Dosage Characterization as Part of the Effectiveness Technical Section

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Effectiveness Technical Section

- Dosage Characterization
- Substantial evidence of effectiveness
  - Pivotal effectiveness study (studies)
- All Other Information for Effectiveness
- Freedom of Information Summary for Effectiveness
  - Dosage characterization
  - Substantial evidence
- Labeling for Effectiveness

Dosage Characterization

- Dosage includes:
  - Dose or dose range
  - Dosing frequency
  - Dosing duration
- How did you arrive at the proposed dosage?
  - What information you have to support it?
Animal Drug Availability Act of 1996 (ADAA)

- ADAA eliminated the requirement for dosage titration to determine the minimum effective dose
- Before the enactment of the ADAA, FDA could not approve a new animal drug at a dose that exceeded the dose reasonably required to accomplish the intended effect
  - Typically supported by adequate and well-controlled dose titration studies that characterize the critical aspects of the dose response relationship

ADAA – cont.

- Dosage justification and dose-response characterization may be supported by:
  - Dose titration studies
  - Pilot studies
  - In vitro studies
  - Scientific literature
  - PK/PD
- Summary of information used for dosage characterization should be submitted as part of the Effectiveness TS
  - Part of the FOI Summary (Effectiveness)

ADAA – Dosage Characterization

- Generally, the parameters measured in dose characterization studies relate the proposed dosage or dosage range to the proposed indication
- Dosage characterization does not need to be demonstrated by substantial evidence
- Confirmation of the effectiveness of the selected dose (dose range) requires demonstration by substantial evidence
- If a dose range is used on the label, information should be provided on how the dose range was selected
- The appropriate structure and timing for submitting dosage characterization information should be discussed with CVM
Examples of Dosage Characterization: Laboratory Models and Pilot Field Studies

- Small-scale studies conducted under controlled conditions to demonstrate drug’s effectiveness
  - Related to the proposed indication
  - Indication of effectiveness at the proposed dose
- Not part of substantial evidence of effectiveness
- No GLPs, GCPs
- Not necessarily the final formulation

Examples of Dosage Characterization: Use of Literature

- Published literature – has not been commonly used for substantial evidence of effectiveness
  - Conditions for using literature for substantial evidence are described in GFI #106: The Use of Published Literature in Support of New Animal Drug Approval (2000)
- However, published literature (including case studies, model studies in a limited number of animals) is commonly used to support a proposed dose (dosage characterization)

THE END
- ...of the formal Dosage Characterization section
- But there is more
  - ...on how PK can help in establishing effectiveness
Other Helpful Information for Establishing Effectiveness

- For novel and/or unique products, it helps to work with CVM early on to identify any potential issues related to drug development
  - Exchange of information
  - Education of CVM staff
  - Gain knowledge on the new product to help formulate risk questions
    - Pharmacology, mechanism of action, toxicology

Role of PK in Effectiveness Evaluation

- PK information is not required for every drug but a tool for knowledge acquisition
  - Depends on drug/class, indication, target species and class of animals...
- Information to help us ask appropriate questions:
  - Discovery / early development data used by sponsors to decide on drug development ("proof of concept")
  - Pilot PK data with non-final formulation(s)
  - PK data from other species
  - Information on similar drugs
- Questions are asked in order to gain knowledge and formulate risk questions
  - Ultimately, the answers to these questions will guide the development process
- Information to help sponsors choose the right path

Example of Role of PK in Dose Selection

- Describing the exposure (dose)-response relationship
  - “Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known.”
    - From CDER GFI “Exposure-Response Relationships”, April 2003
Example of Role of PK in Dose Selection

- For any desired extent of exposure:
  \[ AUC_{0\text{--}inf} = D \cdot F / Cl \]
  \[ D = AUC_{0\text{--}inf} \cdot Cl / F \]

- \( F \) (bioavailability) – dependent on:
  - Animal (host) physiology (age, gender, disease, etc.)
  - Route of administration
  - Formulation
  - Physico-chemical characteristics of drug

- \( Cl \) (clearance) – dependent on:
  - API (including dose – for non-linear kinetics)
  - Animal physiology

Example of Role of PK in Effectiveness Evaluation

- Questions that PK may help answer:
  - Will the product used under field conditions perform in a manner identical to that of the product batches tested in the safety and effectiveness studies?
  - Batch-to-batch uniformity
  - Performance at expiry
  - Shelf life of reconstituted product (e.g., injectable solutions, suspensions and microspheres)?

Example of Role of PK in Effectiveness Evaluation – Cont.

- Questions that PK may help answer:
  - Are the doses for which safety is tested adequate to cover the doses needed to insure efficacy for the labeled indications?
  - Between-animal variability
  - Is the timing of clinical observations in the pivotal effectiveness study adequate to support the label claim (e.g., time to cure)?
  - For antimicrobials, has the study been designed with attention to the duration of time required for the drug (and any active metabolite) to be eliminated from the body, thereby allowing for an evaluation of the likelihood of relapse?
PK/PD Approach

- Especially important for antimicrobial drugs because of the developed PK/PD targets.
- Effectiveness predictions based on patterns of antimicrobial activity (time-dependent vs. concentration-dependent effect).
  - Time-dependent effect:
    - T>MIC, AUC/MIC ratio
  - Concentration-dependent effect:
    - AUC/MIC or Cmax/MIC

Source: http://www.thepigsite.com/articles/contents/09-07Burch1.gif

Establishing a PK/PD Relationship

- What are the active (i.e., unbound) drug concentrations (PK) associated with the proposed dosing regimen?
  - Additional concerns:
    - Presence of active metabolites
    - Stereospecificity
    - Are blood concentrations reflective of tissue concentrations?
- How does the drug work (PD)?
- What is the exposure-response relationship?
  - E.g., 2 pathogens can have the same MICs but completely different kill curves.
- What is the PK/PD target (e.g., 40% T>MIC; AUC/MIC = 100h)?

PK/PD Approach - Antimicrobials

VAST* Recommended PK/PD Targets for antimicrobial drugs (from CLSI** M37-A3 document):
- Aminoglycosides:
  - Cmax/MIC ≥ 8
- Fluoroquinolones:
  - Gram negative organisms: AUC/MIC ≥ 100
  - Gram positive organisms: AUC/MIC ≥ 40
- β-Lactams:
  - S. pneumoniae T>MIC ≥ 60%
  - S. aureus: T>MIC ≥ 40%
  - Enterobacteriacea spp.: T>MIC ≥ 80%

*VAST = Veterinary Antimicrobial Susceptibility Testing
**CLSI = Clinical and Laboratory Standards Institute
Limitations of a PK/PD Approach for Antimicrobial Drugs

- MIC determination – based on an in vitro system
  - Not a true estimation of the in vivo effects
- In vivo factors that influence antimicrobial effect:
  - Anti-inflammatory effect
  - Post-antibiotic effect
  - Biofilm formation
  - Drug’s ability to interfere with bacterial colonization
  - Drug effect on toxin production

Recommendations from the 2008 AAVPT Workshop on New Approaches for Development of Antimicrobial Drugs in Companion Animals*

- Essential information for the approval of new antimicrobials for dogs and cats:
  - Pharmacokinetic data in the target species
  - Description, if known, of PK/PD behavior of the drug to be considered or for the drug class
  - Microbiologic activity of the drug
- Information that can be used for supplemental approvals:
  - PK/PD data indicating that the drug meets accepted targets (e.g., T>MIC, AUC/MIC) for the MIC of pathogens causing the infection
  - However, PK/PD data alone cannot be used in support of effectiveness, which should always be confirmed in a field study conducted under clinical conditions of use


What are H Submissions?

- Contain supportive information intended to:
  - Provide justification in support of the design of a study protocol
  - Describe pharm/tox characteristics of a compound
  - Provide background information prior to a development plan meeting
- Please note, H submissions should not be a place for data dump!
  - Strictly aimed to answer specific questions
Questions?

THANK YOU!
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