

Feed Use Animal Drug Combinations

Important Dates in Feed Use Combinations

- Prior to 1983
- 1983 (October) – Guideline for Drug Combinations for Use in Animals
- 1988 - Generic Animal Drug and Patent Term Restoration Act (GADPTRA)
- 1996 – Animal Drug Availability Act (ADAA)
- 2003 – Animal Drug User Fee Act (ADUFA)
- 2008 – Animal Generic Drug User Fee Act (AGDUFA)
- Current – ADUFA III – “Exploring”

Pre-1983

- DESI Standards for old combinations (pre '62)
- Somewhat haphazard requirements
- Full blown studies *may* have been required for effectiveness for newer combinations.
 - Dose titrating of all the drugs in the combination, when used together. (Sometimes four corner studies.)
 - Target Animal Safety?
 - Human Food Safety?
 - Environmental Considerations?

1983 - Guideline for Drug Combinations for use in Animals

- Must submit information and data to demonstrate that each drug makes a contribution to the combination.
 - “Non-interference” studies - one drug does not harm the actions (indications) of another.
 - Dose Titration Data “generally” not required
 - If the drug has production claims and has been previously approved for the use at that particular dosage or within a given range.

1983

- Target Animal Safety was assessed in the field effectiveness study.
 - Human Food Safety – Tissue Residue Studies
 - Chemistry, Manufacturing and Controls - Yes
 - Environmental – Categorically Excluded.
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- Note: DESI drug combinations were not subject to the 1983 Guideline.

ADAA Provisions - Combination New Animal Drugs

- *Streamlined* approval process (in practice no additional effectiveness/safety data required) for certain combinations - see 21 CFR 514.4(c)
- Purpose
 - Reduce burden on drug sponsor
 - Shorten approval time

Underlying Assumptions Combinations

- The *separate approvals* of each drug in the potential combination contain a demonstration of their effectiveness and safety
 - In essence each individual drug is *approved* under its own NADA number
- Each drug's individual effectiveness and safety are *maintained* when combined if certain conditions are met

Criteria for Streamlined Process Combinations – cont.

- No more than one antibacterial
 - Due to concerns about antimicrobial resistance
 - Ionophores or arsenicals are NOT considered antibacterials for the purposes of ADAA*
- Each drug brings a unique claim
 - that is on the Type A medicated article label
 - the same species with the same dosage and routes of administration

Criteria for Streamlined Process Combinations – cont.

- Appropriate concurrent use
 - Drugs are intended to treat different conditions likely to occur simultaneously with sufficient frequency in a species
- Drugs are physically compatible
 - Applies to water delivered drugs
- Drugs do not have disparate dosing regimens
 - Conflicting feeding directions

Fail Criteria for Streamlined Process Combination New Animal Drugs

- If the combination doesn't meet the criteria for the streamlined process, then a sponsor must demonstrate by *substantial evidence*, 21 CFR 514.4(a), that the combination will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling and that each active ingredient or animal drug contributes to the effectiveness of the combination new animal drug.

Effect on Various Technical Sections,
When Each Drug Brings a **Unique**
Indication, and All the Other
Assumptions are Met

Technical Sections

- Effectiveness – nothing new required
- Target Animal Safety– nothing new required
- Chemistry, Manufacturing and Controls – nothing new required

Technical Sections – cont.

- Environmental Impact – request a categorical exclusion under 21 CFR 25.33(a)(2)
- Human Food Safety- noninterference residue depletion study
- Labeling- Blue bird labeling
 - Type B and C medicated feeds
- All Other Information –
 - any available information on the combination

Freedom of Information Summary

- Boiler Plate Language - states the sponsor has satisfied the requirements of ADAA
- No discussion of substantial evidence of effectiveness (studies), as it was not required
- No discussion of target animal safety studies, as it was not required.
- Human Food Safety – summary of noninterference residue depletion study
- Exclusivity – Does NOT qualify for marketing exclusivity

Summary

- Standardization of requirements.
- Reduced the scientific requirements for feed use combinations.
- Feed use combination are subject to user fees.
 - ADUFA
 - AGDUFA