De-risking your drug-device combination product ANDA submission: A case-study on leveraging formative human factors data generated by a Drug Delivery Device Developer

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Background

User interface design is a critical component of generic drug-device combination product development that must be considered from an early stage. The FDA guidance on Abbreviated New Drug Applications (ANDA) advises pharmaceutical companies to carefully consider and seek to minimize differences from the Reference Listed Drug (RLD). To assist pharmaceutical companies in identifying user interface differences between an RLD and the Generic Drug-Device Combination Product (GDDCP), the FDA guidance on ANDA detailed how to perform a Threshold Analysis:

Threshold Analysis

Labelling Comparisons — Side-by-side, line-by-line comparison of the relevant sections of the prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the GDDCP and its RLD

Comparative Task Analysis — Systematically analyze and compare the sequential activities required for the end-users to use the device and administer the drug product

Physical Comparison of Delivery device Constituent Part — Visual, auditory, tactile examination of the physical features (size, shape, feedback) of the RLD, compared to those of the delivery device constituent part of the proposed generic combination product

In the threshold analysis, points of comparisons are classified in 3 different outcomes

Outcome	FDA expectation
✓ No design difference	→ No additional data needed
✓ Minor design difference	→ Rational
✗ Other design difference	→ Additional information/data needed.

A CUHF study assesses whether the differences identified introduce a risk that might impact the clinical effect or safety profile of the generic combination product

Delivery Device Comparison

A Drug Delivery Device Developer (DDDD) can support pharmaceutical companies in their ANDA submission of final GDDCP by authoring a portion of the Threshold Analysis. A comparative analysis is a partial threshold analysis where a DDDD compares the delivery devices on the aspects that are not drug-related.

Comparative Analysis

RLD & GDDCP *(as component)* Device comparisons

- Comparative Task Analysis
- Physical Comparison of Delivery Device constituent parts

✓ Overview of design differences & potential associated risks
✓ Support to pharmaceutical companies to build HF strategy

**Labelling comparison is not is scope of DDDD*

- ✓ If no 'other design differences' are identified, pharmaceutical companies can leverage DDDD data to complete their Threshold Analysis with labelling comparisons.
- ✗ If 'other design differences' are observed, pharmaceutical companies will have to provide additional data to FDA by performing, for example, a final CUHF study with final drug device combination product.

Abbreviations

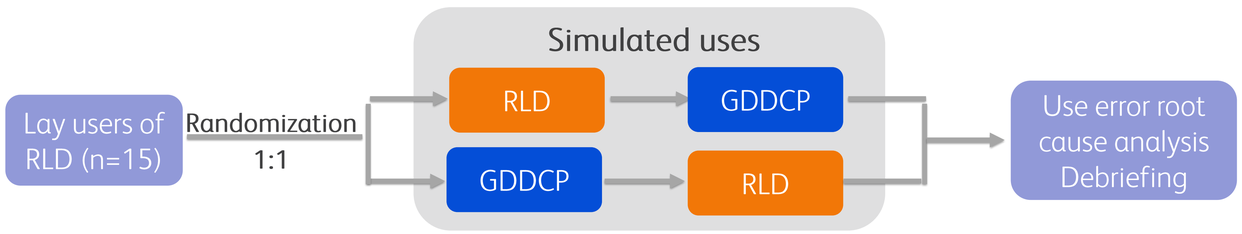
ANDA : Abbreviated New Drug Application
RLD: Referenced Listed drug
GDDCP: Generic Drug Device Combination Product
CUHF : Comparative Use Human Factors
DDDD : Drug Delivery Device Developer

Reference

FDA Draft Guidance: CUHF Studies for a Drug-Device Combination Product Submitted in an ANDA, January 2017.

Formative CUHF Study

A DDDD can conduct a formative CUHF study (with GDDCP filled with water) with a low number of users to obtain insight on the user errors rate of a final CUHF against the RLD.



A Formative CUHF Study:

- Does not replace the final CUHF study
- Provides insight on the use error rate and potential related risks
- Is a basis to design the final CUHF study with final combination product as per the FDA guidance (e.g., sample size, non inferiority margin)

Case Study: A 3-Step vs 4-Step Autoinjector Comparison

BD Physioject™ Disposable Autoinjector (GDDCP) compared to Tirzepatide Autoinjector (RLD)

Comparative Analysis:

Similar features
✓ Activation button ✓ 360° viewing window

BD Physioject™ Disposable Autoinjector

Other differences identified	Potential consequence
x **Different unlocking mechanism** RLD: Turn lock ring to unlock GDDCP: press needle cover to unlock	→ Cannot unlock the autoinjector **Potential risk: delayed treatment**
x **Different end of dose indicators** RLD: visual and audio GDDCP: visual	→ Premature removal of the device **Potential risk: underdosing**

Formative CUHF Study:

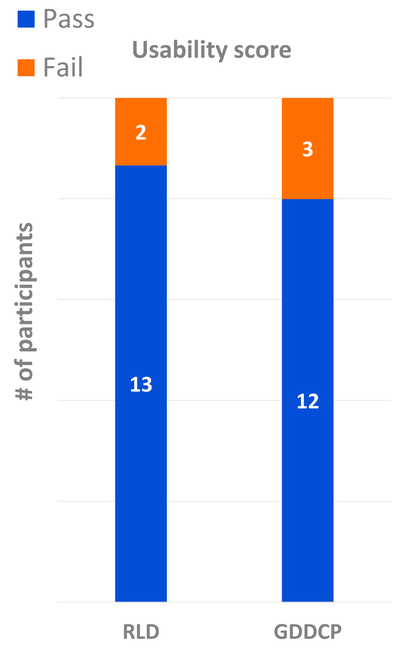
Two tasks were impacted by an "other design difference" and assessed in the study:

- Unlock the device
- Wait until the injection is complete

Results:

- ✓ Same use error was observed: premature removal of the device
- ✓ No use error observed with the unlocking mechanism
- ✓ No new risk has been identified in this formative study

	RLD	DDCP
Use error rate	0.13	0.2
Within subject correlation	0.8	



Conclusion

- In this formative study, the BD Physioject™ Disposable Autoinjector appears to be a suitable candidate to be a GDDCP of the compared RLD.
- DDDDs can support pharmaceutical companies to de-risk their ANDA submission by proactively developing supportive documentation and conducting formative CUHF studies to support final CUHF study design and risk evaluation.