Challenges and Opportunities in the Development of integrated Drug Device Combination Products

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Introduction

- Device requirements in a Pharma environment
- Challenges
  - Dynamic development programs
  - Evolving regulatory expectations
  - Complex supplier networks
- Opportunities
Pharma versus Device

Clinical study vs. Human Factors study

Extractables & Leachables vs. Biocompatibility

Patient vs. User

Stability Testing vs. Verification Testing

Quality by Design vs. Design Controls

ICH C9 vs. ISO14971
Pharma versus Device

- Extractables & Leachables
- Biocompatibility
- Clinical study
- Human Factors study
- patient
- user
- Stability Testing
- Verification Testing
- Quality by Design
- Design Controls
- ICH C9
- ISO14971
Stability vs. Design Verification

• Legal Manufacturers are required to ensure device functionality by Design Verification, i.e. by demonstrating that Design Input Requirements are met.

• This may be done by testing, tolerance analysis, mathematical modeling or certificate review

• This may be, and often is, outsourced to suppliers, but it remains within the responsibility of the legal manufacturer, with respect to the adequacy of e.g.:
  – Acceptance criteria
  – Sample size
  – Test methods
  – Quality system
Stability vs. Design Verification

**Stability Testing**
- **inter-batch variability**
- extrapolated

**Design Verification**
- **intra-batch variability**
- rarely extrapolated

**Typically small sample size**

**Statistically significant sample size**
Clinical studies vs. Simulated use studies

- Use errors are a known source of risk for any medical device and therefore need to be understood and managed.
- Simulated-use Human Factors studies are an adequate (and safe!) way of studying user behaviour and provide insights on use errors a clinical study in many cases could not provide.
Clinical studies vs. Simulated use studies

**Clinical data**
- Clinical trial
- Quantitative results
- Statistically powered

**Behavioral data**
- Human Factors study
- Semi-quantitative results
- Not statistically powered

**Higher risk**

**Lower risk**
Why is it a challenge to be agile and respond swiftly to changing requirements of dynamic development programs?
Dynamic programs

Potential drivers, a few examples...

• The program is accelerated, due to breakthrough therapy designation
• Clinical trial results prohibit home-use
• Indications are added or dropped from the development program
• Competitive intelligence mandates a change in strategic direction altogether
Dynamic programs

Example 1 - Late Design Input

- Drug and device characteristics have the potential to impact each other...

  ...but with the primary mode of action being the drug constituent part, it is typically the device constituent part that will be adjusted.

- For delivery devices of parenteral drugs, critical Design Input becomes available rather late.

Viscosity  Fill  Volume  Shear stress  Materials

Dose accuracy  Light exposure
Quick detour: Design Controls

- For Device Development activities a specific methodology is mandated by ISO13485 (EU) and 21CFR820 (US).
- Design Input is supposed to be established at the beginning of that process.
- Any change to that initial element will need to be traced through the entire development documentation.
Dynamic programs
Platforms... and their limitations

• One way to address this challenge is by establishing technology platforms.

• With these standardized technologies generic development work can be frontloaded, e.g. by non-molecule specific Design Verification testing.

• This also may offer the opportunity to leverage data across programs.

• But: The device that works for everything will likely not be ideal for anything.

• Generally a nimble quality system, well embedded processes and (flexible) templates will help to minimize the development timelines.
Dynamic programs

Example 2 – Changing indications

• Often the mode of action of a particular drug allows the treatment of different diseases.

• Pharma companies therefore regularly expand the label of approved medicines to new indications. The process to justify these additional indications is well established from a clinical perspective.

• There is little involvement from technical development, as long as the primary packaging does not change.

• For a device (and a combination product) the indication is relevant Design Input. A change may impact the entire Design History File and requires diligent assessment.
Dynamic programs
Example 2 – Changing indications

What could go wrong? And how often? Any difference between the established and the new indication will be evaluated to understand, whether the risk profile changes.

Example:
Different clinical effect of an overdose, due to different bodyweight characteristics?

Example:
Different probability of intramuscular injection due to different thickness of subcutaneous tissue layer, in case of wrong needle insertion?

Example:
Different probability to cause a systemic infection in case of needle-stick injury, due to weaker immune system?

Example:
Different probability of mishandling due to dexterity impairments?

**SEVERITY (S)**

**PROBABILITY (P)**

**RISK**

Based on the updated risk profile, additional mitigations may be required.

Probability hazardous situation leads to **harm**

Probability failure leads to **hazardous situation**

Probability a **failure or use error** occurs
Dynamic programs
Strategies to deal with it...

• Build device awareness throughout the organization.

• Ensure that relevant information (i.e. Design Input) is made available as early as possible.

• Standardize to an extent feasible, i.e develop “platforms” on different levels as well as templates.
Why can it be a challenge to keep up with regulations that are constantly evolving?
Evolving regulations

Example 1 – Risk management

- Roche had used descriptive categories for “probability of harm” in device FMEA’s.

<table>
<thead>
<tr>
<th>Score</th>
<th>Category</th>
<th>Criteria</th>
<th>Probability of harm (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Very high</td>
<td>Certain to occur routinely</td>
<td>&gt; 6210</td>
</tr>
<tr>
<td>8</td>
<td>High</td>
<td>Occurs frequently</td>
<td>≤ 6210 &gt; 1350</td>
</tr>
<tr>
<td>6</td>
<td>Moderate</td>
<td>Occurs occasionally</td>
<td>≤ 1350 &gt; 233</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>Has not occurred often</td>
<td>≤ 233 &gt; 3.4</td>
</tr>
<tr>
<td>2</td>
<td>Remote</td>
<td>Not expected to occur</td>
<td>≤ 3.4</td>
</tr>
</tbody>
</table>

- This, while previously accepted, was criticized in a pre-approval inspection as inadequate.

- Roche then changed procedures to quantitative categories for “probability of harm”.

• Roche had used descriptive categories for “probability of harm” in device FMEA’s.
Evolving regulations
Example 1 – Risk management

• Ultimately this resulted in a more coherent and robust risk management file, that facilitates communication and is easier to defend, for example in respect to:
  – Direct traceability of Human Factors study results to the usability FMEA.
  – Assessment of Design Verification issues to determine whether these result in unacceptable risk

• However, establishing this approach required significant effort and adds considerable complexity to the risk management process.
Evolving regulations
Example 2 – Untrained user data

• For home-use medication administered by self-injecting patients, Roche’s intended use statement typically prescribes that users will have to be trained.

• This training is reflected in HF validation study protocols, an approach consistent with previous health authority guidance.

• In a recent HF validation study, the protocol was submitted to the authority for review and accepted in 2015.

2011
“If you stated in your labeling and the instructions to the prescriber that training is necessary then training should be included. Assuming that intended users should be able to use the device without any training or review of the IFU is not realistic.”
Evolving regulations
Example 2 – Untrained user data

• In the pre-submission meeting about a year later where the HF validation results were supposed to be discussed it was revealed that now data from untrained users would be required as well.

• Ultimately another, supplemental study was required.

• Roche will collect data on untrained users in future HF studies but maintains that this is to be considered (and evaluated as) a foreseeable misuse scenario, if training is defined in the intended use of the product.

2016
“... our thinking regarding training has evolved. We are now concerned that the inclusion of all trained participants does not adequately reflect real-life use of the product... «
Evolving regulations
Strategies to deal with it...

• Engaging with health authorities early on and frequently will help to avoid (most) surprises.

• Taking ownership of the entire risk management file will enable swift, consistent and transparent response to risk profile changes.
Why can it be challenging to rely on a vast network of external suppliers and service providers?
Reliance on suppliers

Background

• Even in many large Pharma companies a significant part of the device development work is outsourced:
  – Mechanical engineering
  – Prototyping
  – Process development
  – Usability testing
  – Strategy consulting
  Etc.

• Customers will have to rely on program management, technical expertise, documentation and compliance.
Reliance on suppliers
Example – Raw material changes

Case study:

• Change of raw material lead to an increase of insertion torque for a plunger rod.

• Several potential root causes were identified and correction measures explored:
  – process parameters adjusted
  – lubricant added to resin
  – mold polishing applied

• Ultimately the use of CT scan enabled identification of thread dimensions of the plunger in its compressed state.
Reliance on suppliers

Example – Raw material changes

• Based upon these CT scans the best matching thread design of the plunger rod was identified.

• Thread design was fine tuned by samples from inexpensive trial tools.

• By use of a plunger rod surrogate a fast first check of functionality could be performed.

Supposedly minimal changes may require a lot of and very close collaboration between supplier and pharmaceutical company.
Reliance on suppliers
Strategies to deal with it...

• Enough internal expertise is required,
  – to be able to make informed sourcing decisions
  – to assess the adequacy of the services provided
  – to build a mutually trustful relation
Summary

*Is it really worth the effort?*

Development of combination products presents many challenges.

- **Dynamic development programs** collide with a very ‘sequential’ Design Controls methodology.

- **Evolving regulations** demand constant adaptation and make it difficult to establish consistent and effective processes.

- **Reliance on suppliers** requires an in-depth understanding of device technologies and associated regulatory principles.
Opportunities

• Minimize medication errors
• Improve adherence
• Provide users with a better experience
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Doing now what patients need next