U.S. FOOD & DRUG ADMINISTRATION

REGULATORY PERSPECTIVES

Challenges and Opportunities

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Purpose

- We are here to discuss the challenges and opportunities of the new animal drug approval process
  - Some that we see
  - Some that you see
- Seek your input on ways to improve the process
  - Breakout sessions
- Proactive engagement to make the system better

ONADE's Mission

- We efficiently approve quality, safe and effective new animal drug products through a science-based approach in a regulatory environment.
- We communicate with our stakeholders and understand the forces that affect them.
- Our actions protect human and animal health

Our public health mission succeeds when we put in the hands of the user:

- an approved,
- safe and effective,
- quality manufactured,
- properly labeled

new animal drug

Early Communication

- Early (ier) targeted interactions (with all stakeholders) to increase predictability of regulatory requirements
  - Meetings with sponsors and other stakeholders
  - focus on scientific issues and identify any issues/roadblocks early on in the process
  - Discuss alternative proposals early in development

Maximize use of existing information

- Use of literature
- Use of preliminary data/pilot studies
- Use of data generated internationally
- Collaborative data sharing across FDA
  - Ex: Toxicology (or other) data in a human drug approval package to support an animal approval package

New Approaches

- Drug approval is based on weighing the scientific evidence
- New approaches must continue to meet our regulatory standards
  - Safety: 21 CFR 514(b)(8)
  - Effectiveness: 21 CFR 514.1 & 514.4
- As a regulator, we need to evaluate products based on new technologies and be open to new ideas

Target Animal Safety - Standard

- Adequate tests by all methods reasonably applicable to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling

Target Animal Safety: Challenges and Opportunities

- Data Quality of GLP studies
  - We need to focus on the science
  - Studies conducted to appropriate standard (GLP/GCP)
    - This allows CVM to have confidence in the data
    - This is the sponsor's responsibility
      - Sponsor compliance statement – provides assurance that the sponsor knew what happened in the study and how any deviations from the GLPs could have impacted the study conclusions

Effectiveness – Substantial Evidence

- One or more adequate and well-controlled studies
- Demonstrate the drug is effective for the intended use at the dose or dose range and associated conditions of use prescribed, recommended, or suggested in the labeling

Effectiveness
Challenges and Opportunities

- Global Approvals

  Opportunities:

  Parallel scientific advice

  More efficient approval process - intentionally designed studies that support approval in multiple markets

  Challenges:

  No VICH harmonized guidances for effectiveness

  Use of a negative/positive control

  Differences of causative organism between countries

  Differences of production practices/breeds (food animals)

Effectiveness
Challenges and Opportunities

- Approval of alternatives to antibiotics
  - How to demonstrate effectiveness?
    - It does NOT have to be the same way that an antimicrobial demonstrates effectiveness, but you still have to demonstrate that the product is effective
  - Claims may be more narrow than a traditional antimicrobial claim
    - Products may need to be used in combination

Opportunity

- In veterinary medicine, often have single product sponsor trying to address broad reaching issues under the focus of bringing one product to market
- **Significant opportunity for groups to work together to accomplish common goals (Alternatives to Antibiotics)**

Generic Animal Drugs

- Generic Animal Drug and Patent Term Restoration Act (GADPTRA) signed into law in 1988.
  - provided for the approval of generic copies of new animal drug products that have been previously approved and shown to be safe and effective when used according to their approved labeling

- A generic new animal drug product:
  - has the same active ingredients,
  - in the same concentration, route of administration, and dosage form
  - and is bioequivalent to the approved reference-listed new animal drug product.

Bioequivalence (BE)

- 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.
  - GFI #35: Bioequivalence Guidance

Bioequivalence: Challenges and Opportunities

- Blood-Level Study Design
  - When study other than traditional two-period cross-over design needed
  - Highly variable study design
- Non-systemically absorbed products
  - "Three-Pronged Approach"
    - *In vivo* equivalence
    - *In vitro* equivalence
    - Chemical equivalence

Bioequivalence Studies

- Studies conducted to appropriate standard (GLP)
  - Includes clinical endpoint studies
  - This allows CVM to have confidence in the data
  - This is the sponsor's responsibility
    - Sponsor compliance statement – provides assurance that the sponsor knew what happened in the study and how any deviations from the GLPs could have impacted the study conclusions
- We need to focus on the science

Data Quality Challenges

- The final study report must be an accurate reflection of the raw data
- ***All*** deviations from the protocol must be documented with impact on study conclusions explained
- All aspects of the study must be clearly explained and documented, including all negative/contradictory information
- Study documentation must support the validity of the study conclusions (e.g., can FDA rely on the data to make a regulatory decision?)
- Ensure contemporaneous monitoring/QA
- Pay attention to requirements under Part 11 and for submission of electronically captured data [Electronic Data Capture (EDC)]

Chemistry Manufacturing and Controls

- All of the information in 21 CFR 514.1(b)(2)(i), 514(b)(3-5) should be submitted for a complete CMC technical section.
  - The information needed to satisfy these requirements is further described in:
    - FDA Guidance for Industry
    - VICH/ICH
    - External standard setting organizations (USP, PDA)
    - Question Based Review format in eSubmitter
    - Alternate approaches to what is described are welcome if supported by scientific justification
- All facilities used in the manufacture or testing of the drug substance or drug product must have an acceptable GMP status at the time of approval.

CMC Challenges: CVM Perspective

- Supply chain interruptions
  - OAI inspections and import alerts for foreign facilities
  - Impact of facilities with unacceptable GMP status due to data integrity issues on data submitted to file.
  - Outsourcing of significant portions of the API manufacturing process (starting material vs. final intermediate designation)
- Supply chain interruptions lead to drug shortages. This is especially a public health concern for Medically Necessary Veterinary Products (MNVP).

CMC Challenges: CVM Perspective

- Increased activity by external standard setting organizations (USP, PDA) and the need to monitor this activity to understand impact on the animal health industry
- Increased complexity for product characterization and manufacturing.
  - Pioneer: characterization of biotech products, extended release, natural products (what is the API?)
  - Generic: biomass, physicochemical characterization (Q3) for non-systemically absorbed drugs

Communication Challenges

- Although we have extensive guidance documents and question based review, one-cycle review remains a challenge
- What do you see as opportunities to better communicate and understand CVM's expectations so we can have more timely drug approvals?
- What additional guidance or outreach would you find beneficial?

Breakout sessions Expectations

- We would like your feedback on the steps CVM and the drug industry can take to ensure that quality, safe, and effective drugs are approved in a timely fashion
- Please discuss your challenges and the opportunities for your assigned topic
- Engage to make the system better
- At the end of the day your discussions will generate two lists of issues for further consideration, one for industry and one for CVM

Breakout Session Directions

- Go to your assigned room for the morning breakout session
  - Each room will have a facilitator and CVM representative
  - Write down your ideas on the paper provided
  - Decide at your table your main point to report out
  - Decide within your room your main points to report out
- Lunch
- Report to your assigned room for the afternoon breakout session (and repeat)
- Reporting out of both breakout sessions

Breakout Session Topics

- Global Approvals
- Data Quality
- Supply Chain Interruptions
- BE Study Design
- Other ideas

Thank you