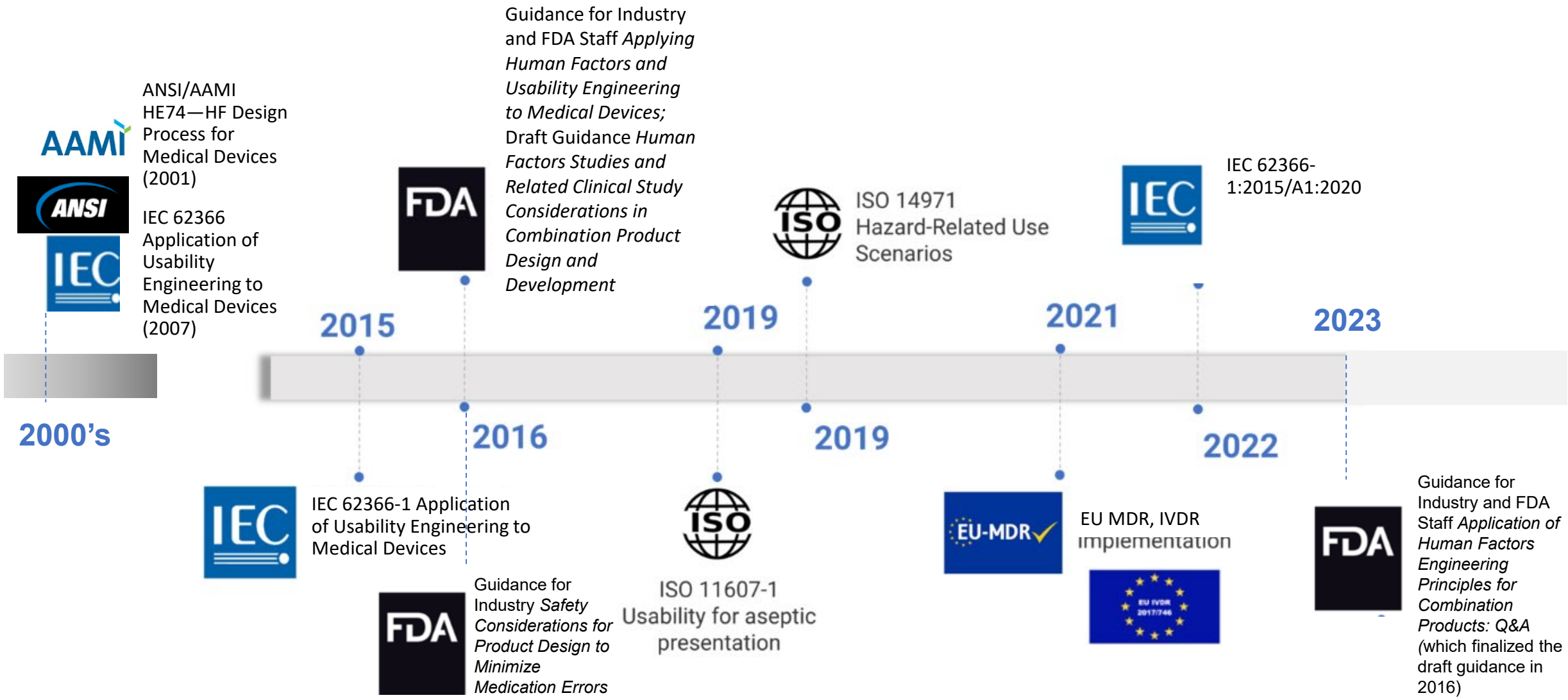
Product Classifications

- CP classification depend on the classification of the constituent part
  - Drug
  - Device… does not achieve its primary intended purpose through chemical action… is not dependent upon being metabolized…
- Pre-filled drug-delivery devices are primarily class II medical devices
- Class II medical devices are subject to both general and special controls
  - Special controls: device-specific controls with its own guidance documents to ensure reasonable safety and effectiveness of the device
- Human Factors Engineering is a necessary control that minimizes medication delivery errors

Why HFE?

- HFE is an essential requirement for all new drug delivery combination product approvals
- Combination product market ~$177.7 B by 2024 (Grand View Research)
- Delivery system is a differentiator or comparator to RLD requiring HF considerations for the product
- Improves time and cost to market
- Ensures safety of the product, ergonomics and user satisfaction

Regulatory Growth Timeline: HFE of Drug-led CP



Considerations for HFE Program

- Device and Drug teams as partners in the CP development process
  - Support with design validation, i.e. usability/HFs, medication errors
  - Understand the intended use, use environment, and intended user population
- What are / How to avoid errors that could occur and result in user harm?
  - How does the user interact with a product in the use environment?
  - What are ways the user can use the product that can lead to medication errors?
  - Are the Labels, IFU clear and accurate?
  - Are there any additional testing needed to satisfy user needs? To ensure safety risks are mitigated before approval?
- Start the HF process as early as possible in development
  - Ensure feedback into the product design
  - Inform risk assessment and subsequent risk controls

HFE Definitions (IEC 62366-1:2015, FDA)

- **HUMAN FACTORS ENGINEERING**: application of knowledge about human behavior, abilities, limitations, and other characteristics to the design of MEDICAL DEVICES (including software), systems and TASKS to achieve adequate USABILITY
- **USABILITY**: characteristic of the USER INTERFACE that facilitates use and thereby establishes EFFECTIVENESS, EFFICIENCY and USER satisfaction in the intended USE ENVIRONMENT
- **INTENDED USE**: use for which a product, process or service is intended according to the specifications, instructions and information provided by the manufacturer. The intended medical indication, patient population, part of the body or type of tissue interacted with, user profile, use environment, and operating principle are typical elements.
- **USE /APPLICATION SPECIFICATION**: summary of the important characteristics related to the context of use of the product. A living document initiated with preliminary HFE research to understand the intended use, users, use environment and other details and limitations around the context of use.
- **USER INTERFACE:** All points of interaction between the user and the product. This includes physical aspects of the device/product, visual, auditory, tactile displays, packaging, labels, IFU, training material, etc.

HFE Definitions (IEC 62366-1:2015, FDA)

- **USE ERROR:** user action or lack of while using the device that leads to a different result than that intended by the manufacturer or expected by the user
- **REASONABLY FORESEEABLE MISUSE**: use of a product or system in a way not intended by the manufacturer, but which can result from readily predictable human behavior. Can be intentional or unintentional.
- **ABNORMAL USE**: conscious, intentional act or intentional omission of an act that is counter to or violates NORMAL USE and is also beyond any further reasonable means of USER INTERFACE-related RISK CONTROL by the MANUFACTURER.
- **USE SCENARIO**: specific sequence of TASKS performed by a specific USER in a specific USE ENVIRONMENT and any resulting response of the MEDICAL DEVICE.
- **CRITICAL TASK:** user tasks which, if performed incorrectly or not performed at all, would or could cause (serious) to the patient or user, where harm is defined to include compromised medical care.
- **FORMATIVE EVALUATION**: USER INTERFACE EVALUATION conducted with the intent to explore USER INTERFACE design strengths, weaknesses, and unanticipated USER ERROS. **Generally performed iteratively throughout the design and development** process, but prior to SUMMATIVE EVALUTION, **to guide** USER INTERFACE design as necessary.
- **SUMMATIVE EVALUATION**: USER INTERFACE EVALUATION conducted at the end of the USER INTERFACE development with the intent to obtain OBJECTIVE EVIDENCE that the USER INTERFACE can be used safely. Relates to **validating the safe use of the** USER INTERFACE.

Case Study – Lyumjev KwikPen

- Eli Lilly; BLA 761109; Approved June 2020
- Lyumjev is indicated to improve glycemic control in patients with diabetes
- Intended use / use environment - for self-administration or administration by a caregiver
- Device component (KwikPen) had previously been reviewed as part of the Humalog approval
- Clinical studies conducted: 18 clinical pharmacology studies and 3 Phase 3 studies
- Human factors differentiation study to demonstrate that Lyumjev pens can be differentiated from other products that users may be taking concurrently (ie, a long-acting insulin pen)

Case Study – Lyumjev KwikPen

Distractor Group C1
Lyumjev KwikPen U-100
Humalog pen
Basaglar pen

Distractor Group C2
Lyumjev KwikPen U-100
Novolog pen
Lantus pen

Distractor Group C6
Lyumjev KwikPen U-100
Lyumjev KwikPen U-200
Lyumjev Junior KwikPen U-100

Case Study – Lyumjev KwikPen

HF study outcome (n = 66 participants)

- In 6 instances, participants selected the wrong pen
  - 5 of these included the selection of other short-acting insulins and would have resulted in no clinically significant harm
  - 1 instance involved the selection of a basal insulin instead of Lyumjev – this error could have clinical significance
- Minor labeling changes were recommended by the Agency, but further HF testing was deemed unnecessary
- NDA approved, product is commercially available
- Reference: Drug Approval Package – FDA review files “Other Reviews” https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761109Orig1s000OtherR.pdf

Combination Product Critical Tasks

- Critical tasks can be analogous to Hazard-related Use Scenarios, a use scenario that could lead to harm
  - Selection determined by the severity of harm, including compromise medical care
  - Threshold is determined by the manufacturer, e.g. task which could lead to medication error
- Combination product critical tasks refer to use-related risks resulting from each of the constituent parts and use of both constituent parts together in a combination product
- Properties of a drug can affect whether the product is successfully administered
  - The viscosity of an ophthalmic solution may make it difficult to administer the right amount of eye drops
  - Chemically irritating formulation could lead to local pain during injection

Combination Product Critical Tasks

- CDER holds a higher standard for “Critical task” than CDRH
- The Agency is particularly interested in the assessment of tasks that:
  - Impact dosing (overdose, underdose, missed dose)
  - Impact administration of the product (wrong site of administration, improper preparation of drug/biologic prior to dosing)
  - Have the potential to result in harm
  - Unintended by the manufacturer or unexpected by the user

Medication errors can occur throughout the medication-use system (https://www.mdpi.com/1424-8247/15/8/977)

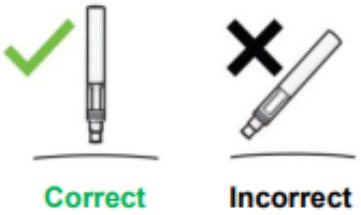
Case Study – Cosentyx (secukinumab) SensoReady Pen

- Novartis; BLA 125504; Approved January 2015
- Indication: Cosentyx is a human IL-17A antagonist indicated for the treatment of plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis, enthesitis-related arthritis
  - First approved for plaque psoriasis
- Intended use / use environment: For use under the guidance and supervision of a healthcare provider; adults may self-administer after proper training
- Reference: FDA approval package and current labeling https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125504

Case Study – Cosentyx (secukinumab) SensoReady Pen

- Human Factors studies reviewed as part of initial approval
- N = 165 participants representative of potential users
  - 94 received training and then returned for a simulated use assessment either 1 or 4 weeks after training
  - 71 were untrained and carried out the simulated use assessment without support to represent the worst-case use scenario
- Trained participants – 7/94 failed to deliver injection
  - 5 failed to activate the pen or hold it against the injection site long enough
  - 2 failed due to moderator intervention to prevent needle stick injuries
- Untrained participants – 6/71 failed to deliver injection due to failure to hold the pen against the injection site long enough
- In addition to injection failures, 20/165 participants experienced difficulty injecting but were able to successfully complete the task

Case Study – Cosentyx (secukinumab) SensoReady Pen



- Based on the HF study results, the instructions for use were updated to address the task failures

Step 6. Starting the injection:

- Press the COSENTYX Sensoready pen firmly against the skin to start the injection **(see Figure J)**.
- The **1st click** indicates the injection has started.
- **Keep holding** the COSENTYX Sensoready pen firmly against the skin.
- The **green indicator** shows the progress of the injection.

Figure J

Step 7. Completing the injection:

- Listen for the **2nd click**. This indicates the injection is **almost** complete.
- Check the **green indicator** fills the window and has stopped moving **(see Figure K)**.
- The COSENTYX Sensoready pen can now be removed.

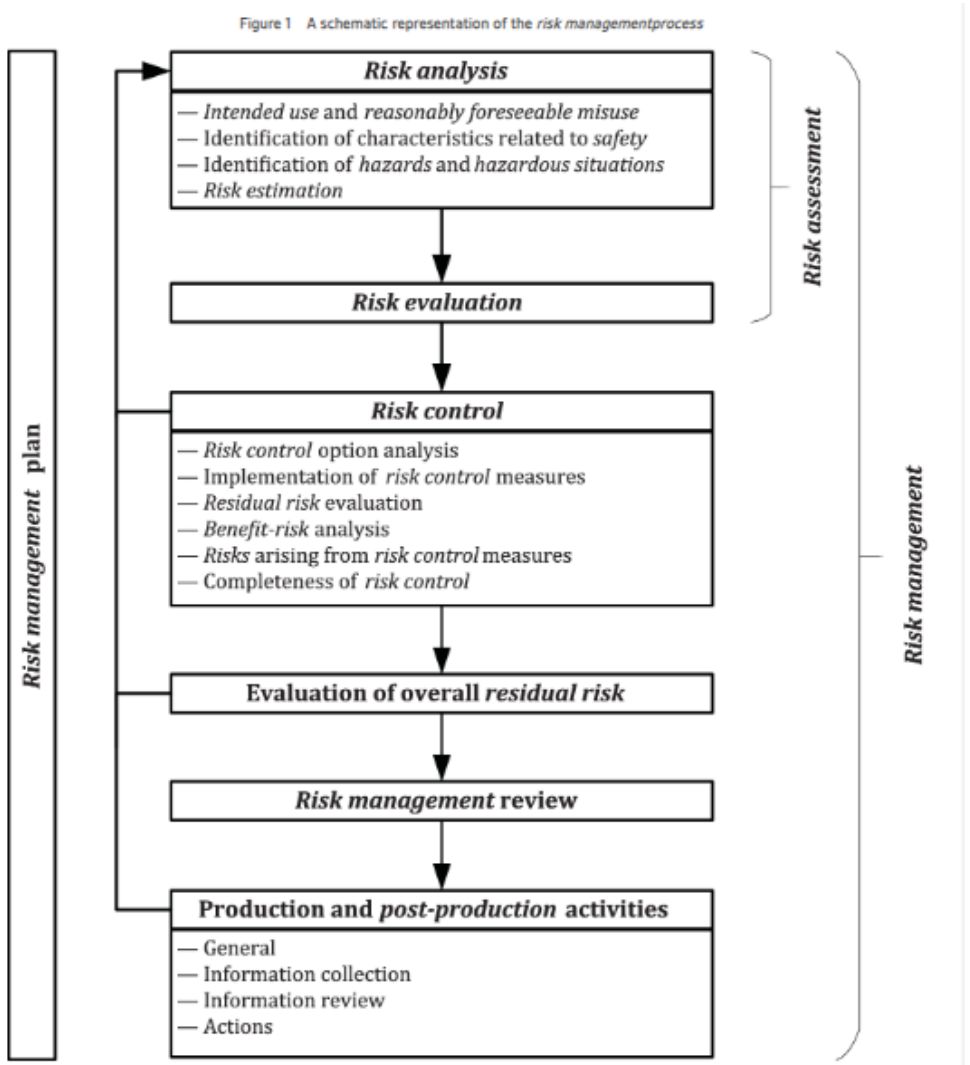
Figure K

HFE Process

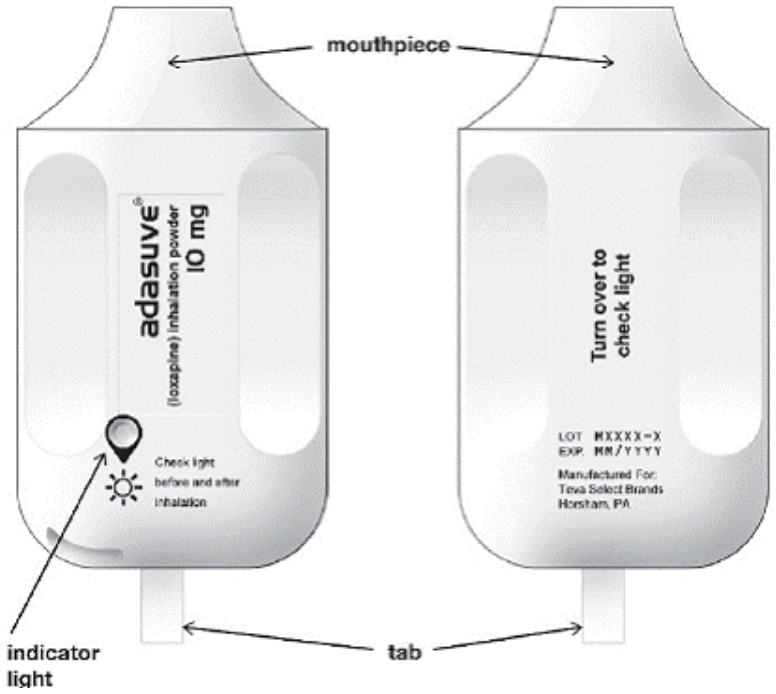
- Purpose
  - To minimize the risk of Use Error and provide safety to the User(s) when used as intended and when considering reasonably foreseeable misuse
  - To enhance usability and user-friendliness
  - To identify critical tasks early on (via formative studies), avoiding potential issues
  - To Confirm that target users can safely and effectively use the final product design (Summative validation study)
- Use Risk-based process to understand what contributes to potential use errors and what can be done to prevent them
  - Analysis scoped to critical tasks (impact the safety or efficacy of the product)

Risk Management in HFE and CP Development

- Assess & control Use-related Risks, including medication error
  - URRA, uFMEA, aFMEA
  - Reduce risk to AFAP
- Assess each constituent part and CP based on the Intended use and indications for use
- Optimize the user interface and CP use during development
- Support post-market issues and events



ISO 14971:2019



Case Study – Adasuve (loxapine) inhalation powder

- Alexza Pharma; NDA 022549; Approved December 2012
- Indication: for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults
- Intended use / use environment: Must be administered only by a healthcare professional and only in a certified healthcare setting
- NDA was initially submitted in December 2009; a Complete Response Letter was issued in October 2010 for concerns about safety in patients with respiratory disease
- The CRL requested that the sponsor conduct a HF validation study with representative healthcare providers and patients
- Source: FDA approval package and current labeling https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022549_adasuve_toc.cfm

Case Study – Adasuve (loxapine) inhaler

- FDA recommendations - conduct a HF validation study to demonstrate the product can be used safely and effectively and to provide the following analyses
  - User performance, use errors, task failures
  - Use-related hazards that could pose a risk to HCPs and/or patients
  - Use of the device in a manner that was unintended or unanticipated
  - Proposed risk mitigation strategies
  - Evaluation of test participant feedback
  - Discussion of any further mitigation strategies or validation testing that may be necessary

Case Study – Adasuve (loxapine) inhaler

Step 1. Open the Pouch

When ready to use, tear open the foil pouch and remove the inhaler from the package (see Figure 1).

Figure 1. Tearing the pouch

When the ADASUVE inhaler is removed from the pouch, the indicator light is off (see Figure 2).

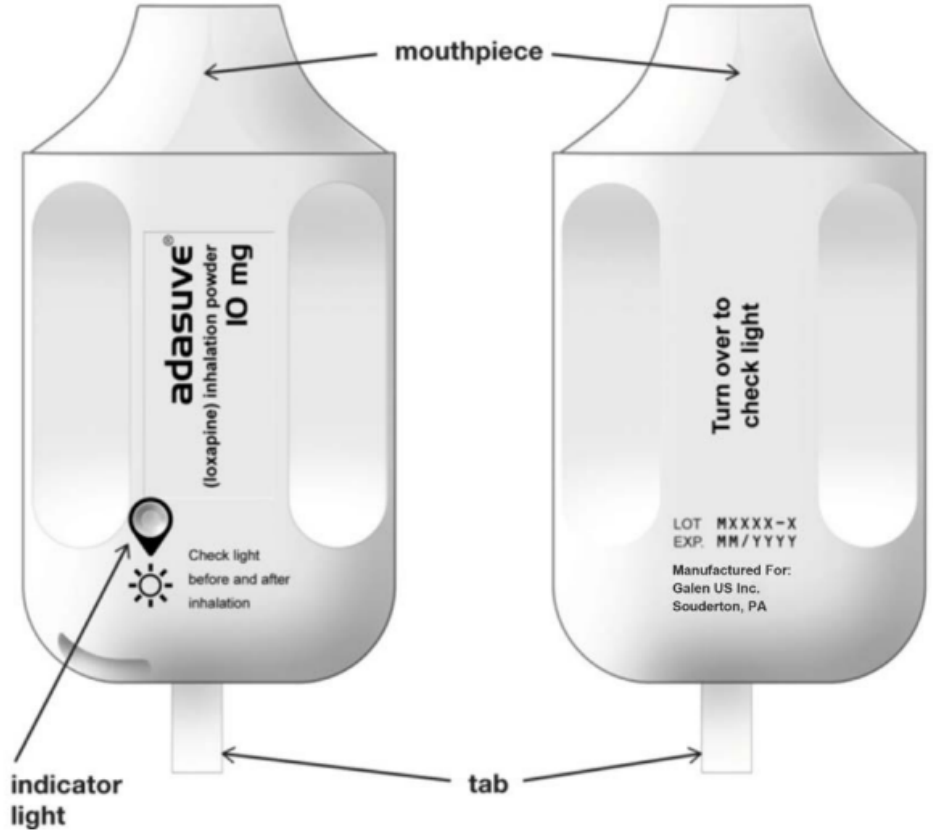
Changes based on FDA feedback and results of HF study:

Location for opening pouch was changed so the device can be removed safely

Device oriented in pouch so that LED light is facing the labeled side of the pouch

Case Study – Adasuve (loxapine) inhaler

Figure 2. ADASUVE Inhaler with Indicator Light



Step 2. Pull Tab

Firmly pull the plastic tab from the rear of the inhaler (see Figure 3). Check that the green light turns on. This indicates that the inhaler is ready for use. Use the inhaler within 15 minutes after removing the tab to prevent automatic deactivation of the inhaler. The green light will turn off, indicating that the inhaler is not usable. Discard the inhaler after one use.

Changes based on FDA feedback and results of HF study:

Relocate product name, dosage form, and strength to same side as LED button to minimize error from not verifying that LED light is on

Add note stating the significance of LED light

Case Study – Adasuve (loxapine) inhaler

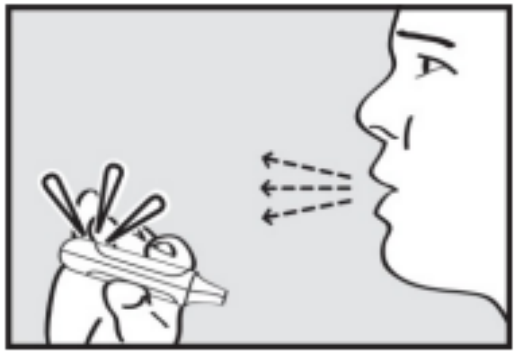
Step 3. Explain Procedures to the Patient

Explain the administration procedures to the patient prior to use, and advise the patient that it is important to follow the instructions. Inform the patient that the inhaler may produce a flash of light and a clicking sound, and it may become warm during use. These are normal.

Step 4. Instruct the Patient to Exhale

Instruct the patient to hold the inhaler away from the mouth and breathe out fully to empty the lungs (see Figure 4).

Figure 4. Exhale



Changes based on FDA feedback and results of HF study:

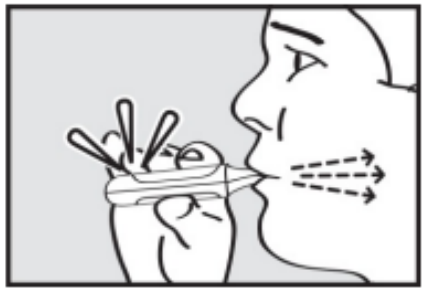
Notify patient that there may be a flash of light and a clicking sound so they are not startled

Case Study – Adasuve (loxapine) inhaler

Step 5. Instruct the Patient to Inhale

Instruct the patient to put the mouthpiece of the inhaler between the lips, close the lips, and inhale through the mouthpiece with a steady deep breath (see Figure 5). Check that the green light turns off indicating that the dose has been delivered.

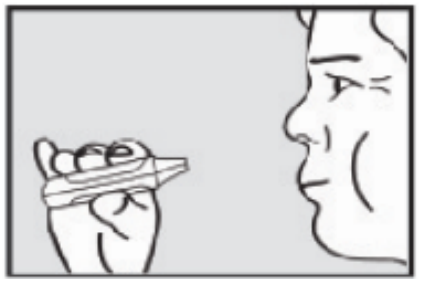
Figure 5. Inhale



Step 6. Instruct the Patient to Hold Breath

Instruct the patient to remove the mouthpiece from the mouth and hold the breath for as long as possible, up to 10 seconds (see Figure 6).

Figure 6. Hold Breath



Changes based on FDA feedback and results of HF study:

Specify how long patient should hold breath after inhaling

Light turns off to indicate dose has been delivered

Expectations for HF Regulatory Review

- Compiled information from activities conducted in the HFE process (HFE package)
- Risk-based HF Submission Category determines what information in the marketing submission
- FDA: pre-review process for manufacturers to seek feedback on HF approach
- EU, Other countries: no pre-submission interaction with the health authority; HF summative study report is submitted as part of MAA review
- Review is based on the question at hand specific to the type of submission

Table 1. Recommended minimum human factors information that should be provided for a marketing submission based on HF Submission Category

Recommended information (Report section numbers from Section V below)	HF Submission Category		
	1	2	3
Conclusion and high-level summary (Section 1)	✓	✓	✓
Descriptions of: • Intended device users, uses, use environments, and training (Section 2) • Device-user interface (Section 3) • Summary of known use problems (Section 4)		✓	✓
Preliminary activities • Summary of preliminary analyses and evaluations (Section 5)			✓
Use-related risk analysis • Analysis of hazards and risks associated with use of the device (Section 6) • Identification and description of critical tasks (Section 7)			✓
Details of validation testing of final design (Section 8)			✓

FDA Draft Guidance for Industry and FDA Staff, Dec9, 2022 *Content of Human Factors Information in Medical Device Marketing Submissions*

References

- EN/IEC 62366-1:2015/A1:2020 Medical Devices—Part 1: Application of Usability Engineering to Medical Devices
- IEC TR 62366-2:2016 Medical Devices—Part 2: Guidance on the Application of Usability Engineering to Medical Devices
- ISO 14971:2019 Application of Risk Management to Medical Devices
- FDA Guidance on Applying Human Factors and Usability Engineering to Medical Devices
- FDA Guidance on Application of Human Factors Engineering Principles for Combination Products: Questions and Answers
- FDA Guidance on Safety Considerations for Product Design to Minimize Medication Errors
- FDA Guidance on Instructions for Use—Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products
- FDA Guidance on Bridging for Drug-Device and Biologic-Device Combination Products
- Ed. Susan W.B. Neadle. 2023 The Combination Products Handbook. A Practical Guide for Combination Products and Other Combined Use Systems. CRC Press
- FDA Draft Guidance on Content of Human Factors Information in Medical Device Marketing Submission
- FDA Draft Guidance on Contents of a Complete submission for Threshold Analysis and Human Factors submission to Drug and Biologic Applications
- EMA Guideline on Quality documentation for Medicinal Products when used with a Medical Device
- EN ISO 20417:2021 – Medical devices. Information to be supplied by the manufacturer
- ANSI/AAMI HE75:2009 (R2018) Human Factors Engineering- Design of Medical Devices
- https://www.fda.gov/combination-products/jurisdictional-information/intercenter-agreement-between-center-drug-evaluation-and-research-and-center-devices-and
- https://go.bd.com/rs/565-YXD-236/images/ONdrugDel%20%2883%29%20Feb%202018%20%28BD%29_nongated_Pt%20Exp%20tab_TAB%203-V1.pdf

Thank you

Backup slides