Regulatory Approaches for Generic Drugs: BE of Topical Drug Products

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Agenda

- Bioequivalence issues unique to topical drug products
- Pharmacokinetic (PK) approach
- Pharmacodynamic (PD) approach
- Clinical approach
- In vitro approach
- Waiver of BE requirement (biowaiver)
- Summary and conclusions

Why do bioequivalence (BE) studies of topical products present unique regulatory issues?

Why are BE studies necessary for proposed new generic products?

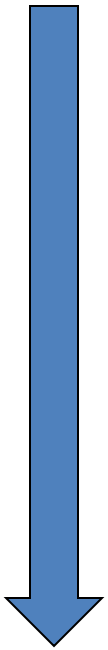
- The US Code and FDA's regulations require that a generic drug product be bioequivalent to its corresponding reference listed drug (RLD) product for marketing approval
- It is not necessary to demonstrate safety and efficacy for the new generic
  - Relies on RLD safety and efficacy data
- If certain criteria are met, FDA may grant a biowaiver

Objective of BE studies in generic drug approval process

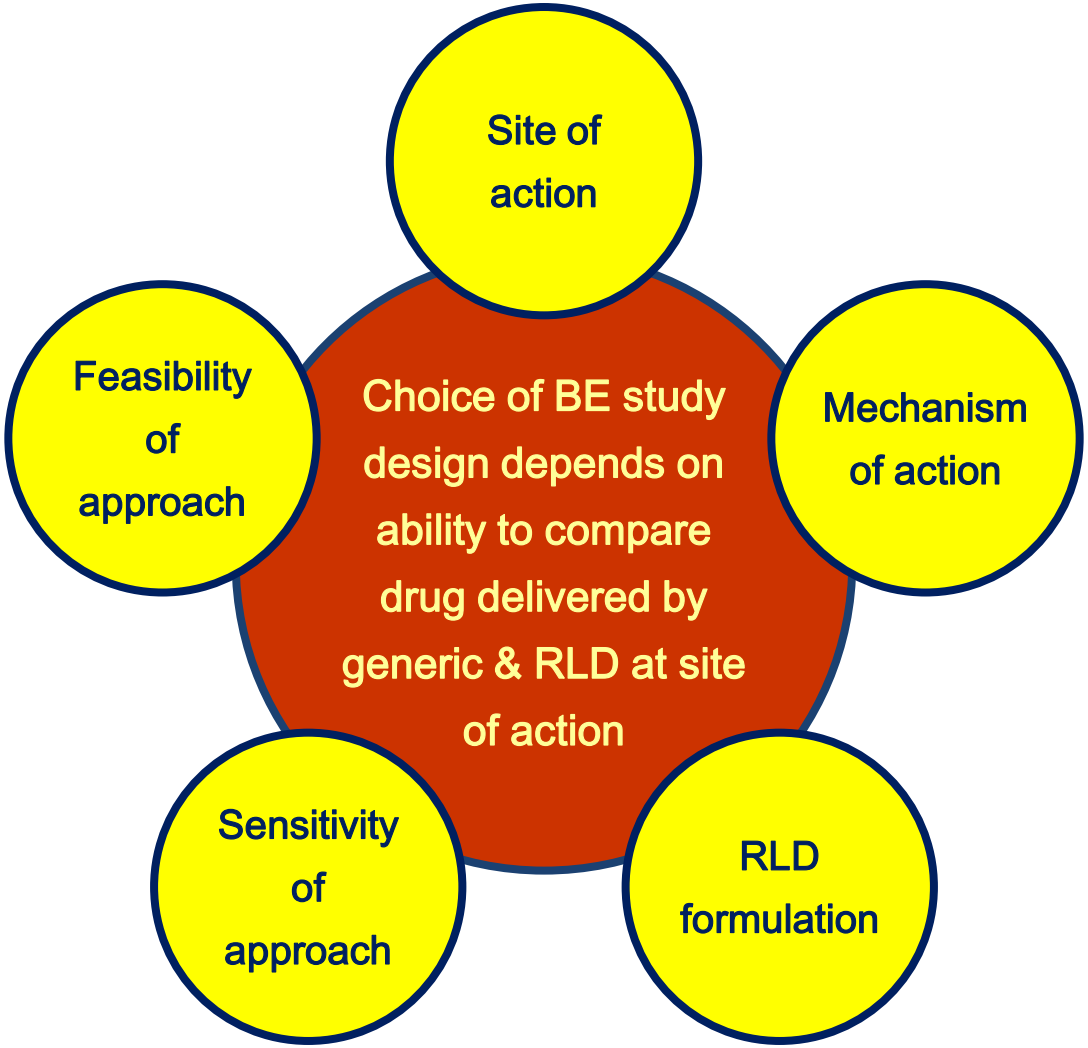
- In an acceptable BE study, the generic and reference product should not show a significant difference in the rate and extent of availability at the site of action
- FDA's regulations list suitable BE approaches ranked by sensitivity, accuracy, reproducibility
- For each new generic topical drug product, FDA must consider
  - The optimal BE approach; or
  - Whether a biowaiver is appropriate

BE approaches, ordered by accuracy, sensitivity, reproducibility

- PK
- PD
- Clinical endpoint
- In vitro
- Any other approach deemed suitable by FDA



Considerations in selecting BE approach for a generic topical drug



Some definitions applied in comparing generic and RLD topical formulations

Terminology	Abbr.	Definition
Qualitatively the same	Q1	Generic and RLD products contain the same active and inactive ingredients
Quantitatively the same	Q2	Generic and RLD products contain the same amounts of active and inactive ingredients
Physicochemical attributes of a topical dosage form	Q3	Generic and RLD products have the same physicochemical properties

Several case studies illustrate how FDA determines an appropriate BE approach for a generic topical product

Application of PK approach: lidocaine topical patch 5%

Application of PK approach: lidocaine topical patch 5%

Drug substance	Indication	Mechanism of action
• An amide-type local anesthetic agent	• Relief of pain associated with post-herpetic neuralgia	• Lidocaine acts on nerves in dermal tissue

Application of PK approach: lidocaine topical patch 5%

Site of action

- Lidocaine penetrates beneath the stratum corneum to reach the site of action in dermal tissue

RLD formulation

- An adhesive material containing 5% lidocaine, to be applied to the skin

Sensitivity, feasibility

- Lidocaine in plasma is proportional to its presence at site of action
- Measuring lidocaine in plasma is feasible

Application of PD approach: fluocinolone acetonide 0.01% topical body oil

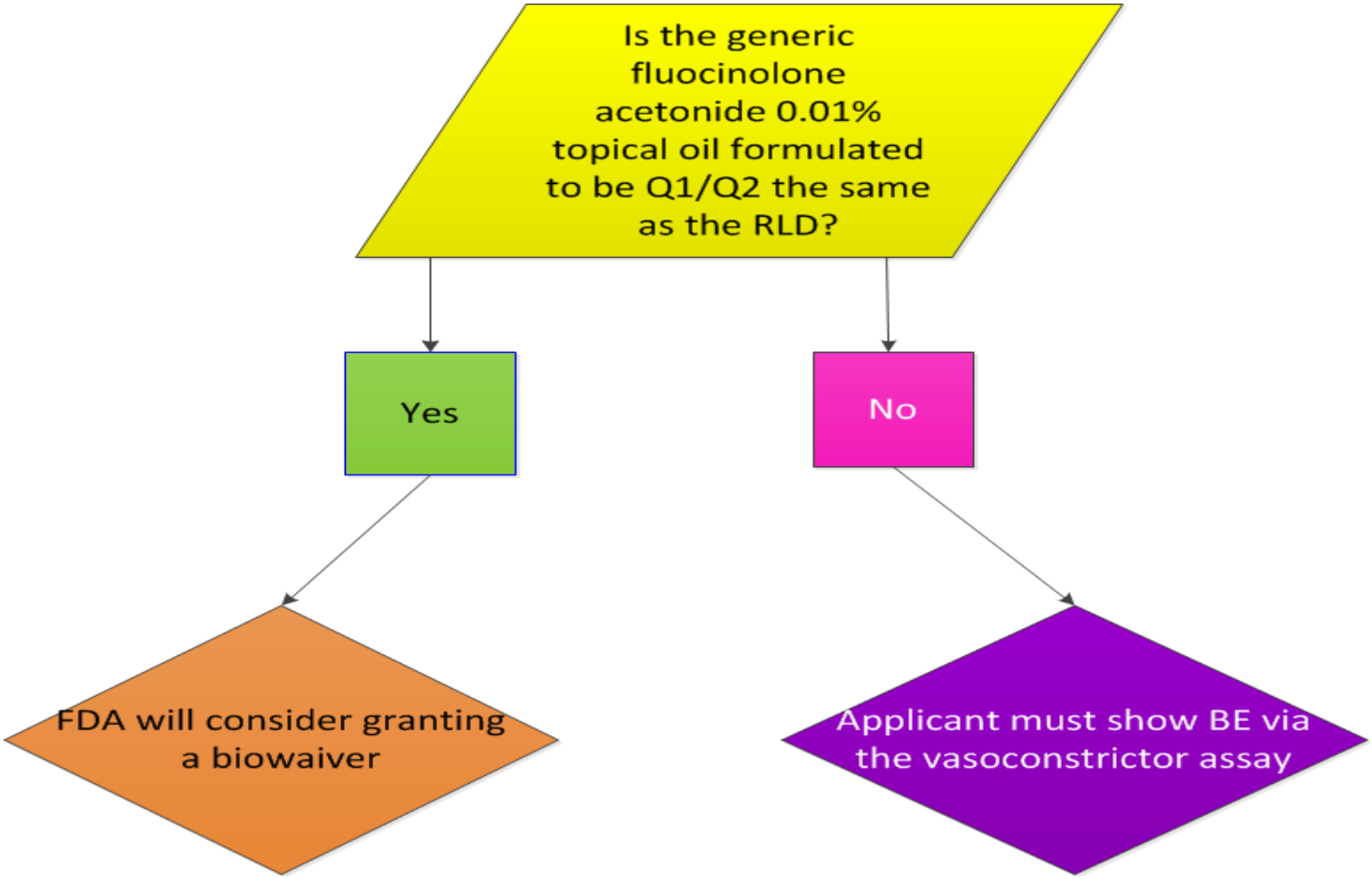
Application of PD approach: fluocinolone acetonide topical oil

Drug substance	Indication	Mechanism of action
• Low-to-medium range potency corticosteroid	• Topical treatment of atopic dermatitis	• Has anti-inflammatory, antipruritic, & vasoconstrictive properties

Application of PD approach: fluocinolone acetonide topical oil

Site of action	RLD formulation	Sensitivity, feasibility
• Absorbed percutaneously; not intended to be systemically absorbed	• A solution of fluocinolone acetonide in a blend of oils	• The PD vasoconstrictor assay can accurately detect rate and extent of availability in skin

Fluocinolone acetonide topical oil: additional considerations for BE



Application of clinical endpoint approach: 5-flourouracil (5-FU) cream 5%

Application of clinical approach: 5-FU cream 5%

Drug substance	Indication	Mechanism of action
• A fluoro-pyrimidinedione which is cytotoxic	• Topical treatment of actinic keratoses (AK) • Treatment of superficial basal cell carcinomas (sBCC)	• Creates a thymine deficiency, provoking unbalanced growth in rapidly-growing cells, such as carcinomas

Application of clinical approach: 5-FU cream 5%

Site of action

- Acts on AK and sBCC lesions in the epidermis and dermis

RLD formulation

- Cream contains 5-FU in a vanishing cream base comprised of several inactive ingredients

Sensitivity, feasibility

- AK treatment is considered more sensitive to formulation performance than sBCC treatment
- It is feasible to perform a clinical endpoint BE study in AK patients

Clinical endpoint BE studies of 5-FU: additional considerations

- Primary endpoint is proportion of subjects with treatment success at study week 6
- Success is defined as 100% clearance of all AK lesions within the treatment area
- A placebo control arm is recommended to
  - Demonstrate that the generic and RLD are active;
  - As a parameter to show that study is sufficiently sensitive to detect differences between products

Application of in vitro approach: acyclovir ointment 5%

An in vitro approach can be used for acyclovir ointment 5%

Drug substance	Indication	Mechanism of action
• A synthetic nucleotide analogue active against herpes viruses	• Initial outbreaks of genital herpes • Treat certain types of lesions caused by Herpes simplex virus	• Converted to acyclovir triphosphate intracellularly • Acyclovir triphosphate stops replication of herpes viral DNA

An in vitro approach can be used for acyclovir ointment 5%

Site of action

- Acyclovir delivered by the ointment functions in the upper layer of the skin

RLD formulation

- Considerably less complex than a cream
- Consists of one active ingredient suspended in a polyethylene glycol base

Sensitivity, feasibility

- An in vitro BE approach more sensitive than a clinical endpoint BE study
- Due to low potency of ointment, a clinical endpoint BE study may not be feasible or reliable

BE of acyclovir ointment 5%: additional considerations

- The generic and RLD products must be Q1/Q2
- To show that generic and RLD are also Q3, conduct in vitro tests to compare
  - Release rates
  - Particle size, viscosity, morphic form, PEG molecular weight distribution
- If not Q1/Q2, conduct clinical endpoint study

For the diclofenac sodium gel 1%, FDA recommends a PK endpoint study and a clinical endpoint study to demonstrate BE

For diclofenac sodium gel 1%, FDA recommends two in vivo BE studies

Drug substance	Indication	Mechanism of action
• Non-steroidal anti-inflammatory	• Relief of the pain of osteoarthritis	• Inhibits cyclooxygenase, resulting in decreased synthesis of molecules associated with inflammatory response

For diclofenac sodium gel 1%, FDA recommends two in vivo BE studies

Site of action

- The joint or local soft tissue
- Diclofenac penetrates the soft tissue
- Diclofenac is also well-absorbed
- Unclear if effects are due solely to local delivery or if systemic delivery contributes

RLD formulation

- A gel comprised of several different inactive ingredients

Sensitivity, feasibility

- A PK study is most sensitive, accurate, reproducible but may be unsuitable if drug acts mainly by local action
- As there is evidence that drug may be locally-acting, an in vivo study with clinical endpoints should also be conducted

The FDA will consider granting biowaivers for topical products provided certain criteria are met

Criteria for granting a biowaiver for a topical solution

- Formulation is a solution for application to skin;
- Generic and RLD contain the same active ingredient in the same concentration and dosage form;
- The generic contains no inactive ingredient or other change in formulation from the RLD that might significantly affect availability
  - e.g, FDA may request in vivo and/or in vitro BE studies if generic and RLD have differences in penetration enhancers

Biowaivers for products coded "AT" in FDA's Orange Book

- Applies to very few topical formulations approved prior to 1962
- Underwent review by the Drug Efficacy Study Implementation (DESI) panels of experts
- Generic and RLD must contain same active ingredient and be of same dosage form
- Examples
  - Erythromycin topical gel
  - Hydrocortisone topical cream

Summary and conclusions

- FDA determines the optimal BE approach for each proposed generic topical formulation on a case-by-case basis
- Approach may be PK, PD, clinical, in vitro
- In determining the optimal BE approach for each product, FDA considers
  - Drug mechanism of action, site of action
  - Complexity of RLD formulation
  - Feasibility, sensitivity of an approach

References

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  - Bioequivalence Recommendations Guidance for the diclofenac sodium topical gel, 1% strength
- http://www.regulations.gov
  - Acyclovir ointment 5%, Docket No. FDA-2012-P-0779
  - Fluocinolone acetonide topical oil 0.01%, Docket No. FDA-2004-P-0215
  - Fluorouracil cream, Docket No. 2004P-0557/CP1
  - Lidocaine patch 5%, Docket No. FDA-2006-P-0356
- 21 CFR Section 320.22 (biowaivers)

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Thank you for your attention!