Using Pharmacokinetics (PK) as a Tool in Product Development and Regulation

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As we move into an era of increasingly complex dosage forms and drugs, pharmacokinetics (PK) has become an important component of the New Animal Drug Application (NADA). This information is invaluable for several reasons, including:

1. To support the assessment of product safety and effectiveness.
2. To support the development of clinically relevant product specifications.
3. To support the creation of product labels that foster an understanding of the endogenous and exogenous variables that can influence the drug response.

http://www.ohe.org/lib/libimgg/01/innovation-diagram.gif
Innovation is Encouraged

Innovation is essential to meet the needs associated with an evolving therapeutic landscape. Creative solutions are fundamental to addressing today's complex challenges.

This translates to innovations in:

• Drug delivery platforms:
  – To minimize animal stress and promote use compliance.
  – To enhance bioavailability
  • Increase drug absorption.
  • Gain access to otherwise inaccessible sites (e.g., brain and eye).
• To develop new molecular entities that meet the unmet needs in veterinary medicine:
  – Oncology drugs.
  – Novel ways to enhance food production/efficiency.
  – Physiologic drugs for the treatment of companion animal diseases.
  – Treat infectious diseases while having minimal influence on microbial resistance (e.g., new therapeutics that target virulence factors).

With the growing complexity of therapeutic targets, formulation platforms, and molecules, we can no longer simply “follow the yellow brick road”.
Early discussions between drug sponsors and CVM are critical – to EVERYONE!

- To identify potential roadblocks in product development:
  - From the perspective of the drug:
    - Are there concerns with the proposed indication?
    - What are recognized safety concerns associated with that drug class?
    - What are the potential sources of variation in drug exposure?
      - Can these sources be defined?
      - Can excessive variability compromise safety and effectiveness in the target population?
    - What additional information will be needed to support the population inferential value associated with the TAS and clinical field studies?

Encouraging early discussions

- From the perspective of the product formulation:
  - What kinds of in vivo and in vitro data will be needed to develop clinically relevant product specifications?
  - Are there factors that can influence the bioavailability of this drug and formulation?
  - Are there any proposed excipients that are of potential safety concern or that may necessitate additional consideration?

Encouraging early discussions

- To identify information that can support:
  - Product labels (insuring appropriate use by veterinarians).
  - Protocol development:
    - TAS
    - Field effectiveness trials.
  - Support the analysis of clinical data:
    - TAS
    - Field effectiveness trials
  - Support the development of chemistry and manufacturing specifications
Meet Early in the Development Process:
• To identify the kinds of questions that will need to be addressed if this drug/formulation goes to market.
• To support sponsor “GO-NO GO” decisions

Pre-Pre-Submission Conference

What do we know from earliest research efforts on this drug? What are the remaining unknowns that can influence safety and effectiveness in the target population? How can these questions be answered?

How can we use existing information to more efficiently answer therapeutically-important concerns?

FDA-Sponsored Research

To support the development of new animal drug products, CVM has assumed an active role through:

• Encouraging CVM-sponsor interactions
• Spearheading efforts to generate the much-needed information specific to veterinary medicine:
  – Through interactions and collaborations with other professional organizations.
  – Through scientific research efforts.

In an effort to minimize sponsor burden and to help us frame questions, CVM is supporting multiple research and collaborative efforts!
Examples of CVM PK Research Efforts

- Exploring variability in drug metabolism across canine breeds (a collaborative effort between ONADE, NIH and the CVM Office of Research).
- Determining if separate TAS studies are needed across classes of chickens (a drug metabolism study being done in collaboration between CVM's ONADE and the OR).

Examples of CVM PK Research Efforts

- Development of physiologically based PK models to help ONADE frame our questions for review of canine drugs (a collaborative effort between ONADE and CDER).
- Defining drug solubility classification across species (a collaborative effort between CVM and the USP).
- Defining the methods for ascertaining clinical breakpoints: an update of methodology (a collaborative effort between CVM and the Clinical and Laboratory Standards Institute).

Examples of CVM PK Research Efforts

- Defining clinically relevant product specifications:
  - Oral dosage forms: critical path research project between ONADE and the University of Maryland.
  - Parenteral products: ONADE efforts
- Identification of animal models that can be used in lieu of ivermectin-sensitive collies (a critical path research project between ONADE and OR).
CVM’s goal is to have a strong foundation upon which we can carefully determine which questions are/are not essential for any given application, to know if there are existing data (publically available or through our ongoing research efforts) where we can answer questions without additional studies, to help direct sponsors to potential ways of answering questions through the literature, and to help in protocol development when studies are needed.

What is in the RED BOX?

PREDICT

LEARN

CONFIRM
Use of PK to Support Substantial Evidence of Effectiveness (SEE):

As part of SEE, we need to be confident that the results obtained are likely to be repeatable, and that valid inferences can be drawn to the target animal population.

CFR 514.4(b)(3)

Examples of PK Questions that may be asked to Support the Design of an Efficacy Study:

- Is the timing of the clinical observations adequate to measure therapeutic success?
- For antimicrobials, has the study been designed with attention to the duration of time required for the active moieties to be eliminated from the body, thereby allowing for an evaluation of the likelihood of relapse?
- Have we adequately defined and covered conditions and patient characteristics that can influence the PK-PD?

Examples of PK Questions That Facilitate TAS Study Protocol Design and Data Interpretation

Safety:
- Is toxicity related to peak concentrations or duration of exposure?
- What clinically relevant conditions will maximize drug exposure (e.g., food effects) or the risk of a toxic event (e.g., local GI effects of NSAIDs)?
- When should animals be observed for signs of toxicity?
- Are there toxic metabolites that need to be considered when assessing the time for observations?
- What was the actual range of exposures experience by the animals in the TAS study? How does that relate to the range of concentrations likely to experienced by the patient population?
In this course, there will be three PK-related lectures:

- **Sanja Modric**: How sponsors can use PK to support effectiveness.
- **Marilyn Martinez**: How sponsors can use PK to support protocol development and analysis of data generated in TAS studies.
- **Ian Hendricks**: The use of PK to support product bioequivalence.

**CONCLUSION**

- PK provides an invaluable **roadmap** for supporting product development.
- Early submission of data enables CVM to work with drug sponsors to **optimize product development plans**.
- PK information provides invaluable **label information** for the practitioner to support an understanding of how the product will perform in a patient population.
- PK data supports the development of clinically relevant **product specifications** that can be invaluable for minimizing the additional in vivo studies that may be necessary to support changes that often occur over a product’s market life.

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