Strategies for Human Factors and Clinical Studies for Combination Products

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Combination products (drug + injection device) are increasingly prevalent in competitive injectable markets

- Increasing number of therapeutic areas with injection devices
- Injection devices available with launch of product (not only used as a lifecycle improvement)
- Next generation devices
- Multiple device options provided for a drug product

Pre-Filled Syringe
Syringe pre-filled with drug

Needle Safety Device
Automatic needle cover

Auto-Injector
Automated needle insertion and injection

Pen Injector
Multiple doses
Manual needle insertion
The Rheumatoid Arthritis market is an example of a maturing competitive market with many injectable devices.

**Subcutaneous Injectable RA Products in the U.S.**

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orencia®</td>
<td>PFS - Subcutaneous</td>
</tr>
<tr>
<td>Cimzia®</td>
<td>Ergonomic PFS, Vial “pack”</td>
</tr>
<tr>
<td>Simponi®</td>
<td>SmartJect®, PFS with Needle Safety</td>
</tr>
<tr>
<td>Humira®</td>
<td>PFS (20mg/0.4ml), Humira® Pen</td>
</tr>
<tr>
<td></td>
<td>PFS (extended flange) (40mg/0.8ml)</td>
</tr>
<tr>
<td>Enbrel®</td>
<td>PFS 25 mg, SureClick™</td>
</tr>
<tr>
<td></td>
<td>PFS 50mg (extended flange)</td>
</tr>
<tr>
<td>Kineret®</td>
<td>PFS (with optional SimpleJect reuseable auto-injector)</td>
</tr>
<tr>
<td>Lyophilized</td>
<td>Lyophilized Powder (vial → vial adaptor + diluent syringe)</td>
</tr>
</tbody>
</table>

Timeline:
- 2000
- 2002
- 2004
- 2006
- 2008
- 2010
- 2012
Injection device technologies are advancing

**Auto-injector technologies** are becoming more prevalent and diverse
- Mostly single use disposable
- Higher doses administered (volume and viscosity) with some technologies
- Improved human factors
- Variety of features/benefits and options

- *Molly™* Scandinavian Health Limited
- *SDI MIX+NIT™* Scandinavian Health Limited
- *ConfDose®* West Pharmaceuticals
- *YpsoMate®* Ypsomed
- *Oval Medical Technologies*
- *RebiSmart™* Merck Serono

**New manual injection technologies** to ease administration are emerging
- Ease manual self-administration
- Specialized flanges
- New form factors

- *BD Safety finger flanges*
- *West SelfDose™*
- *Cimzia®*

**Patch injector technologies** have emerged due to the need for delivery of high doses
- Large administered volume
- Injects over several minutes or longer
- Wearable

- *SmartDose®* West Pharmaceuticals
- *Flex-Therapy®* Unilife
- *PatchPump®* SteadyMed Therapeutics
- *Self-Injection Device Roche*
- *BD™ Microinfuser* Becton Dickinson
- *Auvi-Q Sanofi / Intelliject*
Rapid growth of injection devices in the pharmaceutical industry has led to key development challenges

- **Adequacy of human factors testing and Design Validation data**
  - Evolving regulatory expectations (primarily FDA)
  - Complaints with existing commercial products related to use errors

- **Requirements for clinical testing for combination products**
  - Why to employ what type of testing
  - Bridging pharmacokinetic / bioequivalency studies
  - Health authority requests for “ease-of-use” or “clinical handling” studies
Human Factors is a scientific discipline focused on the interface between the user and the device

- **Exploratory (formative) testing** is used to inform and optimize device design
  - Cognitive and ergonomic interactions with the operation of the device
  - Assess attributes of user population
  - Typically simulated and mimic actual use environment (e.g. light, noise, distractions)
  - Identify and mitigate use errors in the design and/or instructions for use

- **Design Validation (summative testing)** confirms the design meets the user needs
  - User can operate the devices safely and effectively
  - Risks are mitigated to an acceptable level

- **Human Factors studies are not**
  - Market preference studies
  - Clinical studies with an independent objective and endpoint
Use tasks are categorized for criticality based on risk and device dependency

• **Identify critical tasks based on risk**
  – Unsuccessful completion of a task has the potential to lead to patient harm (e.g. needle stick or incomplete dose)
  – Risks are rated based on the severity of the potential to patient harm

• **Determine device dependent (essential) vs. independent (ancillary) tasks**
  – Essential tasks must be performed for the device to work as intended (e.g. to administer drug) and success can be controlled by the design
  – Ancillary tasks support the device operation and are highly dependent on compliance with instructions (e.g. inspect product in window)
  – Device design must not hinder execution of ancillary tasks (e.g. viewing window to allow for inspection of drug must be present)
Our perspective is that only device-dependent tasks that can lead to patient harm should be used as criteria for Design Validation

Note: Severity ratings per ISO 14971: Medical Devices - Application of Risk Management to Medical Devices

Clarity of Instructions for Use can be tested with device independent tasks
An Impact Assessment is a useful tool to determine the extent to which existing human factors data can be leveraged.

<table>
<thead>
<tr>
<th>Type of Change</th>
<th>Risk Assessment</th>
<th>Justification and Strategy for Validation Study</th>
</tr>
</thead>
</table>
| • User population and environment  
  • Device performance (e.g. injection time, force to remove cap)  
  • Ergonomics or physical appearance (e.g. color, tactile, shape, auditory) | • Impact of change on severity and occurrence of use errors  
  • Potential for new risks  
  • Complaints information | • Existing validation data fulfills needs, or  
  • Leverage existing validation data with supplemental data, or  
  • Repeat full design validation |
Obtaining reliable usability information in clinical studies with other endpoints is challenging

- **Human factors and clinical studies have conflicting objectives**
- **Clinical study design to assess usability must allow for use errors**
  - Use errors may confound clinical data or pose ethics issues
  - Such assessments should not be part of pivotal studies
- **Device clinical bridging studies (PK/BE) are not an appropriate means to assess usability**
  - Typically performed in a controlled setting by a HCP to minimize variability that may confound results
  - Healthy Volunteers (typically used for PK/BE) may not be representative of users
  - Some use errors could result in incomplete drug dosing
- **Controlled clinical setting does not allow for representative use**
  - Clinical study participants often have more extensive training than representative users
- **Usability should only be assessed by a Human Factors expert**
  - Formative usability information can be obtained in a clinical study if users are observed by a Human Factors expert
  - Clinicians are not trained to assess usability
  - Patients cannot reliably self-assess usability

Cannot be used to make reliable conclusions on usability
Simulated use human factors studies are typically adequate for injection devices

• Mimic operation of the device in every way (except actual injection)

• Commercial training infrastructure for the marketed product should be robust

• Actual use human factors studies with placebo poses challenges
  – Placebo may perform differently than the drug product due to differences in formulation properties (e.g. viscosity)
  – May require development of a viscous placebo or a different device design to mimic actual device performance with the drug

• Actual use human factors studies may be appropriate for unique situations
  – Properties of the drug that can make injection unusually painful
  – Completion of task requires sensory feedback from injection site (e.g. skin sensor)

Testing with actual injections in patients should be for the purposes of assessing clinical outcomes when the device is operated properly
Roche’s approach is to design the clinical studies based on level of risk posed to safety and efficacy.

Timing of Change
- Examples...
  - During Phase 3
  - Post-Market

Clinical Attributes
- Examples...
  - Wide Therapeutic Window
  - High PK Variability

Device Configuration Change
- Examples...
  - Pre-filled Syringe → Auto-Injector
  - Change in Flange Shape

Assess the risk of the device changes

Clinical Bridging Strategy

The purpose of clinical bridging studies is to assess comparability between configurations (not usability).
Various clinical factors need to be considered in designing the bridging strategy

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>Considerations</th>
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<tbody>
<tr>
<td>Data Variability</td>
<td>Power study appropriately to detect differences in configurations</td>
</tr>
<tr>
<td>Experience with device in previous clinical studies</td>
<td>Previous PK/BE data available may be sufficient to justify no additional assessments</td>
</tr>
<tr>
<td>Commercial experience with product (vs. pipeline)</td>
<td>Extensive existing safety and efficacy data may be sufficient to justify no additional assessments</td>
</tr>
<tr>
<td>Therapeutic Window</td>
<td>Narrow therapeutic window drugs have higher potential for safety issues</td>
</tr>
<tr>
<td>Site rotation/injection site dynamics</td>
<td>Need for injections in multiple sites adds complexity (devices may operate differently depending on skin firmness)</td>
</tr>
</tbody>
</table>
The risk of the device changes should be evaluated

<table>
<thead>
<tr>
<th>Change due to new or modified component or device</th>
<th>Potential Impact</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Product contact material change (e.g. luer to staked needle pre-filled syringe)</td>
<td>Product quality</td>
<td>IM (vs. SC) injection</td>
</tr>
<tr>
<td>Change in injection technique (e.g. component change enables new hand posture)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Change in injection depth/angle (e.g. 45° to 90°)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Different pressure applied to or compression of skin at injection site</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Change in injection or flow rate (e.g. smaller needle or faster injection due to device design)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Volume injected or number of injections</td>
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# Hierarchical categories to consider for bridging strategy

<table>
<thead>
<tr>
<th>Strategy Category</th>
<th>Description of Strategy</th>
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| A                 | • Analytical (e.g. aggregation)  
|                   | • Functional testing (e.g. injection time) data  
|                   | • No additional clinical assessment |
| B                 | Bioequivalence Comparison  
|                   | • BE Study: Direct comparison of reference to new device in healthy volunteers in a single dose study  
|                   | • PK Characterization Study: Comparison to historical data  
|                   | • Test in patients or multi-dose only if needed for disease/molecule  
|                   | • HCP administered in a controlled setting |
| C                 | Other Clinical Assessments  
|                   | • Potential to include device in open label extensions (safety)  
|                   | • Injection site reaction assessments |
## Risk-based bridging strategy scenarios

<table>
<thead>
<tr>
<th>Technology Change Scenario</th>
<th>Potential Impact of Device Changes and Material Changes</th>
<th>Risk</th>
<th>Clinical Strategy</th>
</tr>
</thead>
</table>
| Change in shape of needle safety device | • Similar ergonomics and hand posture/grip  
• No impact on administration | Low | A  
No clinical assessment |
| After Phase 3 and before Launch | | |  |

| Pre-filled syringe with needle safety Auto-Injector | • Change in injection rate  
• Different angle/injection depth  
• New hand posture / injection technique  
• Different pressure applied to injection site | Low / Medium | A + B  
Potential for No Clinical Study or Conduct BE study |
| During Phase 3 | | |  |

| Vial Patch Infuser | • New primary container  
• Change in injection rate  
• Change in angle/depth  
• Larger volume  
• Different pressure applied to injection site  
• New hand posture / injection technique | Medium / High | A + B + C  
BE Study  
Potential for other clinical assessments |
| During Phase 3 | | |  |
Concluding Remarks

- Combination products are becoming an increasingly important element of commercial product strategy in competitive markets.

- A robust human factors program is not only a regulatory requirement, but also a good business practice.

- Human factors studies are the most rigorous means to assess usability.

- Clinical bridging strategies should be risk-based and designed to assess clinical outcomes with a new device (not usability).
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