



## **CLINICAL TRIALS AND HUMAN FACTORS USABILITY TESTING**

Pamela A. Davol, Clinical & Regulatory Manager • IBC Life Sciences • May 2013

*“Information contained in your pre-IND meeting package indicates that you intend to administer a human factors questionnaire during the clinical study. CDRH recommends that you conduct a formal human factors/usability validation study to demonstrate that your intended users are able to use (the product) safely and effectively. Such a study should be conducted with the to-be-marketed embodiment of your drug-device combination product.”*

**- Food and Drug Administration  
Center for Drug Evaluation and Research**

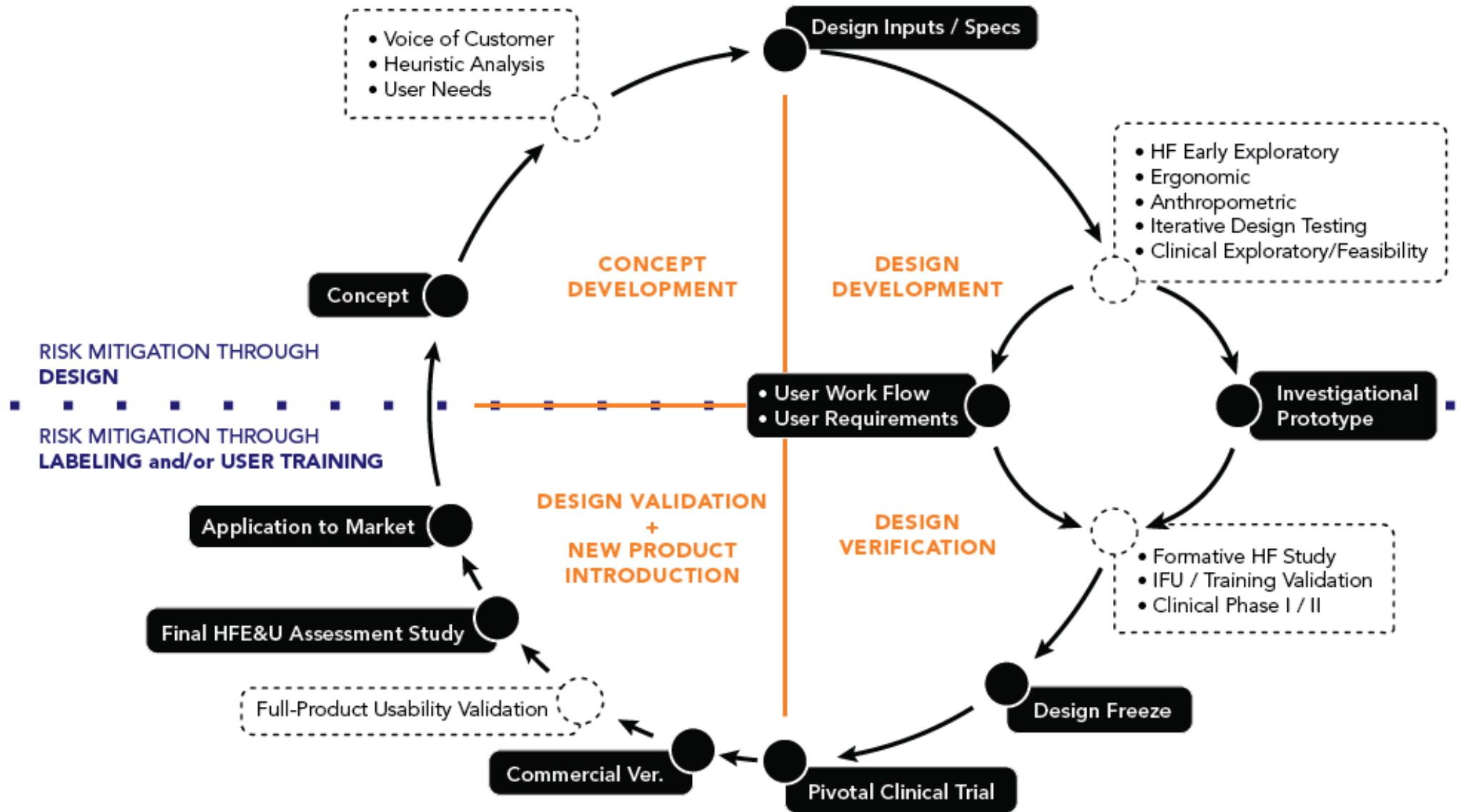
## Comparison of Study Models

Study Component	Typical Minimum Requirements	
	HF Validation Testing	Clinical Testing
<b>Device</b>	Final Design/Comparable	Investigational Design
<b>Labeling (including IFU)</b>	Final Design/Comparable	Investigational Design
<b>Packaging</b>	Final Design/Comparable	Investigational Design
<b>Use-Related Tasks</b>	Essential & Safety Critical	Essential
<b>User Training</b>	Realistic training levels (ranges from no formal training to formal training)	Formal training for all users
<b>Use Environment and Conditions</b>	Simulated: All key aspects of real-world use and anticipated hazards i.e. worse case scenarios	Artifactual: Controlled conditions i.e. best case scenarios
<b>Study Participants</b>	All major end-user groups	One or more defined user groups (i.e. predictive/prognostic enrichment)
<b>Use Error Data Collection</b>	Real-time, Actual; Objective Observation; Subjective User Feedback	Indirect; Outcomes-based Patient Reported Outcome (PRO)-based
<b>Use-Error Intervention</b>	Never	Always

*“Human factors and usability studies should be conducted on the device concurrent to Phase II...and the finalized release version of the device should be used in the Phase III clinical trials. After the pivotal trials are complete, the device shouldn't be modified.”*

**- Food and Drug Administration  
Center for Devices and Radiological Health**

# Traditional Product Design, HFU & Clinical Study Integration Approach



# Limitations of Human Factors Usability Testing

## + ADVANTAGES

- Presents minimum risk
- Allows evaluation of all use scenarios presenting risk
- Allows use evaluation during all product error states

## - DISADVANTAGES

- Only evaluates a simulation of product use
- Susceptible to Hawthorne effect and simulation artifacts
- Does not provide proof that a product actually works

# Limitations of Clinical Testing

## + ADVANTAGES

- Evaluates real-life product use
- May occasionally identify unexpected product risks
- Product users receive formal training to ensure controlled use conditions in order to minimize impact of the user variable on study outcome
- Provides proof that a product actually works

## - DISADVANTAGES

- Typically conducted under optimized conditions
- Cannot be used to evaluate known hazardous scenarios due to patient risks
- Not representative of real-world use conditions or user training
- Increases study risks related to use of actual patients

## Advantages for Integrating HFU Testing and Clinical Testing

- Overall results from the study will be more typical of what may be expected for both product safety and therapeutic performance/efficacy in the real world.
- Pre-defined use-errors may be applied as a criteria for rejecting certain data to evaluate patient clinical response to therapy.



# Integrating Human Factors Usability Testing Into Clinical Studies

## Three Examples of Integrative Approaches

Example	Center Jurisdiction	Product Classification
1	CDRH	Drug-Eluting Coronary Stent System
2	CDER	Drug Inhalation Device
3	CBER	Vaccine Microneedle Systems

# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.1 Drug-Eluting Stents

**There are multiple design and use problems associated with stents:**

- Bulky and require a large guide catheter
- A majority are introduced over two guide-wires, which can crisscross or lead to improper device orientation
- Stent systems are rigid and are difficult to advance to the target lesion in cases of significant proximal tortuosity (i.e. twisting of the blood vessel)



# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.1 Drug-Eluting Stents

- **Type of Clinical Trial**
  - First-in-human, feasibility study
- **User and patient populations**
  - Surgical Cardiologist(s)
  - Patients with symptomatic heart disease due to coronary artery lesions
- **Usability Test Methods and Tools During Clinical Testing**
  - Usability Observer Present During Stent System Placement/Removal
  - Clinician instructed to “talk-out-loud” during placement/removal
  - Timing of placement procedure
  - Imaging placement confirmation by independent reviewer
  - Audio/Visual Recording of Placement Procedure
  - Clinical Use Observation Data and Interview Form

# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.1 Drug-Eluting Stents

- **Data Collection**

- Documentation of Objective Observations; examples:

Observation	Potential Associated Failure Modes
Stent System Damage During Placement	extensive handling/manipulation ; use of incorrect stent balloon insufflation medium; inducing negative pressure within the system; repeated reintroduction and retraction of stent through the guide wire; balloon rupture from high insufflation pressure
Difficulty placing	guide-wire crisscross; use of guidance wires with unsuitable lumen size
Difficulty removing system after placement	Failure to deflate the balloon prior to removal; damage to the system during placement.
Gaps between stent and lesion	Incorrect orientation/placement
Stent dislodgement	Placement of proximal stents prior to distal stents within the same vessel
Localized bleeding, hematoma, or pseudoaneurism	using additional wires, snares, and / or forceps to remove system; applying too much force when resistance felt during system removal.

- Post-Placement Clinician Debriefing/Subjective Interview; example:

**Study moderator:** *“I noticed that you experienced some difficulties placing the stent in the position that you wanted. Could you please tell me more about your experience and thoughts about that?”*

# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.1 Drug-Eluting Stents

- **HF Study Evaluations**
  - Number of Successful vs. Failed or Close-Call Placements
  - Occurrence of Failure Mode Events
  - Root-cause analysis based on user feedback
- **Primary Clinical Endpoint**
  - Target lesion failure

# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.2 Drug Inhalation Device

### Design and Use problems associated with Drug Inhalation Devices

- Improper fit of device components to achieve a seal during delivery
- Incorrect positioning of device during delivery
- Inadequate inhalation during drug delivery



# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.2 Drug Inhalation Device

- **Type of Clinical Trial**
  - Randomized, double-blind, placebo-controlled safety and efficacy trial
- **Population**
  - Patients with chronic bronchial asthma
- **Usability Test Methods and Tools During Clinical Testing**
  - Usability observation of untrained patient use with placebo/unfilled device
  - Audio/Visual Recording of Administration Procedure
  - Use Observation Data and Interview Form
  - Clinician trains patient formally with correct procedures for use with placebo/unfilled device
  - Drug and delivery device dispensed to patient for clinical evaluation
  - Patient daily journal to record user experiences

# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.2 Drug Inhalation Device

- **Data Collection**

- Documentation of Objective Observations; examples:

Pre-Clinical Evaluation Observation	Potential Associated Failure Modes
Difficulty administering the drug	Incorrect loading of drug; failure to activate drug release mechanism; incorrect positioning during activation of drug release mechanism; incorrect positioning of inhaler during delivery; failure to achieve a complete seal around the mouthpiece; failure to inhale adequately
User discomfort	Incompatible mouthpiece design

- Pre-Clinical Evaluation Debriefing/Subjective Interview; example:

**Study moderator:** *“When administering the drug do you feel that you inhaled deeply enough? Why or why not?”*

- Post-Clinical Evaluation Observations and Debriefing
  - Cleaning
  - Storage
  - Transporting



# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.2 Drug Inhalation Device

- **HF Study Evaluations**

- Pre-clinical evaluation occurrence of use-errors and/or close-calls
- Pre-clinical evaluation root-cause analysis based on user feedback
- Post-clinical evaluation of product use patterns based on daily journal
- Post-clinical evaluation debriefing

- **Primary Clinical Endpoint**

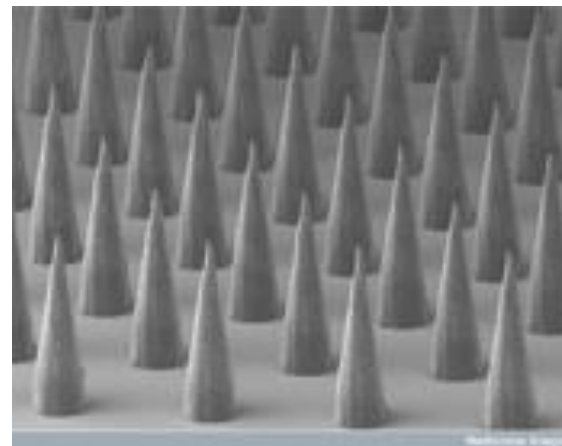
- Change from baseline peak expiratory flow (PEF) during the treatment period

# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.3 Vaccine Microneedle Systems

### Potential Product Design-User Interface problems associated with Vaccine Microneedle Systems

- Failure of release or reduced release of the immunogen
- Non-optimal size to allow manipulation during application
- Failure to assemble and use applicator system correctly
- Incompatibility between patch and applicator



# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.3 Vaccine Microneedle Systems

- **Usability Test Methods and Tools During Clinical Testing**
  - Usability Observer Present During Vaccination
  - Trained versus untrained system users
  - Immunogenicity testing 21-days post vaccination
  - Audio/Visual Recording of Placement Procedure
  - Clinical Use Observation Data and Interview Form

# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.3 Vaccine Microneedle Systems

### • Data Collection

- Documentation of Objective Observations; examples:

Observation	Potential Associated Failure Modes
Difficulty attaching vaccine patch to patient skin	Failure to remove the release liner on the vaccine patch; failure to pre-cleanse skin at attachment site; sub-optimal design of patch size
Difficulty activating vaccine patch microneedles	Incorrect assembly of patch applicator; insufficient pressure applied during applicator activation; incorrect placement of applicator adapter during patch activation; failure to activate applicator tip during patch activation; failure to remove pin to activate microneedle plenum spring pressure; incompatibility between applicator and patch design
Vaccine leakage from patch during removal	Incomplete patch activation; removal of patch applicator before applicator tip retracts
Localized bleeding or bruising	Use of extensive force with applicator during patch activation

- Post-Placement User Debriefing/Subjective Interview; example:

**Study moderator:** *“I noticed that you experienced some difficulties activating the patch after attaching to this patient. Why do you think that occurred?”*

# Integrating Human Factors Usability Testing Into Clinical Studies

## Ex.3 Vaccine Microneedle Systems

- **HF Study Evaluations**

- Occurrence of use-errors and/or close-calls
- Root-cause analysis based on user feedback
- Comparison of vaccine titers in patients immunized by trained versus untrained clinicians

- **Primary clinical endpoint**

- Vaccine titer and/or challenge

## Summary

- Human factor usability testing performed only during clinical testing does not adequately fulfill FDA's HFE & U reporting requirements for validating that the product design-user interface is reasonably safe and effective for the intended users, uses and use environments.
- Distinct differences in the objective and thus methodology of clinical testing versus HF testing can present challenges to integrating HFU testing into clinical studies.
- One potential advantage of integrating HFU testing methods into clinical evaluations is that outcomes from the study may be more typical of what may be expected for both product safety and therapeutic performance/efficacy in the real world.
- There are viable opportunities to integrate HFU testing with early, exploratory clinical studies of all types of combination products to inform product design and development prior to design freeze and pivotal clinical trials.



Thank You

[Ximedica.com](http://Ximedica.com)

**Pam A. Davol**  
Clinical & Regulatory Manager

T: 401.626.3334  
[pdavol@ximedica.com](mailto:pdavol@ximedica.com)

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**Providence**  
Minneapolis  
Hong Kong