Comparative Threshold Analysis – So Near, Yet So Far …

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May 21, 2024

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Comparison of user interface (UI) of the generic Drug-device combination product (gDDCP) to RLD UI

Labelling comparison

Side by side, line by line comparison of

- Prescribing information
- IFU
- Device labels, carton labels
- Device constituent parts descriptions

Comparative task analysis

Applicants should perform

- Comparison of the tasks for the proposed gDDCP against the RLD

Physical comparison of DDCP UIs

Perform visual & tactile examination

- Examine physical features of the RLD
- Compare the same with the drug delivery constituent part of the gDDCP

Outcome of Threshold analysis

- ✓ No design difference
- ➢ Minor design difference
- ❖ **Other design differences**

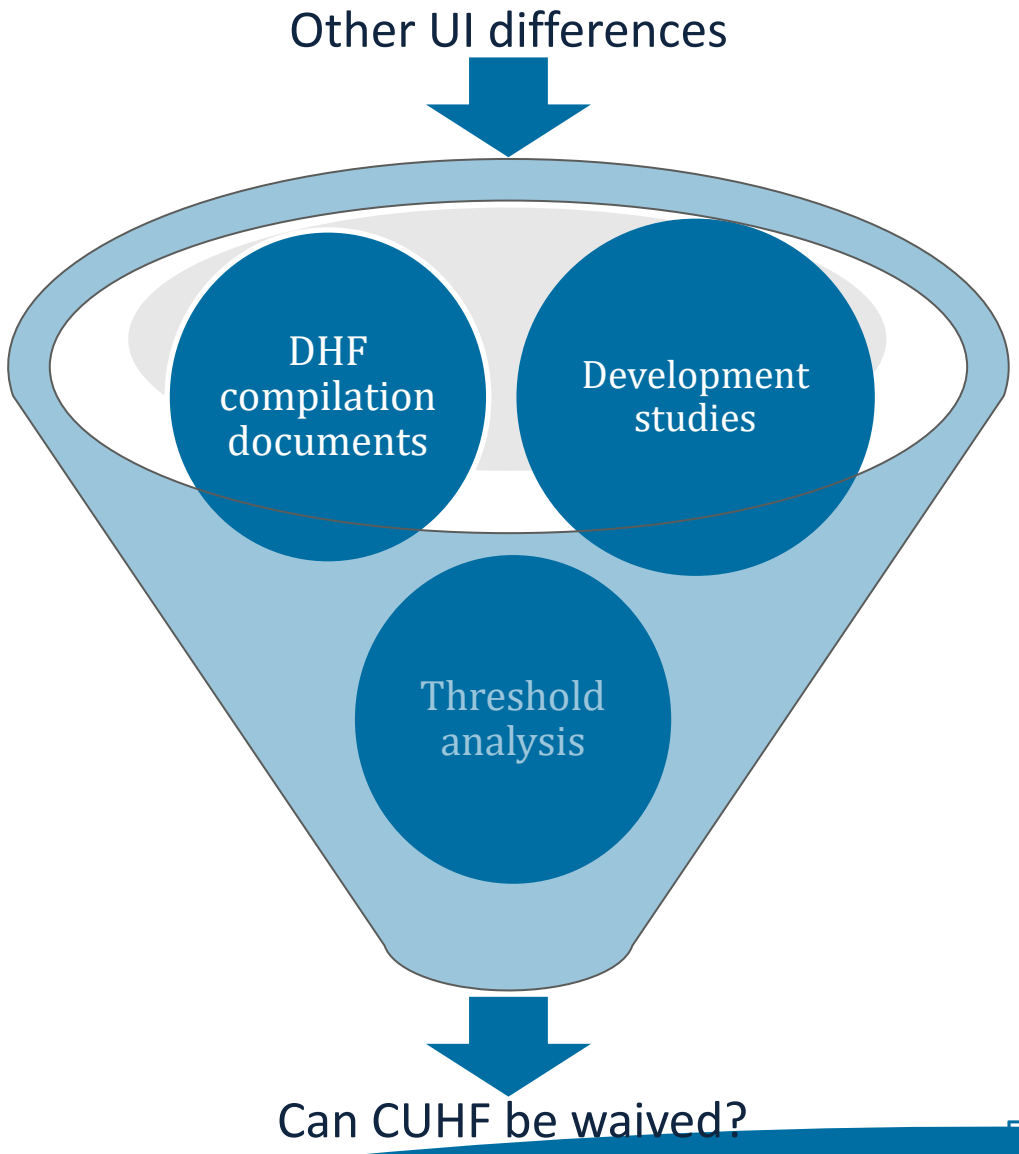
- IP implications
- Manufacturing issues
- Budget constraints

- If UI design difference has impact on the external critical design attribute that involves administration of the product
- Difference may not be considered ‘minor’
- Applicants to consider modifying the device design
- Provide additional information
- Data from CUHF studies
- Prove that no risk is introduced during substitution of RLD with proposed gDDCP

Project delays

Generic product development is a time sensitive affair, thus proposal to justify ‘other’ UI differences based on available data from product development should be considered.

- Design & development of gDDCP involves multi dimensional research
- Extensive studies are done as a part of development e.g. CMC characterization (cleaning, priming-repriming, robustness), bioequivalence (in vitro & in vivo), reliability studies (for emergency use products)
- All above studies demonstrate & prove device performance is comparable to reference product
- Hazard lists, risk analysis & risk mitigation done as a part of Design history file (DHF) compilation – exhibit substantial evidence for gDDCP performance in actual use scenario
- Threshold analysis takes the sponsor step closer to ANDA approval; however, approval seems so far when other UI differences exist!



Background:

- ✓ Nasal spray product T requires more priming shots as compared to R
- ✓ Due to different bottle size & hence the dip tube length

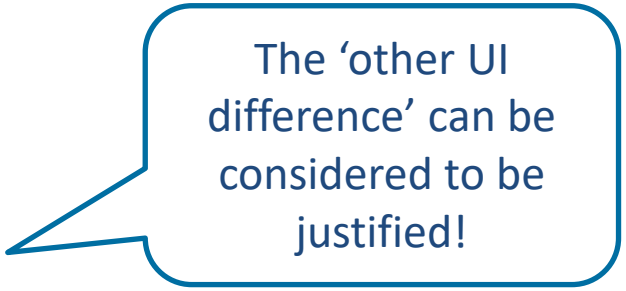
Priming instructions for R	Priming instructions for T
Push bottle with thumb FIRMLY and QUICKLY **5-6** times or until a fine spray appears. Now your pump is primed.	Push bottle with thumb FIRMLY and QUICKLY **6-7** times or until a fine spray appears. Now your pump is primed.

CMC drug product characterization studies:

- Equivalence of product performance is demonstrated as a part of priming-repriming studies
- Done as a part of development

Steps taken to mitigate risk:

- Clear indication on the IFU as well as product carton
- Demonstration of drug content from sprays 5, 6 & 7 – T v/s R
- Establish that substitutability of T product does not introduce any new risk



Background:

✓ Oral liquid product T provides lesser number of syringes with the product as compared to R

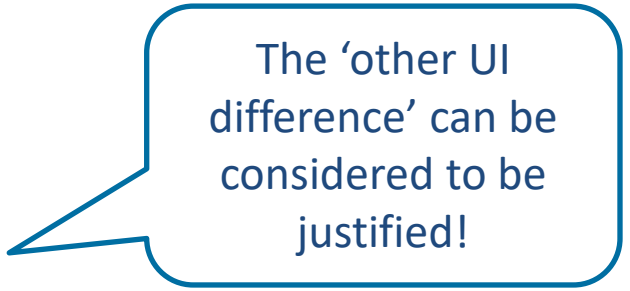
Use instructions for R	Use instructions for T
Use the second syringe for the remaining volume of the medicine to be taken.	Reuse the first/same syringe for the remaining volume of the medicine to taken.

Studies using the T device:

- Comparative Dose Accuracy Studies with T and R products

Steps taken to mitigate risk:

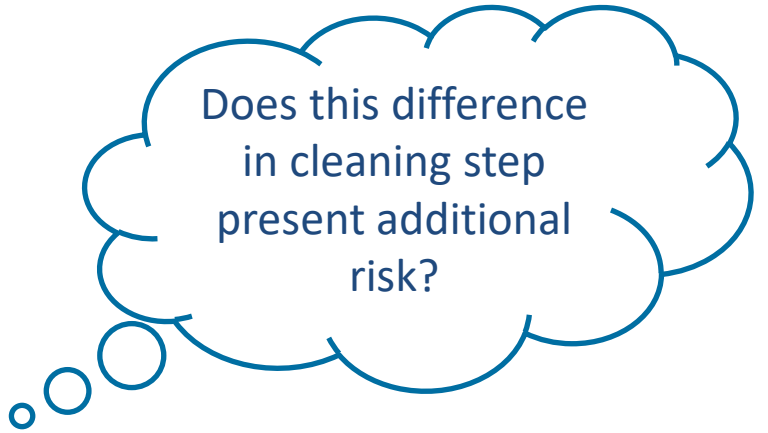
- Clear indication on the IFU as well as product carton
- Demonstration of drug content is comparable – T v/s R
- Establish that substitutability of T product does not introduce any new risk



Background:

- ✓ Inhaler device with a different mouthpiece design – due to IP implications
- ✓ Cleaning step for T device different from R

Cleaning instructions for R	Cleaning instructions for T
Open the **mouthpiece by pulling it upwards**. Open the base by lifting the button. Clean the device with warm water.	Open the **mouthpiece & base** by lifting the button. Clean the device with warm water.

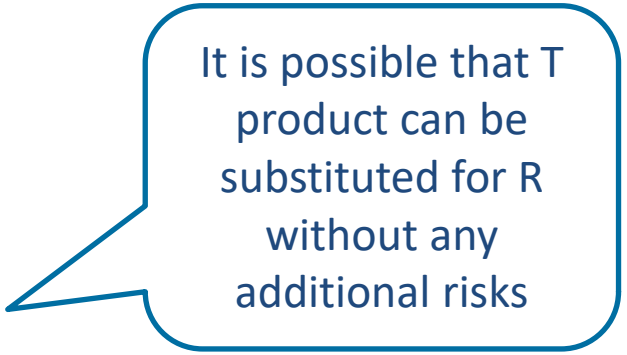


Studies done using the T device:

- Cleaning study for the T device as per IFU instructions
- Risk assessment for incomplete cleaning of T device
- Impact of following the R cleaning instructions on the T device

Steps taken to mitigate risk:

- Demonstrate comparable performance of RLD & gDDCP
- No impact of difference in the cleaning steps (tasks)



Background:

- ✓ Product intended to be used as an emergency medicine
- ✓ T device design is different from R (side actuation button as compared to bottom actuation)

Dosing instructions for R	Dosing instructions for T
Press the **XXX coloured** plunger at the **bottom** with your thumb to deliver the dose.	Press the **XXX coloured** plunger at the **side** with your thumb to deliver the dose.

Does this difference in the location of the plunger pose an additional risk?

Studies done using the T device:

- Reliability studies as a part of performance demonstration for emergency use product
- Bioequivalence of T & R (in vitro as well as in vivo)
- Risk management as a part of Design History file

T & R products can be proposed to be used interchangeably

Steps taken to mitigate risk:

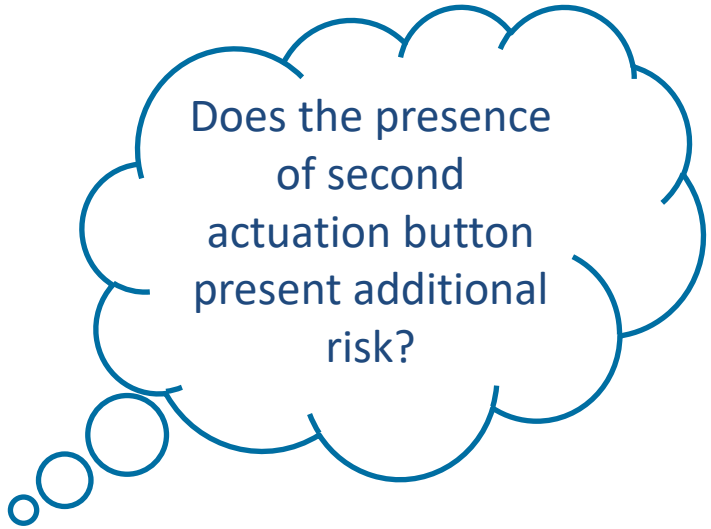
- Ensuring product performance consistency through extensive comparative testing
- Appropriateness of use of T device in emergency use

Background:

Device is intended to deliver 2 doses of medicament

T product design is different & has 2 actuation buttons as against 1 of R

Dosing instructions for R	Dosing instructions for T
Push the plunger with thumb. Breathe in while pushing the **plunger** till end of stroke. Check dose indicator for successful delivery of first dose. Repeat above steps for **second dose**. Check dose indicator for successful delivery of second dose.	Push the **blue plunger** with thumb. Breathe in while pushing the **blue plunger** till end of stroke. Check dose indicator for successful delivery of first dose. For second dose, push the **yellow plunger** with thumb. Breathe in while pushing the **yellow plunger** till end of stroke. Check dose indicator for successful delivery of second dose.



Risk mitigation:

- IFU & label clearly mentions to check successful delivery of first & second doses
- User accustomed to use the single button R device would be used to checking dose delivery indicator

Background:

- ✓ Product is a single use DDCP
- ✓ R device has a device-integrated safety feature to prevent accidental dose delivery
- ✓ T product has a safety feature built into the product via packaging

Instructions for R	Instructions for T
Remove the product from the pack. **Separate the XXXXXX (safety feature).** Administer the dose of the medicine by pressing.	Remove the product from the pack by **twisting the XXXXXX (safety feature).** Administer the dose of the medicine by pressing.

Can accidental dose delivery occur from the T product?

Studies done for the T device:

- Device robustness to prove that the accidental dose delivery does not occur during storage & transit
- Transport worthiness as a part of product performance testing

Although the UI difference exists, no risk is identified for substituting T for R

Steps taken to mitigate risk:

- Demonstrate the efficiency of the packaging of the T product to prevent accidental dose discharge
- Users do not have to perform any additional tasks before using the T product

- Differences in the gDDCP (as compared to RLD) would more likely exist due to multitude of factors
- Threshold analysis outcomes may end up having an outcome of ‘Other design differences’
- Current FDA guidance for Threshold analysis (January 2017) does not provide detailed classification & illustrations to ‘Other differences’
- An attempt is made to propose to leverage comprehensive & exhaustive data generated during product development – to ‘justify’ other differences
- The ultimate aim is to reduce turn-around time for gDDCPs whilst mitigating user risk to substitutability of generic DDCP
- A midway can be worked upon which could enable acceptability of generic device without performing CUHF studies
- Increasing number of complex DDCPs being available; elaborate information provided in the guidance may be beneficial to sponsors of gDDCPs

Thank You

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