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International Pharmaceutical Aerosol Consortium on Regulation & Science

DDL2018
DRUG DELIVERY TO THE LUNGS

# Human Factors

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# Human Factors

Human Factors / Usability Engineering focuses on the interactions between people and devices. The critical element in these interactions is the **device-user interface, and demonstration of safe and effective use.**

*'…application of knowledge about human behaviour, abilities, limitations, and other characteristics to the design of medical device' (EN ISO 62366-1:2015)*

*'…the application of knowledge about human capabilities (physical, sensory, emotional, and intellectual) and limitations to the design and development of tools, devices, systems, environments, and organizations…..*
*The primary HFE concern… is to ensure that medical devices can be used safely.' (ANSI/AAMI HE75:2009/(R)2013)*

*'The application of knowledge about human behavior, abilities, limitations, and other characteristics of medical device users to the design of medical devices including mechanical and software driven user interfaces, systems, tasks, user documentation, and user training to enhance and demonstrate safe and effective use.' (FDA, CDRH, 2016)*

*'…refers to how a person will interact with the systems surrounding them, including the technology they use.'*
*'…..uses knowledge from such diverse subjects as anatomy, psychology, engineering and physiology to help design products that suit the user, for more effective and safer use.' (MHRA, HF & UE Guidance, 2017)*

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# Human Behaviour

- Addressing the safety and effectiveness of medical device use requires first coming to grips with the nature of human "users".
- Users aren't machines they are humans using machines.
- One example: in the early 1980s secretaries using computer mice for the first time thought they were foot pedals like dictation machines or sewing machines and therefore put them on the floor.
- "Adverse Events involving medical devices or equipment can lead to serious problems, including incorrect or delayed diagnosis and treatment or patient injuries. When errors involving medical devices recur repeatedly, people typically blame the users instead of the real culprit, which is often a poorly designed interface between the medical device and the user." *(Article from June Nursing 2008, Volume 38, Number 6, Pages 62-63)*

**Human Beings don't always behave the way we expect OR do what we want them to do!**

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# ‘Recent’ History of Human Factors

- Human Factors / Usability Engineering thinking 10/15 years ago:
  - No consistent approach to device development within Industry – ranged from application of engineering to packaging development principles
  - Link between device and drug developers not always strong
  - No clear regulation on expectation of device development content in regulatory submissions
  - Device use was often presented as ‘patient preference’ or ‘ patient ease of use’ data – combination of marketing studies and clinical studies with add-on questionnaires

- Emergence of more advanced technologies, patient advocacy and device complaints on patients ability to use devices drove more focus on Usability Engineering
  - Ensuring the device is designed with the intended user population in mind
  - Driving feedback on usability of device into engineering design during development
  - Place more accountability on device developer for end-use of device
  - Consideration of the device as a delivery system to enable effective use of a drug/medicine

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# ‘Recent’ History of Human Factors

US regulatory landscape cf. Human Factors changed ‘rapidly’ given specific device complaint-types

- A period of time where Industry was unclear on requirements for Usability Engineering, case-by-case feedback on Study protocols sometimes provided by FDA
  - Hold up in device development programs, regulatory review, additional review cycles, additional studies, unclear how study results would be interpreted
- CDRH Draft Guidance on Human Factors issued which was considered by Industry as helpful to provide some clarity on requirements and to define a more consistent approach
  - Still left Industry with challenges in application to different device–types, interpretation of data, risk profile of drug being delivered.

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# Key Principles of Human Factors

- Human factors: “how a person will interact with … the technology they use”
- HF principles are applied “to minimise the risks from human error”
- Human Factors in Healthcare, National Quality Board Concordat, Nov 2013:
  “a wider understanding of HF principles … will contribute significantly to improving the quality of care for patients”
- Therefore manufacturers should “design … medical devices with HF … principles in mind”

# Human Factors: Current Landscape

- Increased focus by Regulatory authorities and within Pharma companies on application of usability engineering during device development and Human Factors as part of that.
- This landscape has driven Industry to come together to discuss and focus on Human Factors in device development
- Significant amount of Human Factors (HF)-related guidance's issued over recent years, including establishing requirements for HF-related assessments in numerous Guidance's (refer to back-up slide):
  - Helpful to provide consistency in expectations to Industry.
  - Positive IPAC-RS engagement with MHRA on device development topics, including Human Factors
  - Little opportunity for public engagement with FDA on Human Factors-related guidance to-date.
- Differing opinions often offered by different Global Regulatory Agencies on requirements; sometimes on a per-product basis – a continuing challenge
  - Review of human factors-related data by regulators during review includes device, product, clinical, labelling and safety reviewers

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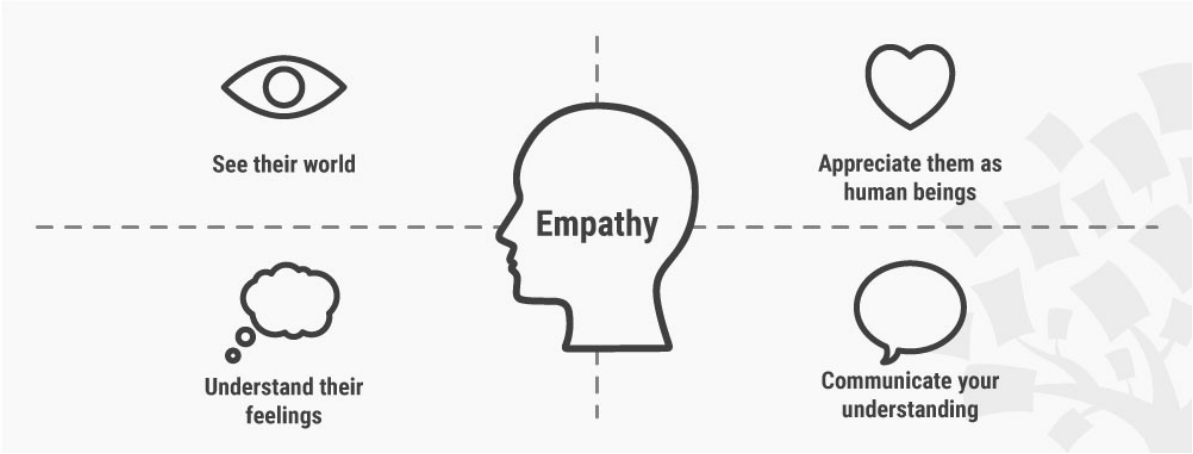
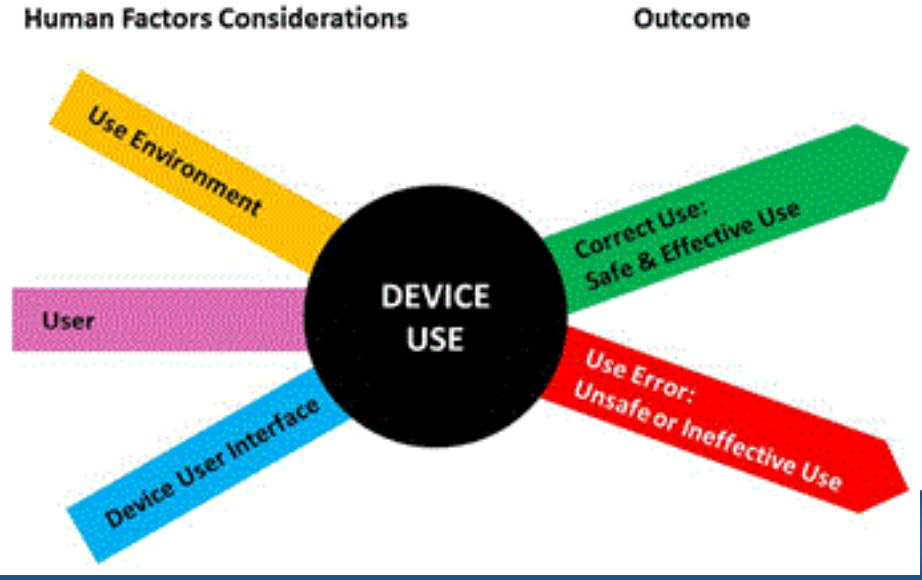
# Human Factors as part of Risk Management

- "A HFE process … should … be applied by … manufacturers in the identification, assessment and mitigation of potential patient safety risks; also in the analysis of incidents that have occurred, in order to identify learning and put into place corrective actions to improve device design." (*MHRA)*
- IPAC-RS emphasises that HFE supports good user interface design, with associated user/patient benefits, but that the regulatory focus should be on HFE as part of the wider risk management process and risk-benefit assessment
- HFE, as a risk management process, is applied throughout development and through post-market as part of lifecycle management



# Human Factors as part of Risk Management

- The objective of regulatory focused HF is to minimise use-related risk as far as practicable and to ensure that residual use-related risks are acceptable
  - Demonstration of Safe and Effective Use by intended users, in intended use environment
- No device is risk free, not all errors/risks are equal
- A residual risk profile, that cannot practicably be reduced further, can be judged acceptable *if* the medical benefits outweigh the overall residual risk
  - *requires assessment with consideration of potential clinical, safety and quality impact*
- The HF process, integrated within device development, provides the analytical & empirical evidence that the above objective* has been met

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# Key Elements of Definitions

- **User interface (common)**
  - includes all sources of information (i.e. instructional material, labeling, packaging) and training (inc manuals)
- **User group (ISO 62366)**
  - subset of intended users who are differentiated from other intended users by factors that are likely to influence usability, such as age, culture, expertise or type of interaction with a medical device
- **Critical task (FDA CDRH HF guidance)**
  - a user task which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care
- **Critical use error**
  - a use error which would or could result in serious harm to the patient or user
- **HF validation study** (FDA HF guidance – previously referred to as summative HF)
  - testing conducted at the end of development to provide evidence that the user interface can be used safely
- **Residual risk** (from ISO 14971)
  - risk remaining after risk control measures have been taken
- **Risk/benefit analysis** (description from ISO 14971)
  - if a residual risk is not judged acceptable ... and further risk control is not practicable, the manufacturer may ... determine if the medical benefits of the intended use outweigh the residual risk
  - if ... evidence supports the conclusion that the medical benefits outweigh the overall residual risk, then the overall residual risk can be judged acceptable

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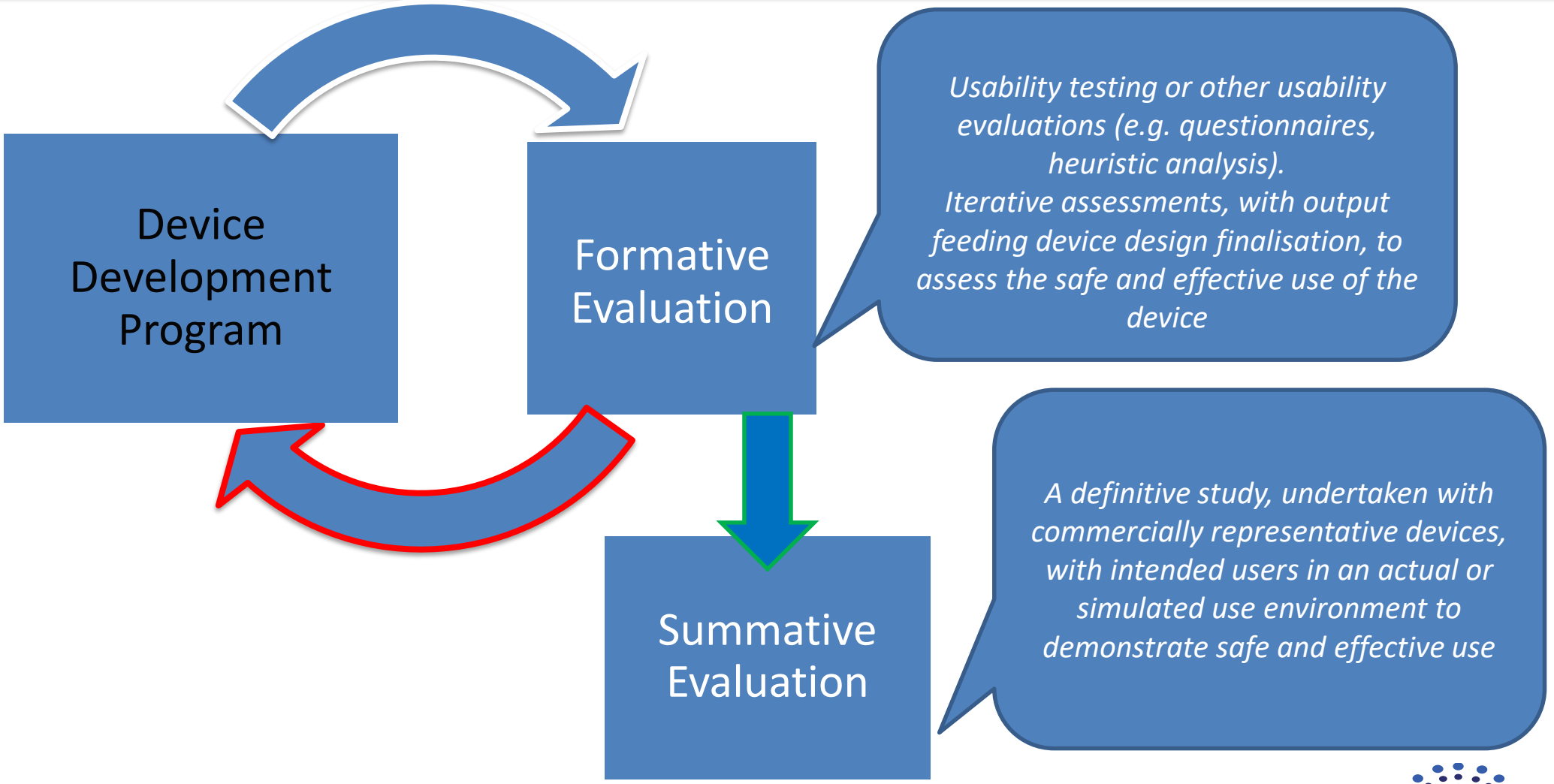
# Human Factors within a Device Development Program

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# Formative vs. Summative/Validation Human Factor Studies

| Formative Usability Testing* | Summative/Validation Usability Testing* |
|---|---|
| A development study completed in the development process of device design to improve the user interface and reduce or eliminate use-related risks. | A definitive study completed at the end of the device design program to demonstrate that the user interface has an acceptable use-related risk profile, and/or that where critical use-related risks remain these could not have been reasonably mitigated or eliminated through design |
| Completed as part of an iterative cycle feeding into design development and risk management. | Completed as an input into Design Control Design Validation and used for acceptability for Market Supply. |
| A demonstration by a representative user of their use of a prototype device, observed and assessed by an independent moderator. Formative testing can also include cognitive walkthroughs and formative inspections (such as heuristic analysis, expert reviews and standard reviews to determine problems not surfaced by user performance). | A demonstration by intended users of all critical tasks associated with intended use, with a commercially representative device to validate that the user can use the device in a safe and effective way. Study sessions must be in actual or simulated use environment. |
| Studies typically involve small numbers of participants (e.g. 5-8) of a specific user group | Studies typically involve e.g. 15-20 participants from each user group. |
| May include objective (e.g. observed) data and/or include subjective (e.g. self reported) data. | |
| May include post test interviews to facilitate root cause analysis | |

**: terms used in FDA/CDRH and/or HE75; adopted as 'standard' Industry terminology to differentiate differing stages of assessments throughout the device development lifecycle. Study outline/objectives/intent summarised here.*

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# Consideration of the User(s)

- Definition of User Groups
  - Age profile, demographics, co-morbidities, patient/caregiver relationships, concurrent therapies……
- Importance of understanding interaction of User and Caregivers in young/elderly
  - Actual responsibilities of user and caregiver in drug delivery
  - Studies need to assess the actual use environment
- Understand the HCP environment for the medicinal product under evaluation
  - Prescription by GP or Specialist
  - Training needs and by whom
  - Home use, hospital or other environment
- User Engagement
  - If User fails to engage with drug delivery requirements: intentionally decides to do something other than as directed by HCP or by IFU
  - Responsibility of User

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# Consideration of Use Environment during Human Factors Studies

- Simulated-use environment
  - Participants may not always consistently demonstrate behaviours consistent with the actual ‘in-use’ environment.
  - Need to ensure the environment and participant /moderator interaction provides for the best possible simulation of actual use.
- HF Study-outcomes to be assessed against the actual ‘in-use’ environment
  - If participants self-correct an error during execution of a task, or where the use of such a device inherently requires some learning behaviour for first-time use by naïve users, this can be assessed appropriately for the device under assessment

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# Human Factors Simulated Use Sessions

Controlled 1:1 interviews

Simulated use

Non-Clinical

Non-Dosing

Demographic consideration

US recruitment

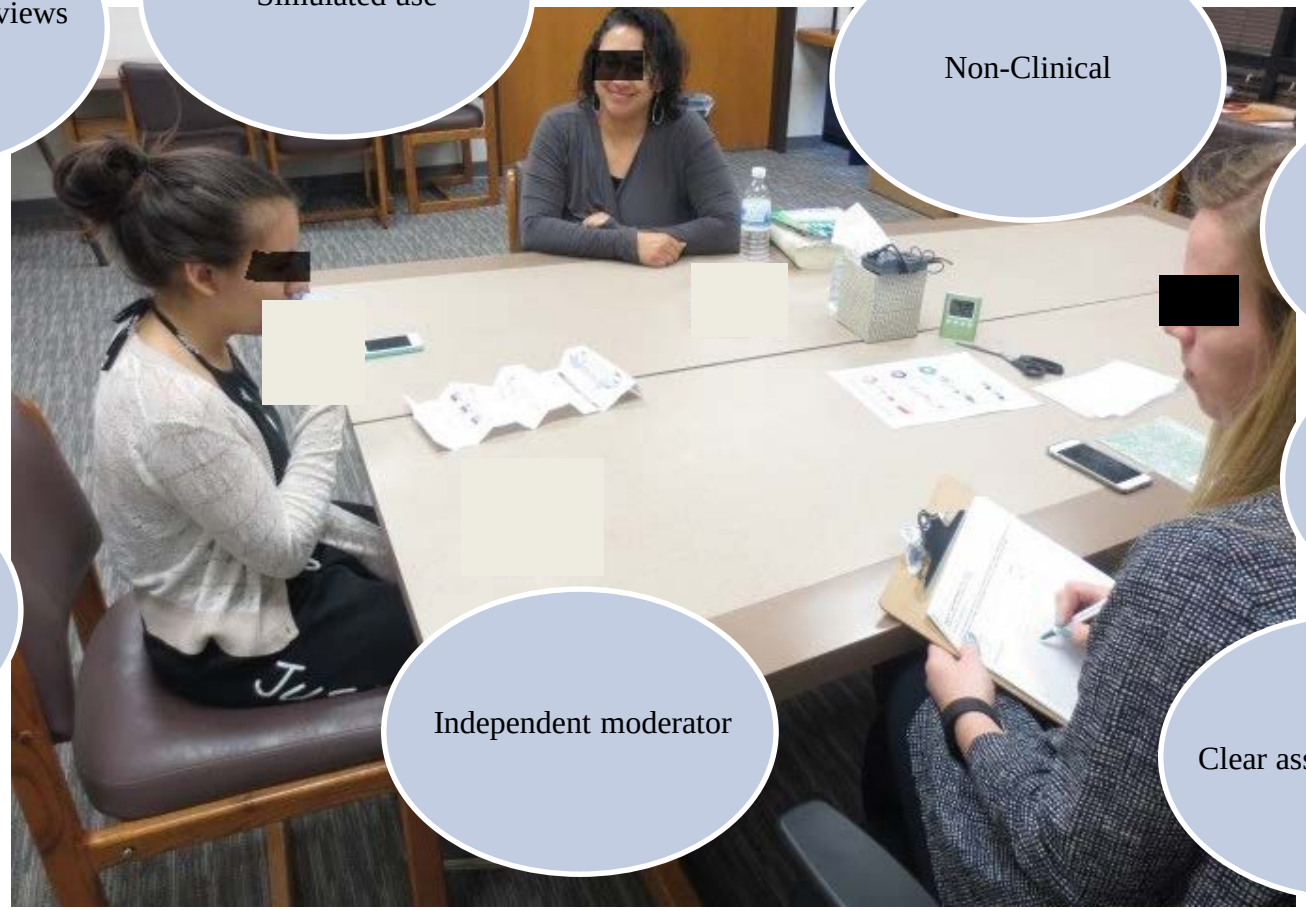
Intended Users

Empty inhalers

Independent moderator

Clear assessment criteria

Age groups



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# Incorporation of Risk Management Principles

- Consideration to the therapeutic effect of the specific drug being delivered and its intended user population
  - the consequences (risks) to the patient of the potential impact of a suboptimal dose delivery for an emergency-response medication are different from the consequences (risks) of the same “error” (a suboptimal dose) with a maintenance-therapy drug.
  - the behaviour of the patient / end user in an emergency response situation can be different to when taking medication for chronic long-term treatment.
- Establish the differing use errors for a delivery system against the impact to drug delivery to the patient
  - develop use error classifications to establish drug-specific acceptable / not acceptable errors
    - define critical use errors to enable use errors observed in Human Factor studies to be assessed for their impact to the patient in terms of impact on dose delivery and safety.

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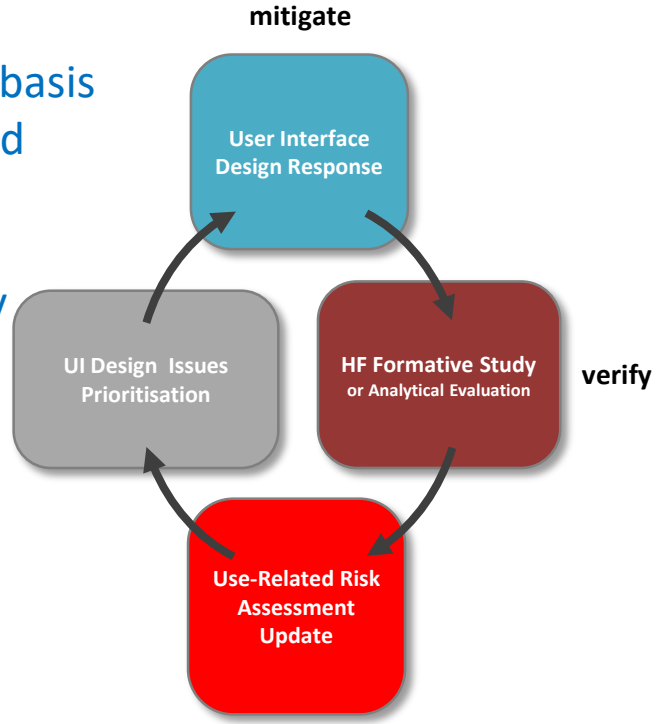
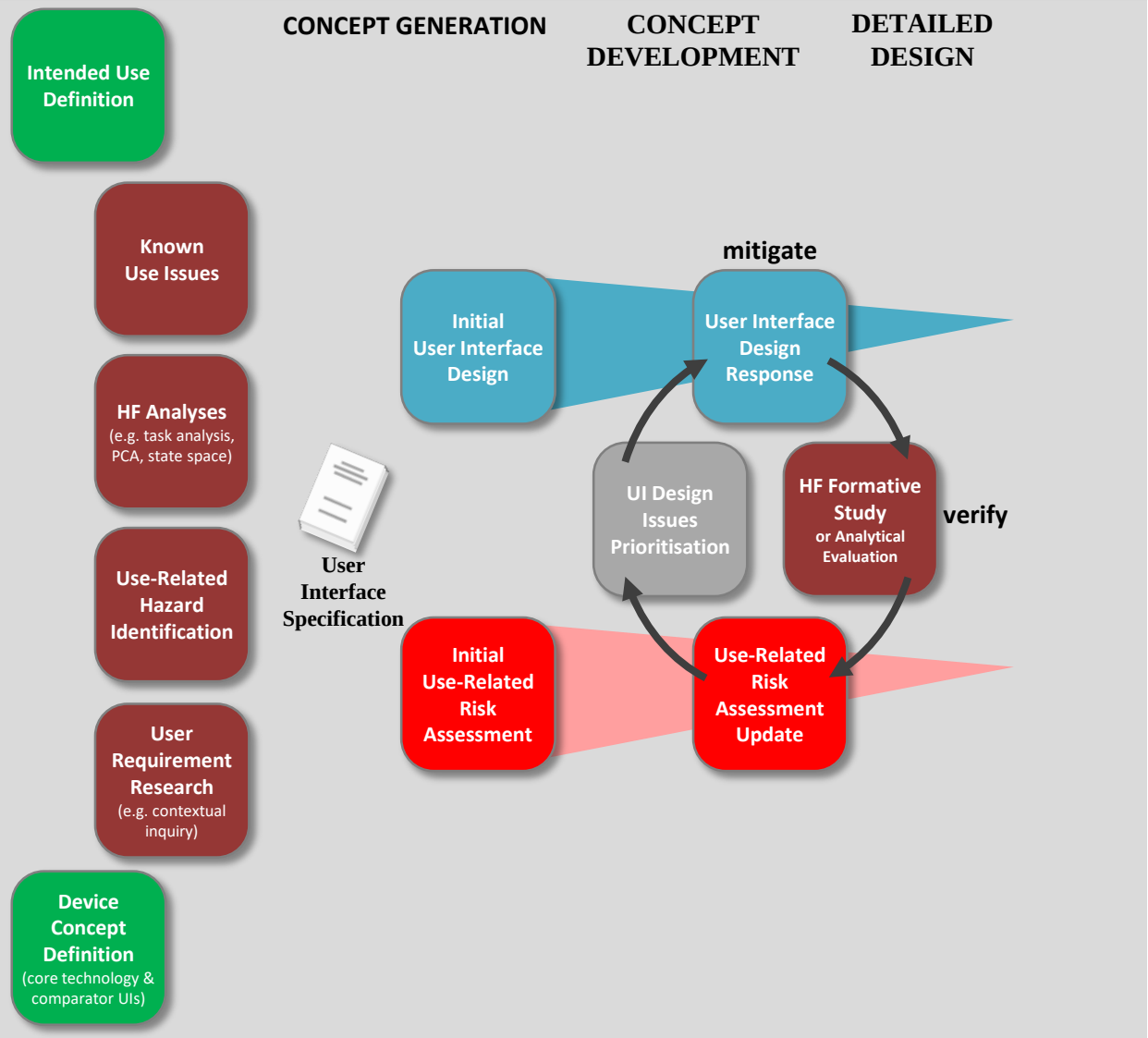
# Human Factors Engineering (HFE) Process Overview

- core of HFE is *iterative* design/development and testing/evaluation of the user interface to minimise use-related risks
- safety critical HF issues are prioritised, on basis of the *severity of potential harm* associated with them
- *simulated use study* is a core methodology



# Human Factors Engineering Process Overview




- a number of HFE activities *prepare* the iterative user interface development

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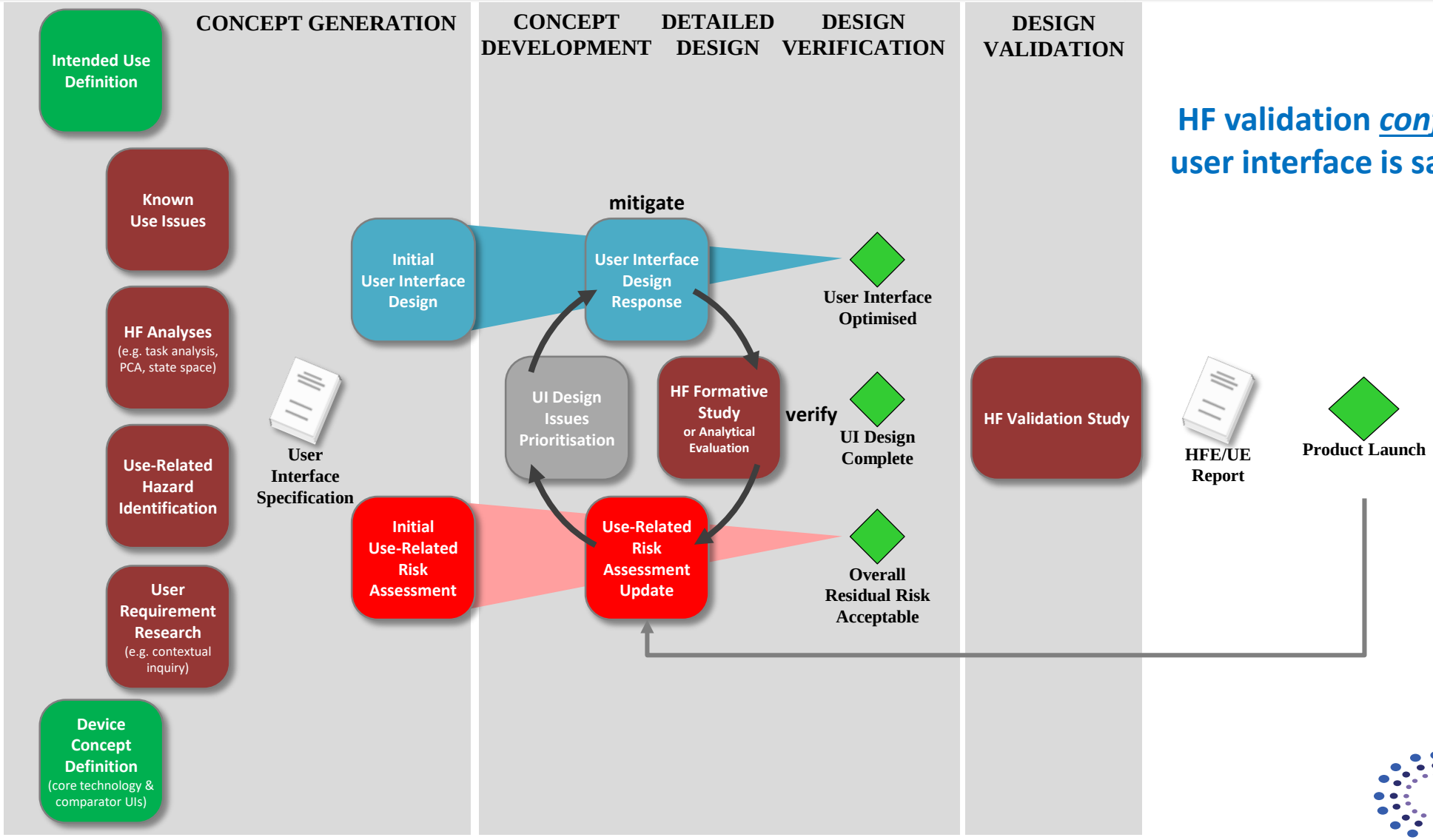
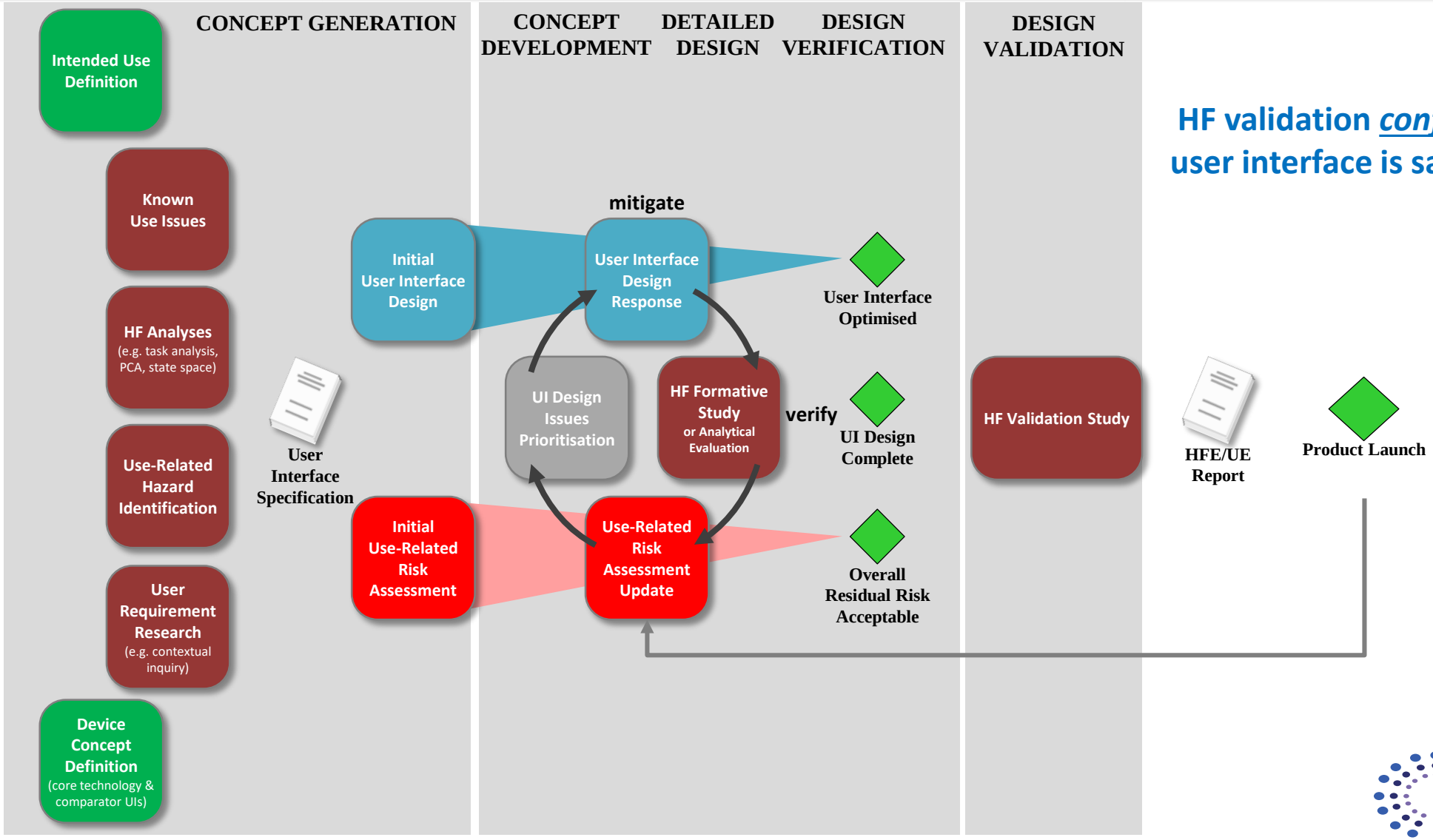
# Human Factors Engineering Process Overview




**HF validation *confirms* that the user interface is safe & effective**

# Human Factors Engineering Process Overview




**HF validation *confirms* that the user interface is safe & effective**

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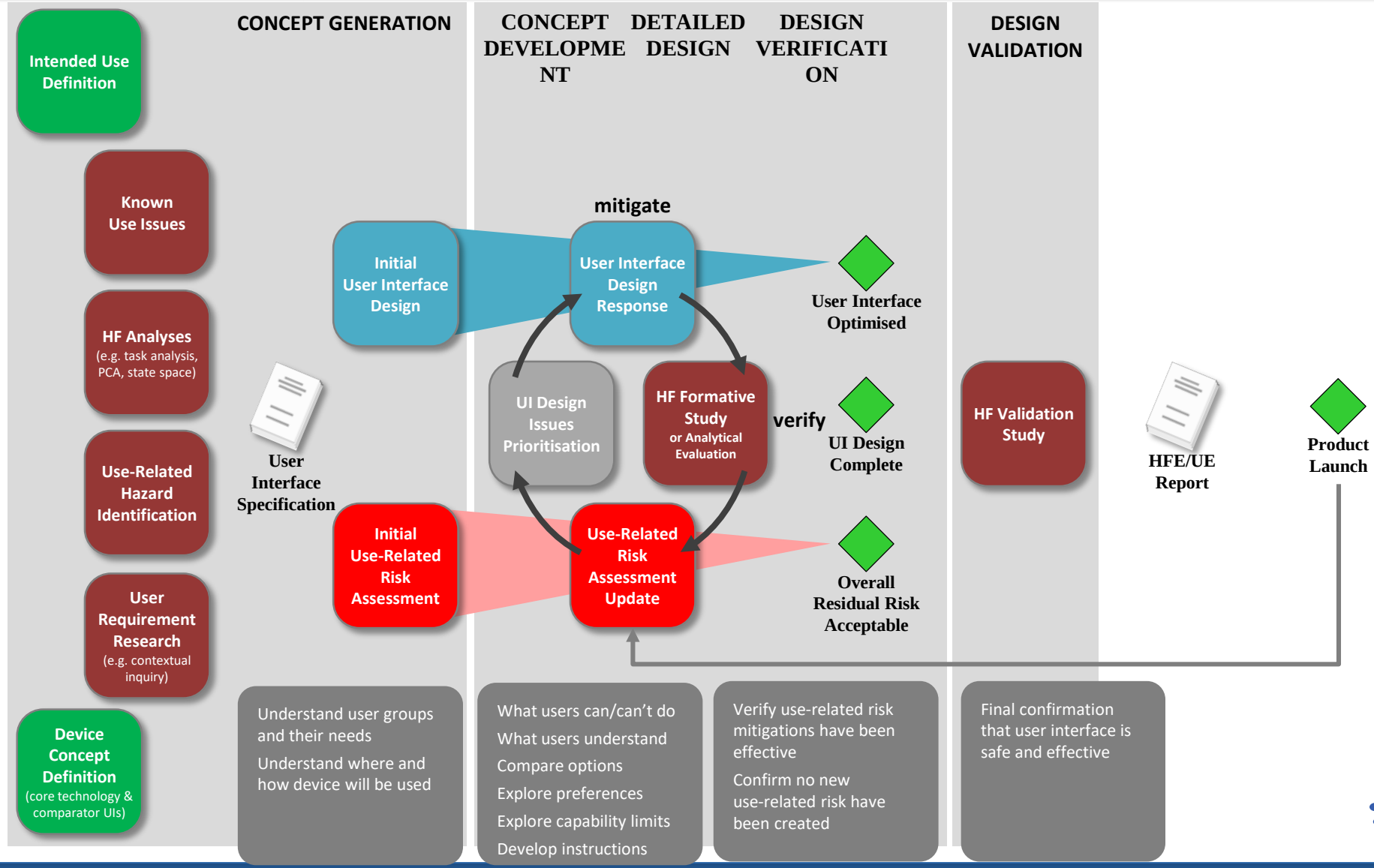
# Human Factors Engineering Process Overview

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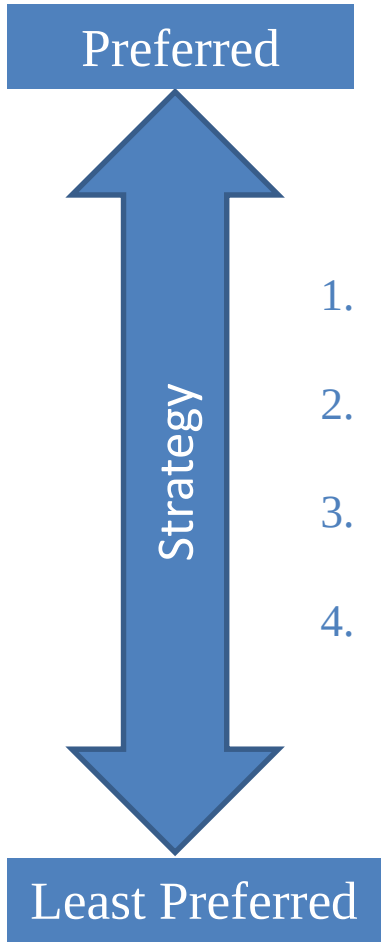
# Risk Mitigation / Minimisation Strategies




1. Eliminate risk through design change/modification.
2. Protect or guard against the hazard through design change/modification.
3. Warn the user about the hazard (information for safety), include information in IFU/PIL
4. Train users to avoid the hazard.

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# Expansion of Usability/ User Assessment Data-Set

- Emerging requests in development of certain classes of drugs to conduct '**In-Use**' Patient Studies
  - In-vivo, dosing studies
  - No clinical endpoints
  - Assess patient use of the device and robustness post patient use
    - In addition to simulated-use Human Factors Studies, and, Device Verification Studies (in-vitro laboratory testing)
  - Study size defined on a case-by-case basis based on study objectives wrt device, however much smaller than a clinical study

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# Human-Factors for Generic Drug-Device Combination Products

- A **generic drug product** is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use..': *Abbreviated NDA (ANDA) Pathway*
- In relation to the RLD, generic products are expected to be:
  - **Pharmaceutically Equivalent:** The same active ingredient, dosage form, strength, route of administration and meet the same compendial standards (strength, quality, purity, and identity)
  - **Bioequivalent:** No significant difference in the rate and extent of absorption of the active ingredient at the site of action
  - **Therapeutically equivalent**: can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling
- **Human Factors Assessments:**
  - demonstration that users of the RLD can use the proposed substitutable product without the need for additional training or HCP intervention
  - assessment of the risk for potential errors associated with use of the proposed generic product due to differences in the device-user interface from that of the RLD

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# Human-Factors for Generic Drug-Device Combination Products

**Comparative Analysis:** *'Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry (FDA, Jan 2017)'*

- 3 Threshold Analysis: Assess each element of proposed generic delivery device constituent parts vs that of the RLD:
  1. Labelling: '… side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions....'
  2. Comparative Task Analysis: '…systematically dissect the use process for …. both …and analyze and compare the sequential and simultaneous manual and intellectual activities for end-users interacting with both the products. ….analyse the differences with the goal to characterize the potential for use error.'
  3. Physical comparison of the delivery device constituent part: '…examine (e.g., visual and tactile examination) the physical features …and compare them ...'
- **Comparative Analysis Outcomes:**
  1. No Design Differences
  2. Differences in Design

# Human-Factors for Generic Drug-Device Combination Products

- *Minor Differences*: key linkage to the risk profile of the drug product
  - Acceptable if there is no impact on an external critical design attribute
  - Consideration of end user profile important: HCP-administered drugs vs lay Users who may have less knowledge of delivery systems
- *Other Design Differences*
  - If there is a potential that any differences in the design may impact an external design attribute
    - Consider modifying the device
    - Comparative Use Human Factors Studies may be required
      - Noninferiority (NI) based study design with primary endpoint being comparison of error-rates (proposed generic should not be worse than that of the RLD);
      - significant participant numbers may be required based on statistical power of study required
- Guidance still in Draft; feedback on Industry input awaited
  - Key point of Industry Feedback relates to Comparative Use HF Study design
  - Comparative Use could also be assessed with an RLD-User arm within a traditional Human Factors Summative Study

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# What to include in regulatory submissions to FDA

'Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications', *Draft Guidance, Sept 2018*

- Provides detailed list of requirements for Human Factors & Threshold Analyses/Comparative Analysis Submissions to FDA
  1. *Use-Related Risk Analysis*
  2. *HF Validation Study Protocol*
  3. *HF Validation Study Results Report*
  4. *Threshold Analyses*
  5. *Comparative Use HF Study Protocol*
  6. *Comparative Use HF Study Results Report*
- Timelines for review of submissions by FDA and provision of written comments to sponsors:
  - By fiscal year (FY) 2019, review 50% of HF protocol submissions …. within 60 days
  - By FY 2020, review 70% of HF protocol submissions …. within 60 days
  - By FY 2021, review 90% of HF protocol …. within 60 days

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# Human Factors Considerations: Key Takeaways

- Human Factor Studies *are not*
  - clinical studies: they are non-dosing studies with no clinical end-points. (Safety observations are reported)
  - marketing studies: they are not an assessment of preference, ease of use

- Combination product HF is different in some important ways to 'general' medical device HF:
  - drug delivery devices are often based on core platform technologies that are well established and well understood - influencing the appropriate balance of analytical and empirical HF activity
  - use-related hazards must consider the medicinal product
  - clinical effectiveness is established in clinical trials
  - drug delivery device usability is typically evaluated in non-clinical simulated use HF studies

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# Human Factors Considerations: Key Takeaways

- Primary objective of Human Factors is to minimise use-related risk.
- Human Factors Studies are conducted in a simulated use environment and focus directly on the User interface with the device
  - how they handle it, with/without training or Instructions for Use (IFU), what errors are made
  - assessing use across the labelled patient profile: consideration of age, co-morbidities, caregivers, use environment
  - inclusion of training (delivery & materials) must be aligned with commercial intent
- Data fundamentally qualitative:
  - the nature of use errors & their root causes matter far more than the numbers of observed errors.
  - each error observed is assessed for its impact on user safety and impact to dose delivery – through linkage to the combination product risk management process
- Devices for Generic Combination Products require demonstrate of no more than minor differences from the RLD, or demonstration (through a NI Comparative Use HF Study) of no worse error rate than RLD
- Continued emergence of guidance's related to Human Factors, including acknowledgement of requirements in some FDA Product-Specific Guidance's (PSG's, e.g. Sumatriptan Nasal Spray, Nov2018)

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# Backup Slides

All slides will be posted on the IPAC-RS website after the workshop.

# Guidance's & Standards

- ANSI/AAMI HE75:2009/(R)2013 Human factors engineering – Design of medical devices
- Applying Human Factors and Usability Engineering to Medical Devices, Feb 2016 (FDA, CDRH)
- Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, Draft Guidance for Industry and FDA Staff, February 2016
- Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry (FDA, Jan 2017)
- Human Factors and Usability Engineering – Guidance for Medical Devices Including Drug-device Combination Products, Version 1.0, September 2017, MHRA
- Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations, FDA Guidance for Industry, April 2018
- Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications, Guidance for Industry and FDA Staff, Draft, Sept 2018
- FDA Draft Guidance on Sumatriptan, Nov 2018, FDA Draft Guidance on Zolmitriptan, Nov 2018

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