FDA/CVM DEMONSTRATING BIOEQUIVALENCE

Dr. Ian Hendricks
Veterinary Medical Officer
Division of Generic Animal Drugs
Center for Veterinary Medicine
U.S. Food and Drug Administration

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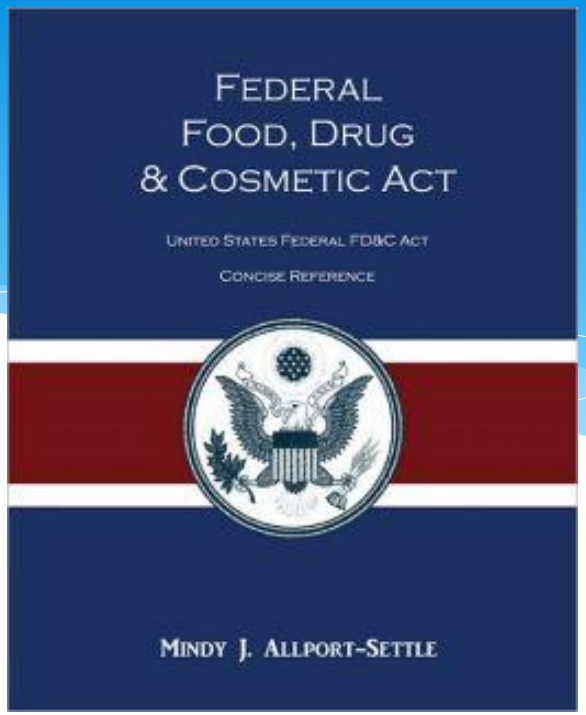
Discussion Objectives

* **Federal Food, Drug, and Cosmetic Act**
* **Requirements for Approval**
* **Suitability Petitions**
* **Hybrid Generic Applications**
* **Demonstrating Bioequivalence**
* **In Vitro Bioequivalence Pathways**



Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988 provides FDA the statutory authority to:

Approve abbreviated new animal drug applications (ANADAs) for a generic copy of an approved off-patent reference listed new animal drug (RLNAD)

Pathways Towards Approvals

* **A phased review followed by an administrative application – Technical sections are reviewed under the generic investigational new animal drug (JINAD) file. The administrative ANADA is submitted after all the technical sections are complete.**

* **A traditional application - An ANADA is submitted as a complete application (data for all technical sections included) and reviewed.**

Technical Sections

* **Bioequivalence – *in vivo* studies to show that the generic drug product is bioequivalent to the RLNAD or a waiver from the requirement to conduct the bioequivalence studies.**
* **Chemistry, Manufacturing, and Controls (CMC) - Meet specific CMC and facility requirements.**
  - **Must be manufactured according to current Good Manufacturing Practice (cGMP) regulations; 21 Code of Federal Regulations (CFR) Parts 210 to 226**

Technical Sections

* **Patent & Marketing Exclusivity - Provide patent certification for patents claiming the drug substance, drug product, or method of use, and address marketing exclusivity.**

* **Environmental Impact – Every application must contain an environmental assessment (EA) or a request for categorical exclusion from an EA; 21 CFR Part 25**

* **Human Food Safety - Address the need for tissue residue depletion studies for drug products used in food-producing animals**

* **Labeling - Submit appropriate labeling that is similar to that of RLNAD**

Requirements for an approval of an ANADA

* **Identify the proposed generic product and the approved RLNAD**
* **Demonstrate that the proposed product has the same:**
  - **active ingredients**
  - **concentration**
  - **dosage form**
  - **route of administration**

Changes to the RLNAD Formulation

* **Different inactive ingredients (excipients)**
  - **In most cases this applies to preservatives, anti-oxidants, and excipients used to adjust or to maintain the pH of the formulation.**
  - **The different excipient must be shown to be safe.**
    - **Safety can be based on the excipient being included in a formulation previously approved for the same dosage form.**
    - **If the excipient has not previously been shown to be safe, studies will need to be conducted to demonstrate safety.**

Permissible Changes from RLNAD

* **Suitability Petitions (SP)**
  - **A SP is a type of citizen petition submitted in compliance with 21 CFR 10.30, requesting FDA to grant or deny a specific changes to a RLNAD**
    - ➢ **The request and FDA's response are publicly disclosed**
    - ➢ **The SP is submitted to Division of Dockets Management***

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* **www.fda.gov/RegulatoryInformation/Dockets/default.htm**

Changes allowed under a SP

* **Permissible changes include any of the following:**
  1. **Route of administration**
  2. **Dosage form**
  3. **Strength (concentration)**
  4. **One of the active ingredients in a combination new animal drug; (same pharmaceutical class)**
  5. **Change in one of the Type A medicated articles in a feed use combination new animal drug**
* **More than one change may be requested in one SP**

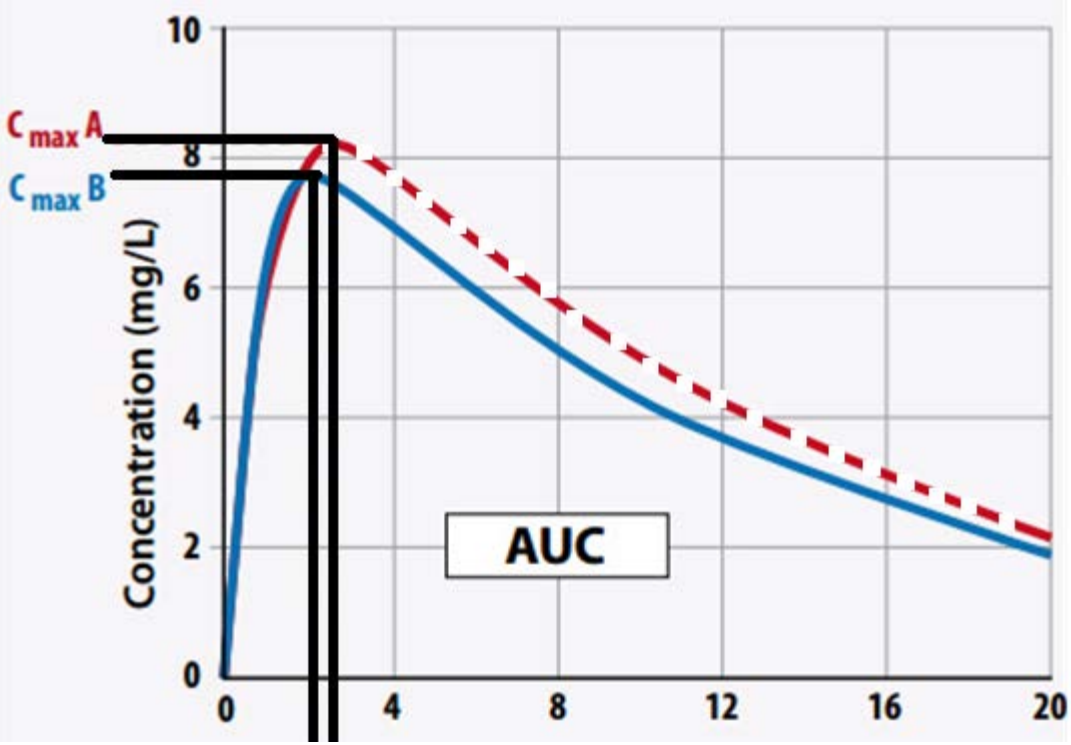
Denial of a Suitability Petition

* **FDA will approve a SP unless it determines that the proposed permissible change(s) would require any of the following:**
  - **Investigations to show the safety or effectiveness of the proposed generic new animal drug**
  - **Investigations to show the safety for human consumption of any residues in food**
  - **Significant labeling changes that may jeopardize the safe or effective use of the product**

Other Paths for Allowable Differences

* **Generic sponsor may seek to add an innovative change (e.g., addition of a new indication or species)**
* **Criteria**
  - **Generic product must be bioequivalent to the RLNAD**
  - **Safety and/or effectiveness (and potentially human food safety) studies are required for the innovation**
* **Process**
  - **One Step – Hybrid pathway: original application and innovation are approved simultaneously**
  - **Two Steps – innovation is a b1 supplement to an approved ANADA**

Demonstrating Bioequivalence & Biowaivers



Two products are considered to be bioequivalent when they are equally bioavailable; that is, equal in the rate and extent to which the active ingredient(s) or therapeutic ingredient(s) is (are) absorbed and become(s) available at the site(s) of drug action.

Demonstrating Bioequivalence

Bioequivalence Studies (order of preference):

1. ***In vivo* blood level bioequivalence studies**
2. **Pharmacologic End-point studies**
3. **Clinical End-point Studies**

Bioequivalence Studies

* **Bioequivalence studies are conducted when a *proposed* product does not qualify for a biowaiver.**
* **Bioequivalence studies are conducted for each major species for which the RLNAD is approved.**
* **Bioequivalence studies must be conducted in accordance with current Good Laboratory Practice (cGLP) standards (21 CFR Part 58).**
* **For information on analytical method validation, bioequivalence study design, and statistical methods consult the Guidances for Industry (GFI) under "References".**

Alternative to Demonstrating Bioequivalence

* **Waivers from the requirement to conduct *in vivo* bioequivalence studies (Biowaivers) are considered:**
  - **For certain drug products based on formulation comparison between the RLNAD and proposed generic (e.g. solutions). GFI 35.**
  - **Based on the solubility of the API or the drug product if the final drug product is a solution or is expected to immediately go into solution after introduction into the GI tract. GFI 171.**
  - **For additional tablet strengths if one tablet strength has been shown to be bioequivalent in an *in vivo* blood level bioequivalence study.**

Categories of Products Eligible for Biowaivers: GFI 35 and GFI 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 animals not used for food**
* **Inhalant volatile anesthetic solutions**
* **Type A medicated articles and soluble powder oral dosage forms**

Current Difficulties

* **Insoluble, non systemically absorbed, locally acting products:**
  - **Blood level studies are not possible**
  - **Do not qualify for a biowaiver under GFI 35 or GFI 171**
  - **Clinical end-point studies may be impractical**
  - **Examples: Intra-mammary products; Type A medicated articles; and Topical products**

In Vitro Bioequivalence Pathway

* **Represents an alternate pathway to demonstrate bioequivalence.**

* **NOT considered to be a Biowaiver**

Generic Copies are not allowed

* **Recombinant products**
* **Genetically engineered products**

Reference Guidance

* **Guidance for Industry:**
  - **#5 – Drug Stability Guidelines**
  - **#35 – Bioequivalence Guidance**
  - **#85 – Good Clinical Practices (VICH GL9)**
  - **#145 – Bioanalytical Method Validation**
  - **#171 – Waiver of *In Vivo* Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles**

* http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm

Further Information

Dr. John K. (Ken) Harshman

Director, Division of Generic Animal Drugs

* **240-402-0845**
* john.harshman@fda.hhs.gov

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