Effectiveness in Food - Producing Animals

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HFV-130
Division of Therapeutic Drugs for Food Animals

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We are responsible for therapeutic products for:
- Cattle
- Swine
- Chickens
- Turkeys
- Aquatic Species
- Small Ruminants (Sheep and Goats)
- Honey Bees

The Division of Therapeutic Drugs consists of three teams:
- Aquaculture Team (HFV-131)
- Antimicrobial Drugs Team (HFV-133)
- Antiparasitic and Physiologic Drugs Team (HFV-135)
One or more adequate and well controlled studies

Traditionally, effectiveness has been demonstrated via dose confirmation studies and field studies. Sometimes validated model studies are also used, if appropriate for the indication. These types of studies can provide substantial evidence of effectiveness for many types of products. The appropriate design for effectiveness studies will vary, depending on the drug.

Dose Confirmation Studies

Generally small *in-vivo* studies conducted in the laboratory or under representative field conditions. These studies may include endpoints for confirming effectiveness that are not typically feasible for a large scale study. Animal numbers will depend on the endpoint and the type of statistical analysis. These studies are typically used for antiparasitic products and are often used in conjunction with field studies to demonstrate effectiveness for certain types of products.

Field Studies

Generally conducted under field use conditions and in multiple geographic locations. The number of animals required to support an indication is based on the expected variation, the predetermined success criteria, and the desired statistical power.
Validated Model Studies

Generally, validated model studies use challenge models or induced infection models and are used to demonstrate effectiveness when some aspect of the effectiveness study cannot be adequately represented or evaluated using field conditions. As with other types of effectiveness studies, the number of animals used in the study will depend on the endpoint and the type of statistical analysis.

Validated Model Studies

- Model validation includes the following:
  - The model shows that the study endpoints are clinically relevant and scientifically accepted;
  - The model shows that clinical disease induced in the model is as representative as is practical of natural infection in terms of morbidity levels and clinical presentation;
  - The model demonstrates that results are reproducible (i.e., by using different investigators and conducting the model at two or more sites); and,
  - If the model is being used to demonstrate effectiveness against a pathogen: the model should demonstrate or provide justification that the pathogen isolate used for challenge is representative of recent North American field isolates.

Effectiveness Studies

- Studies should be conducted to provide independent substantiation and inferential value
- Studies should include the measurement of appropriate variables that demonstrate the effectiveness of the drug
- Studies should be conducted by experts possessing appropriate training and experience
Appropriate Variables

Appropriate variables will be determined by:
- Study design
- Target pathogen and its associated disease
- Target species/class
- Test article
- The claim

Available Guidance Documents Addressing Effectiveness

- CVM GFI #40 Draft Guideline for the Evaluation of the Efficacy of Anticoccidial Drug Combinations in Poultry
- CVM GFI #49 Target Animal Safety and Drug Effectiveness Studies for Anti-Microbial Bovine Mastitis Products (Lactating and Non-Lactating Cow Products)
- CVM GFI #56 Protocol Development Guideline for Clinical Effectiveness and Target Animals Safety Trials
- CVM GFI #85 VICH GL9 – Good Clinical Practices

Available Guidance Documents Addressing Effectiveness

- CVM GFI #90 Effectiveness of Anthelmintics: General Recommendations
- CVM GFI #95 VICH GL12 – Efficacy of Anthelmintics: Specific Recommendations for Bovines
- CVM GFI #96 VICH GL13 – Efficacy of Anthelmintics: Specific Recommendations for Ovines
- CVM GFI #97 VICH GL14 – Efficacy of Anthelmintics: Specific Recommendations for Caprines
- CVM GFI #110 VICH GL16 – Specific Recommendations for Porcine
- CVM GFI #114 VICH GL 21 – Specific Recommendations for Poultry - Gallus Gallus
Available Guidance Documents
Addressing Effectiveness

- CVM GFI #123 Development of Data Supporting approval of NSAIDS for Use in Animals
- CVM GFI #178 Design/Evaluation of Effectiveness Studies – Swine Respiratory Disease Claims

CVM understands that the development of new products and technologies require innovation. In many cases the standard paradigms do not apply. CVM welcomes the opportunity to work with you to explore and develop new venues for demonstrating effectiveness.

Outreach in HFV-130

HFV-130 strives to recognize what drugs are needed by the food animal industry and understand how the products we approve will be used. To accomplish this we:

- Attend scientific meetings
- Accompany veterinarians in the field
- Invite guest lecturers from academia, clinical practice, and industry to present lectures at CVM
- Conduct extensive literature searches on relevant topics
- Work with sponsors to arrange educational opportunities
- Create educational materials for the public via the Animal Health Literacy program
Challenges

- Each team in the Division of Therapeutic Drug for Food Animals faces challenges that are specific to the types of products they handle.

HFV-131 - Aquaculture

- Communication between the public data generating partners and the drug sponsors to facilitate the approval of aquaculture products
- Developing recommendations for effectiveness studies to demonstrate substantial evidence of effectiveness for large, diverse groups of fish

HFV-133 Antimicrobial Drugs

- Design of prevention studies
- Determining if minimum levels of effectiveness (minimum measure of success that must be achieved for the product to be considered effective) are appropriate for antimicrobial claims, and if so, which ones
HFV-135 Antiparasitic and Physiologic Drugs

- Determining how to address antiparasitic resistance in a regulatory environment
- Exploring the use of biomarkers for effectiveness studies for physiologic drugs (ex. pain and inflammation).

What Sponsors can do to facilitate the progress of the Effectiveness technical section

- Talk to us early and often
- Get protocol concurrence
- Properly document the conduct of the study
- Communicate with us when things don’t go according to plan
- Properly document deviations
- Submit well organized submissions

Talk to us early and often

- FOI Summaries – these serve as starting points
- Sponsors should be aware that there are different approaches to approval. We’re willing to entertain new approaches to traditional products and indications.
- If the product utilizes new technologies, we encourage sponsors to talk with CVM about potential challenges (even prior to opening an INAD file). This is also an opportunity for sponsors to educate CVM on the technology before setting up the official pre-submission conference.
Get protocol concurrence

- Protocol concurrence is not required but it is strongly recommended.
- It is to the sponsor’s advantage to talk with us about study design prior to submission of the protocol. Early discussion increases the likelihood of a one cycle protocol review.
- The sponsor may need to submit data to support the design of a study (e.g., an “H” submission)
- Come talk to us when you disagree with a decision.
- Think ahead (collecting sufficient numbers of samples, describing how animals will be removed from studies and how their data will be analyzed, etc.).

Properly document the conduct of the study

- Properly document any changes made prior to initiation of the study as protocol amendments. Completely and concisely explain why the amendment was necessary and its impact on the study. Include the amended protocol in the final study report.
- Data collection forms should be filled out completely
- Data entry should be clear and legible
- Providing an index to the Notes to File is extremely helpful when the Notes to File are extensive
- Define adverse events and document them appropriately

Communicate with us when things don’t go according to plan

- We understand that the unexpected happens during studies. Common occurrences include:
  - Errors in preparation of the test article
  - Errors in administration of the test article
  - Concurrent disease
  - Inclement weather interferes with the collection of pivotal data
  - Errors in sample handling
- It is in your best interest to talk to us as soon as these things happen.
Properly document deviations

- Properly document any changes made after the initiation of the study as protocol deviations. Completely and concisely explain why the deviation was necessary and its impact on the study.
- Deviations can occur during the conduct of a study that do not compromise the validity of the study. In order for us to evaluate deviations, they should be completely and concisely described, including a balanced assessment of the deviation's impact on the study.
- Don't omit deviations – They serve to help us understand how a study was conducted.

Put together complete, well-organized submissions—helpful hints

- Include draft labeling, AOI, and FOI Summary language in each "P" (data) submission
- Identify all sections of the submission with tabs
- Put raw data in logical, sequential order
- Put all of the same type of data together
- Verify that every page is legible and present
- Number each page of the submission from 1 to XXX at a consistent location on each page
- Include a TOC in each volume

Final Thoughts

- For any product, communication at all stages of the project is critical.
- Although we must operate within the bounds of the regulations to ensure that we approve effective products, we are actively seeking and developing new ways to meet those requirements. We invite all of you to be our partners in that endeavor.