Bioequivalence Waivers (Biowaivers)

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Bioequivalence Requirement

- Any person submitting an abbreviated new animal drug application (ANADA) must include:
  - Evidence demonstrating that the generic new animal drug is bioequivalent to the reference listed new animal drug (RLNAD); or
  - Information showing that the generic new animal drug qualifies for a waiver of the requirement to demonstrate *in vivo* bioequivalence (BE).

Biowaiver

- When requirements are met, FDA grants a waiver of the requirement to demonstrate *in-vivo* bioequivalence of a generic new animal drug to the RLNAD
- Substantially decreases the cost and time to approval
- Criteria for a biowaiver are provided in Guidance for Industry (GFI) documents:
  - GFI #35. Bioequivalence Guidance, and
  - GFI #171. Waivers of *in vivo* demonstration of Bioequivalence of Animal drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles
  - Lists are not all encompassing

Drugs Eligible for Biowaivers

(Under GFI #35 and #171)

- Parenteral solutions (IV, IM, SQ)
- Oral solutions or other solubilized forms
- Topically applied solutions
- Other topically applied dosage forms intended for local therapeutics effects in non food animals
- Inhalant volatile anesthetic solutions
- Type A Medicated Articles and Soluble Powder Oral Dosage forms

Drugs Eligible for Biowaivers

- Contains the same active and inactive ingredients in the same dosage form and concentration
- Has the same pH and physiochemical characteristics as the approved RLNAD
- Acceptable differences include buffers, antioxidants, and preservatives – no resulting effect of Bioequivalence

Biowaiver Request

Biowaivers are requested after opening a generic investigational new animal drug (JINAD) file and should include:

- Identify the proposed generic product, including proprietary name (if known), established name, dosage form, strength;
- Identity of the RLNAD including the proprietary & established names, dosage form, strength, sponsor name and (A)NADA number;
- Proposed species and indications for the generic new animal drug

Biowaiver Request

- Side by side formulation comparison of the RLNAD and generic
- Identification of any differences between the 2 formulations
- pH of generic, if applicable
- Particle size of active ingredients, if applicable
- Presence and significance of polymorphs or entantiomers of the active ingredients, if applicable
- Solubility data for Type A medicated articles and soluble powders, if applicable
- Justification for being granted the biowaiver

Biowaiver Request

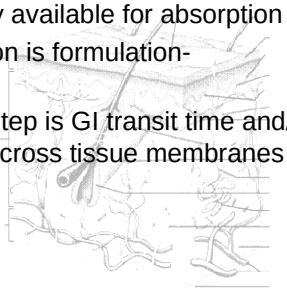
- RLNAD and draft generic labeling
- Certificate of analysis for each ingredient, indicating standards to be used (USP, NF, EP) if available
- Dissolution data for multiple strengths

Multiple Strengths/Adding a Strength

- Contact the Division of Generic Animal Drugs
- Prove Bioequivalence of one strength
- Conduct *in vitro* dissolution studies on the other strength(s)
- Use the dissolution data to support a biowaiver for the different strengths
- Consider CDER's GFI – Dissolution Testing for Immediate Release Solid Oral Dosage Forms

Biowaiver Justification for Solutions

- Drug is already in solution
- Drug is readily available for absorption
- Drug in solution is formulation-independent
- Rate limiting step is GI transit time and/or permeability across tissue membranes



Type A Medicated Articles GFI #171

Two ways to meet BE criteria

1. Comparison of formulations
   - Same active and inactive ingredient(s)
   - Generic is produced using the same manufacturing process as RLNAD
   - Same manufacturer for both generic and RLNAD
2. Demonstration of solubility (amount recovered)
   - USP definition approach
   - Dosage adjusted approach

Type A Medicated Articles

- Demonstration of solubility
  - USP definition approach
    - very soluble, freely soluble, or soluble (chart in GFI #171)
    - solubility determined at pH 1.2, 4.6, and 7.4
  - Dosage adjusted approach
    - largest dose to fluid volume ratio
    - volume of fluid depends on species- ranges from 0.1 l in chickens to 200 liters in cattle (scaled down to size in lab)
    - solubility determined at pH 1.2, 4.6, and 7.4
- Solubility demonstrated at pH 1.2, 4.6, and 7.5 to mimic different areas of GI system

Soluble Powders

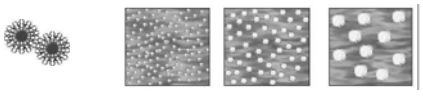
- Conditions for testing in GFI #5 Section IV, F: Drug Stability Guidelines
- Use animal drinking water in the field
- Test recovery of drug in hard and soft water at 25ºC and 37ºC in metal containers
- Sample once visually soluble and test recovery using validated analytical method

Justification for Biowaivers under GFI #171

- Oral soluble powders are in solution prior to administration so they are formulation-independent like parenteral solutions
- Once the active pharmaceutical ingredient (API) from a Type A is exposed to GI fluids, it rapidly dissolves into solution
- It's assumed that the matrix of final feed formulation will have the same effect on the generic as compared to the RLNAD

Non-Solutions

- Non-solutions are not eligible for biowaivers
  - Suspensions, Emulsions, Micro-emulsions, "Micellular solutions", etc.
- Dissolution or disintegration becomes rate-limiting step and is variable from drug to drug
- Different manufacturing processes have a profound effect on the final formulation



Common Problems

- Failure to justify that any change in the formulation will not adversely affect the bioavailability of the generic drug
- Improper characterization of the generic product
- Improper identification of the RLNAD
- Combining multiple requests under one submission

Biowaivers

Thank you

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