Clinical Studies in BE Evaluation of Generic Products

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Division of Clinical Review (DCR)

The DCR primarily deals with those generic drug products that require a BE study with clinical endpoint for demonstrating BE.

Often such drug products are classified as “topical”.

I will now clarify how to determine if a particular drug product is a topical drug product and how the DCR evaluates such drug products, which often results in recommending the conduct of a BE study with clinical endpoint.
Goals

• Clarify the classification of topical drug products.

• Provide a practical overview of the current process of how DCR writes a product-specific Draft Guidance containing a bioequivalence (BE) study with clinical endpoint(s) for a topical drug product and then posts it to the public at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

• Present three “hot topics” facing the DCR, OGD re: BE studies with clinical endpoints for topical drug products.
Classification of topical drug products

The “Orange Book” is the authority.

OGD follows the “Route” listed for the Reference Listed Drug (RLD) in the Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book):
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
Classification of topical drug products (cont.)

1) Select your search method; recommend clicking “Search by Active Ingredient”.

2) Type in name of active ingredient in text box and then click on “RX” (for Prescription Drug Products), “OTC” (for Over-the-Counter Drug Products) or “Disc” (for Discontinued Drug Products) and click on “Submit”.

3) Route is the last word listed in the 5th column from the left (Dosage Form is listed first in the 5th column from the left) for the RLD of interest.
How does something so simple get confused?

1) The RLD may have the word “topical” in their approved tradename; however, the “route” listed in the Orange Book is “transdermal”. For ex., The “route” of “AXIRON (testosterone) topical solution, for topical use CIII” is listed as “transdermal” in both the Orange Book and at Drugs@FDA.
How does something so simple get confused (cont.)?

2) A drug product is applied to the surface of the body; however, the route is not always topical. For ex., a generic firm submitted a waiver request under 21 CFR 320.22(b)(3)(i) [which applies to solution applied to the skin] by stating that their test product is “intended for topical administration to the eye”; however, the “route” listed in the Orange Book for the RLD was “ophthalmic”. Ophthalmic waivers are covered by 21 CFR 320.22(b)(1).

3) Topical Patches are often forgotten about, e.g. Diclofenac Epolamine topical patch, 1.3% (generic to Flector® NDA 021234), Lidocaine topical patch, 5% and the Menthol; Methyl Salicylate topical patch, 3%; 10%.
Good Advice

For the development of a generic drug product, use the “route” listed in the Orange Book for the RLD.

The routes listed in the Orange Book include: buccal, endocervical, implantation, inhalation, injectable, intramuscular (IM), intravenous (IV) (infusion), nasal, ophthalmic, oral, otic, rectal, subcutaneous, sublingual, topical, transdermal, transmucosal, urethral and vaginal.
BE Evaluation of Generic Products

Per 21 CFR 320.24, Office of Generic Drugs (OGD) may approve a drug product based upon:

- In vivo test in humans measuring the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid as a function of time, i.e. BE study with pharmacokinetic (PK) endpoint(s).

- In vitro test that has been correlated with and is predictive of human in vivo bioavailability data.

- In vivo test in humans in which the urinary excretion of the active moiety, and when appropriate, the active metabolite(s), are measured as a function of time.

- In vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and when appropriate, its active metabolite(s), are measured as a function of time, i.e., pharmacodynamic (PD) study.
BE Evaluation of Generic Products, cont.

• Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriated designed comparative clinical trials, for purposes of demonstrating bioequivalence, i.e., BE study with clinical endpoint. “This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence.”

• A currently available in vitro test acceptable to FDA (usually a dissolution rate test) that ensures human in vivo bioavailability.

• Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.

OR per 21 CFR 320.22, by waiver of evidence of in vivo bioavailability or BE.
BE study with clinical endpoint(s)

Currently, 105 Product-Specific Draft Guidances for a topical drug product are posted at:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

How does the OGD write and post a BE study with clinical endpoint(s) for a topical drug product?

• Assign to a primary reviewer in the DCR, OGD
Competing Assignments for DCR primary reviewer’s time

• BE studies with clinical endpoint: write Draft Guidances and review ANDAs, Protocols and Controlled Correspondences (“Controls”)
• Skin irritation/sensitization/adhesion studies for generic transdermals: write Draft Guidances and review ANDAs, Protocols, and Controls
• Review all Protocols for drugs having REMS with ETASU
• Review Bio-INDs
• Review Controls with clinical questions
• Citizen Petitions
• Suitability Petitions
• Safety consults for pending ANDAs
• Clinical consults for other OGD divisions
• Liaison for clinical questions to OND
• Study Latest Approved Labeling for the RLD.
  • Dosage and Administration section
  • Contraindications
  • Warnings and Precautions
  • Drug Interactions
  • Use in Special Populations
  • Clinical Studies
  • Patient Counseling Information

• Obtain and study FDA Medical Officer and Clinical Pharmacology Reviews of the RLD, particularly those studies used to support approval of original NDA and efficacy supplements.
Process of Writing Draft Guidance

- Obtain and study Medical Officer and Clinical Pharmacology Reviews of clinical studies used to support reformulation of the RLD.

- Obtain and study Protocols submitted to the OGD for review that contain a BE study with clinical endpoint.

- Obtain and read References pertaining to RLD or indication; perform PubMed search of Scientific Literature.

- Search for and review advice provided by OGD in the past re: RLD or related drug products in OGD responses to ANDAs, Protocols and Controlled Correspondence submitted to the OGD.
Process of Writing Draft Guidance

• Search for and review currently posted Draft Guidances for the same indication, for the same dosage form, and the same route of administration.

• Write a document summarizing the above information and supporting the posting of the Draft Guidance.

• Write the Draft Guidance based upon the above information and attach it to the document supporting the posting of the Draft Guidance.
Process of Writing Draft Guidance

• If ANDA for specific drug product has been approved OR Indication-specific Guidance posted AND the OGD has no questions, document is sent for secondary and tertiary OGD review. When the document is finalized, the Draft Guidance is placed in the queue for the next quarterly Federal Register (FR) Notice of Availability (NOA).

• Otherwise, a Request for Consultation, containing Draft Guidance and document written to support Draft Guidance, is sent to OND Division that regulates the RLD for comments.
“Hot” Topical Drug Clinical Topics

• In vitro BE methods replacing BE study with clinical endpoint, ex. Draft Guidance on Acyclovir Ointment/Topical, 5% (for generics to Zovirax® NDA 018604).

• Requesting more than one BE study with clinical endpoint, ex. Draft Guidance on Ciprofloxacin; Dexamethasone Suspension/Drops; Otic, 0.3%, 0.1% (for generics to Ciprodex® NDA 021537).

• Requesting both BE study with clinical endpoint and BE study with pharmacokinetic (PK) endpoint, ex. Draft Guidance on Diclofenac Epolamine Patch/Topical, 1.3% (for generics to Flector® NDA 021234).
Draft Guidance on Acyclovir Ointment/Topical, 5%

I. In Vitro option:
To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24(b)(6), under which “[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence” may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:

i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the test and RLD formulations.

iii. Acceptable comparative in vitro drug release rate tests of acyclovir from the test and RLD formulations.
II. In Vivo option:
Recommended studies: 1 study
Type of study: BE Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: 5%
Subjects: Immunocompromised males and nonpregnant females with recurrent herpes simplex labialis
Additional comments: Specific recommendations are provided below.
“Hot” Topical Drug Clinical Topics

Draft Guidance on Ciprofloxacin; Dexamethasone Suspension/Drops; Otic, 0.3%, 0.1%

Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) Study with Clinical Endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 0.3%; 0.1%
   Subjects: Males and nonpregnant females with acute otitis externa
   Additional comments: Specific recommendations are provided below
“Hot” Topical Drug Clinical Topics

Draft Guidance on Ciprofloxacin; Dexamethasone Suspension/Drops; Otic, 0.3%, 0.1%

Recommended studies: 2 studies

2. Type of study: Bioequivalence (BE) Study with Clinical Endpoint
Design: Randomized, double blind, parallel, in vivo
Strength: 0.3%; 0.1%
Subjects: Male and females aged 6 months and older with tympanostomy tubes with acute otitis media
Additional comments: Specific recommendations are provided below.
Recommended studies: 3 studies

1. Type of study: Bioequivalence (BE) with pharmacokinetic (PK) Endpoints and adhesion
Design: Single-dose, two-treatment, two-period crossover, in vivo
Strength: 1.3%
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Specific recommendations are provided below.
“Hot” Topical Drug Clinical Topics

Draft Guidance on Diclofenac Epolamine Patch/Topical, 1.3

2. Type of study: BE with clinical endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 1.3%
   Subjects: Males and nonpregnant females with ankle sprain
   Additional comments: Specific recommendations are provided below.

3. Type of study: Skin irritation and sensitization
   Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
   Strength: 1.3% (Dose: one-fourth of 1.3% patch)
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: Specific recommendations are provided below.