

# Bioequivalency Study Requirements:

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## *The story of the “Generic” AutoInjector*

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# To “BE” or not to “BE”...

From a generic drug development perspective

## 1. Why would a BE study be required?

- Change in formulation?
- Route of administration?
- Comparison of functional attributes?

## 2. What should be considered in BE strategy

- In-vitro vs In-vivo?
- Data requirements for In-vivo study?

## 3. A Case Study – AutoInjector development

- Overview of stability study requirements to determine CPPs
- Correspondence with FDA

## 4. BE vs. HF Studies – what is the difference?

- What, if anything, can be leveraged?



# What Typically requires BE Studies in Generic Drugs?

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- Change in Formulation
  - If using excipient in levels significantly higher than RLD that have been known to have an impact on drug absorbance
  - If drug is long-acting (like a depot formulation)
  - Other examples...
  
- Route of Administration or dosage form
  - If changing formulation in a drug with ROA of subcutaneous or intramuscular, a BE study may be required
  - Almost always required if an oral tablet/capsule

# Why would a Combo Drug Need a BE study??

- **First Line of Defense: Comparison of Key Functional Attributes**

*Feedback received from controlled correspondence: In the abbreviated new drug application (ANDA) submission, you should submit data on comparative in-vitro tests including, but not limited to, 1) **drug volume delivered**, 2) **injection time**, and 3) **force to fire**.*

- *in vitro tests conducted on the bio-lot of your proposed generic drug product compared to the RLD*
- *Must provide specifications of your proposed product's needle gauge and length, needle penetration depth, breakloose force and extrusion force.*

*Your device component of your proposed generic should have **the same external design and external operating principles as the RLD device** to ensure substitutability of your proposed generic product to the RLD.*

# Why would a Combo Drug Need a BE study??

- **First Line of Defense: Comparison of Key Functional Attributes**

- *Provided both products have a comparable needle penetration depth, dispensing time, dispensed volume, and injection force, there should be no significant difference in the absorption profile between the RLD and the proposed AutoInjector.*

<b>Critical functional and performance parameter</b>	<b>RLD</b>	<b>Proposed Product</b>
Needle Gauge and Length	26G ½"	27G ½"
Needle Penetration Depth	6.47 mm	5.5mm +/- 1.5mm
Dispensing Time	1.05 sec	1.0 - 5.0 sec (Target 1.5 sec)
Dispensed Volume	0.51 mL	NLT 0.50 mL
Injection Force	1.68 kgF	0.5 - 1.6 kgF



## Excerpts from CP from King Pharma

### Citizen Petition from King Pharma on Sumatriptan succinate autoinjector (FDA Docket Nos. FDA-2007-P-OI28 and 2009-P-0040)

- “ANDA applicants would be required to provide details on attributes such as *auto-injector design, materials, operating principles, and comparative performance tests* between the auto-injector constituent of the RLD and the auto-injector constituent of the product described in the ANDA
- “*Some auto-injector changes (e.g., a change to the needle hub assembly, different operating principles, and different ergonomics) may require further clinical data because potential clinical consequences might be unknown.*”
- “We agree that comparative performance testing is a requirement for demonstrating bioequivalence of drug/auto-injector combination products. We also agree that to obtain a waiver of in vivo testing for a demonstration of bioequivalence, ***sponsors must provide performance test evidence that includes a demonstration that their auto-injector and that in the RLD have similar needle penetration depth, dispensing time, dispensed volume, and injection force.***”

# KEY TAKE-AWAYS

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- Perform appropriate characterization of functional attributes of RLD vs. proposed generic
- When in doubt, ask FDA... typically through a formal controlled correspondence
- Must always compare your device against the approved RLD device, even if there are other approved generics on the market with same proposed design



# Case-Study: Generic Autoinjector

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- Product under development already had generic autoinjectors approved
  - “The proposed drug product is a pre-filled, fully assembled, ready-for-use, disposable (single use) portable, pen-like auto-injector device with a ‘Push & Button design’ that is similar to the previously approved generic AIs of... ”
  - “The RLD’s Injection system requires preparatory assembly of a pre-filled cartridge with the non-disposable injector prior to each use and disassembly after use”
- Even though generic competitors were approved, all approved products were different than the RLD
- Competitor product did require less steps and was considered to be an “improved” delivery system
- However, always need to prove comparison to RLD, even when other generics are approved

# Summary of Comparative Functional Parameters: RLD vs. Approved Generics

- Generic Functional Parameters (Sun Pharma):

	Shield Remover Removal Force (kgF)	Pre-injection Pushing Force (kgF)	Activation Force (kgF)	Injection Time (s)	Deliverable Volume (mL)	Needle Extension (mm)	Needle Cover Override Force (mm)
Mean	1.98	0.75	0.87	1.35	0.52	5.82	1.48
Min	0.81	0.68	0.80	1.20	0.49	5.28	1.35
Max	3.89	0.82	0.96	1.70	0.62	6.61	1.64
STDev	0.85	0.02	0.03	0.12	0.03	0.28	0.09

- RLD Functional Parameters:

	Shield Remover Removal Force (kgF)	Pre-injection Pushing Force (kgF)	Activation Force (kgF)	Injection Time (s)	Deliverable Volume (mL)	Needle Extension (mm)	Needle Cover Override Force (mm)
Mean	-	-	1.68	1.05	0.51	6.47	-
Min	-	-	1.35	0.87	0.50	5.96	-
Max	-	-	2.09	1.17	0.51	7.02	-
STDev	-	-	0.20	0.09	0.00	0.32	-

## Case-Study: Generic Autoinjector Cont'd

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### Why was a BE study required?

- The difference between the minimum needle extension length was 5.82mm (generic) vs. 6.47mm (RLD)
  - Difference was 0.65mm. FDA considered this difference to be statistically significant to require a BE study to be performed.
- From the Bioequivalence Review of Sun Pharma's Sumatriptan Generic AutoInjector Submission
  - *"Because differences in injection time and other differences in device performance and design, such as the difference in **needle gauge**, might affect the plasma concentration profile and C<sub>max</sub> in particular, we recommend that human PK studies be requested to demonstrate bioequivalence",* in healthy volunteers where the subjects inject themselves using the device
  - "The DBE recommends conducting each of these in vitro tests: 1) **drug volume delivered**, 2) **injection time**, and 3) **force to fire**. These comparisons should be made directly between the stability lot versus the RLD.

# What should be included in BE Study?

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## Overview of In-Vitro data

- Comparative functional testing
  - Does it need to be comparable to RLD??
  - How close must data be??

*“Therefore, while the performance and specifications of the proposed device are generally similar to those of the RLD, the small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK.”<sup>1</sup>*

- Verification testing on surrogate (such as an orange)
  - Needle depth
  - Injection force
  - Other critical functional attributes
  - Need to have enough samples to make it statistically relevant, which can be challenging depending on cost and availability of RLD

<sup>1</sup>: Reference Bioequivalence review for Sun Pharma’s Sumatriptan Autoinjector ANDA

# What should be included in BE Study?

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## Overview of In-vivo data

- Typically a PK study
  - For Sumatriptan example, was a single-dose two-way crossover fasting bioequivalence study in healthy volunteers **where the subjects inject themselves using the device**
  - FDA typically wants real-life patient handling experience incorporated into the clinical study
- May require some aspects of PD depending on adverse reactions as well as if formulation is changing
  - i.e. an increase in one excipient, especially if is the drug product vehicle, may increase pain at site of injection
  - May consider issuing a pain scale to study participants to gather secondary end-point information

## KEY TAKE-AWAYS

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- Basis of in-vitro/functional comparison is ALWAYS the RLD... even when other generics are approved in similar device systems
- Generic developer must clearly define what the critical device attributes are for their particular product... i.e. injection time, needle gauge, needle depth.
  - Critical attributes are typically defined by information from the RLD Package insert, including the route of administration, drug vehicle (i.e. oil vs. aqueous), injection time (if applicable)
  - Most common attributes are breakloose, gliding force, needle depth, etc.
- How close must the data be to obtain a biowaiver?... No straight answer.
  - Best approach is to gather data and approach FDA via Controlled Correspondence



# Difference between Human Factors and BE Study

## Human Factors Study: Typically a part of Design Validation

- Typically used to:
  - Identify and analyze intended users and expected use scenarios and use environments
  - Identify and explore potential device use- related hazards and risks and their potential clinical consequences
  - Explore different design alternatives and identify the potential residual risks assigned to each
  - Ensure potential use errors and failures have been eliminated or limited to the extent possible through appropriate application of human factors methods
- Studies must be performed using commercially representative samples

# Can BE Study be used to Support HF Study?

BE Study	Simulated Use HF Study
Typically performed by clinicians that may not be focusing on device performance so may not receive unbiased feedback	Observed by Human Factors experts who are trained specifically to notice errors in device use
Details from user may not be appropriately documented or transferrable into a clear risk profile	Study is performed under regulated conditions (typically via protocol) and results are documented immediately
Delivery of dose is crucial so study is typically designed to avoid user error	As delivery of dose is simulated, "real-life" errors are more likely to occur.
Less varied population due to recruitment restrictions	Can use a more varied population

**BOTTOM LINE:** can prove challenging to obtain robust data from BE study to support human factor requirements in order to appropriately characterize risks.

- When usability of syringe is potentially studied during the BE study, this data could potentially be used to support risk profile of device but may not provide enough data to avoid performing an independent HF study

# Questions

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QUESTIONS?