Second Annual Animal Drug User Fee Educational Conference:

Public Meeting

July 15, 2025
Docket No. FDA-2024-N-2602

Opening Remarks

Welcome

Matthew A. Lucia, DVM

Director, Office of New Animal Product Evaluation
Center for Veterinary Medicine

Meeting Overview

Walt Ellenberg, Ph.D.
Moderator

Special Advisor
Center for Veterinary Medicine

Points to Consider

- MS Teams Town Hall platform chat, cameras, and microphones are disabled
- Agenda timeline to be followed as closely as possible
- All in-person attendees should sign-in
- We encourage all in-person attendees to wear a name tag
- Refreshments are available at the kiosk outside of the conference room

Points to Consider (cont.)

- Meeting materials will be available:
  - Event page: CVM Public Meeting: Second Annual Animal Drug User Fee Educational Conference - 07/15/2025 | FDA
  - Docket: FDA-2024-N-2602 at www.regulations.gov
  - The video recording will be available on the event page via YouTube

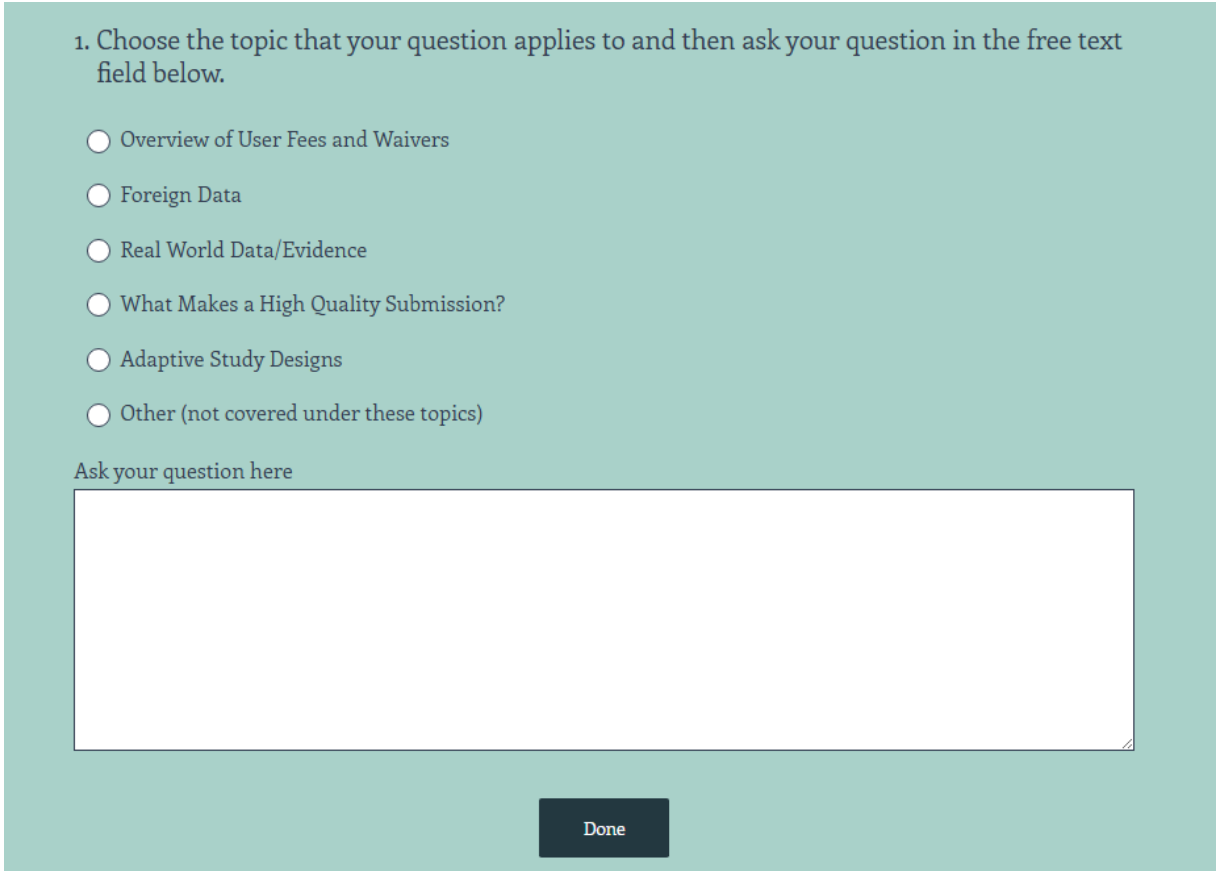
Q&A Format

- Q&A panel sessions to begin at approximately 11:30am and 3:30pm
- Attendees may submit question via the QR code with hyperlink to SurveyMonkey throughout the morning and again in the afternoon
- All questions will be anonymous
- We will answer as many questions as time allows
- All questions will be retained and submitted to the Docket and may provide beneficial information as we develop agendas for future educational conferences
- The QR code will be deactivated after meeting adjourns

Questions? Scan the QR Code or use the URL below

www.surveymonkey.com/r/ADUFA-V-Questions

How to Submit Your Question



Agenda

Approx. Start	Duration	Speaker	Presentation
8:00 a.m.	1 hr.		**Registration**
		Introduction	
9:00 a.m.	5 min	Walt Ellenberg	**Moderator Opening Remarks**
9:05 a.m.	10 min	Matt Lucia	**Welcome**
9:15 a.m.	15 min	Walt Ellenberg	**Meeting Overview**
9:30 a.m.	30 min	Aila Albrecht	**Overview of User Fees and Waivers**
10:00 a.m.	45 min	Ana Lazo, Courtney Flick, Brandi Robinson	**Foreign Data**
10:45 a.m.	15 min	**Break**	
11:00 a.m.	30 min	Emily Smith	**Real World Data/Evidence**
11:30 a.m.	30 min	Walt Ellenberg & CVM Q&A Panel Table	**Q&A Session**
12:00 p.m.	1 hr.	**Lunch**	
1:00 p.m.	1:30 min	Laura Moussa, Jordan DeSilva	**What makes a High-Quality Submission?**
2:30 p.m.	15 min	**Break**	
2:45 p.m.	45 min	Anthony Parker	**Adaptive Study Designs**
3:30 p.m.	30 min	Walt Ellenberg & CVM Q&A Panel Table	**Q&A Session**
4:00 p.m.		Walt Ellenberg	**Closing Remarks**

Animal Drug User Fee Act (ADUFA)
Overview of Fees and Waivers

Aila Albrecht, PMP
Office of Generic Animal Drugs, FDA CVM

Four ADUFA Fee Types

Fee	Fee Type	Revenue percentage
Sponsor	Annual	27%
Application - Original (100%) - Supplemental (50%) - Combination (50%)	One-time	20%
Product	Annual	27%
Establishment	Annual	26%

Sponsor Fee (Annual)

- Paid annually by each applicant that has a new animal drug application (NADA), a supplemental new animal drug application, or an investigational new animal drug (INAD) file
  - The term “animal drug sponsor” means either an applicant named in a new animal drug application or a person that has established a new investigational animal drug file
  - Generates 27% of the target revenue

Application Fee (One-Time)

Each applicant that submits a new animal drug application or a supplemental new animal drug application shall be subject to an application fee

- Original Application (full fee) – Application for approval of any new animal drug
- Supplemental Application (50% fee) – A change in an approved animal drug application for which safety or effectiveness data are required
- Combination applications (50% fee) - New applications involving combination new animal drugs that have previously been separately approved for use in feed or water
- Generates 20% of the target revenue

Product Fee (Annual)

Paid annually by the applicant of a new animal drug application or supplemental new animal drug application for an animal drug product

- The term “animal drug product” means each specific strength or potency of a particular active ingredient in final dosage form marketed by a particular manufacturer. Each NDC (national drug code) number is assessed 1 product fee, which is based on the Labeler Code and Product Code in the NDC
- Generates 27% of the target revenue

Establishment Fee (Annual)

Paid annually by each applicant who owns or operates, directly or through an affiliate, a new animal drug establishment and is named as the applicant in a new animal drug application or supplemental new animal drug application

- The term “animal drug establishment” means a foreign or domestic place of business which is at one general physical location consisting of one or more buildings all of which are within 5 miles of each other, at which one or more new animal drug products are manufactured in final dosage form
- Generates 26% of the target revenue

Establishing ADUFA Fee Rates

- Estimating number of fees
  - Applications - Average number of applications over the five most recent completed years
  - Sponsors, Products & Establishments - Based on most recent May data
- Determining waiver percentages
  - Based on most recent 5-year average
- Inflation factor – Variable Inflation Adjuster
  - Latest 3-year average change in FDA Personnel Compensation and Benefits (PC&B) costs multiplied by the 3-year average change in proportion of FDA PC&B to total FDA costs, PLUS,
  - Latest 3-year average change in Washington-Arlington-Alexandria Consumer Price Index (CPI) all items less food and energy multiplied by the 3-year average change in proportion of FDA non-pay to total FDA costs

Workload Adjuster

- The workload adjuster is calculated using the average of 5 types of applications and submissions (listed below) received over the most recent 5-year period as compared to a rolling base of the most recently completed 5 years.
- Each application or submission type is multiplied by a weighting factor: the percent of direct review hours spent on these applications/submissions for the year
  - New Animal Drug Applications (NADAs)
  - Supplemental NADAs with Safety or Effectiveness Data
  - Manufacturing Supplements
  - Investigational Study Submissions
  - Investigational Protocol Submissions
- The workload adjuster is not invoked unless it exceeds 3% for a second fiscal year in the authorization, and any year thereafter.

Operating Reserve Adjustment

This provision allows FDA to increase or decrease the target revenue to ensure the program has a certain amount of funding in the carryover reserves.

- If the carryover reserve is less than 12 weeks, FDA will increase the fee rates to maintain a 12-week floor.
- If the carryover reserve is greater than 22 weeks in FY 2025, 20 weeks in FY 2026, 18 weeks in FY 2027, and 16 weeks in FY 2028, FDA will decrease the fee rates to maintain these ceilings.

ADUFA Fee Rates

Fee Type	FY 2025 Fee Rate
Application: Full Fee Due when application is filed	$581,735
Application: Half Fee Due when application is filed	$290,867
Product Fee Due annually	$10,705
Sponsor Fee Due annually	$137,446
Establishment Fee Due annually	$157,702

Sponsor Letter Notifications

- Dear Sponsor packages are sent out every year mid-August prior to Annual billing.
- This package includes a letter citing the new fee rates and links to the Federal Register Notice, Instruction page, and 3 verification reports.
- The letters allow sponsors to review documents and notify FDA of any changes prior to FDA sending out the initial invoices in December.

Billing Cycles for Annual Fees

- Initial Billing
  - Sent at end of December for the current FY; due by January 31
  - Includes all sponsors, products and establishments FDA has listed in its database as of October 1
  - For example, in Dec 2025, invoices will be sent for those listed as of Oct 1, 2025
- Clean-up Billing
  - Sent in November for the previous FY; due 30 days after receipt
  - Includes all new sponsors, products, and establishments that were established after October 1, but prior to September 30 of the previous FY
  - For example, in Nov 2026, clean-up invoices will be sent for those listed after Oct 1, 2025, and before Sept 2026

Application Fee Payment

- Complete an ADUFA cover sheet
- Receive a unique Payment Identification Number that links the fee payment to the submission ID
- Pay the application fee
- File the application, including a copy of the cover sheet

Publications

- Fee Rate Publication in the Federal Register
  - Mandated to publish 60 days before the start of the fiscal year (October 1)
- Reports and Plans
  - Financial and Performance Reports: Mandated by Congress to publish 120 days after the close of the fiscal year
  - Financial Plan: Mandated by Congress to publish 180 days after the close of the fiscal year

User Fee Waivers

User Fee Waiver Types

Sponsors may request waivers from or reductions of user fees under the following specific provisions:

- Significant Barrier to Innovation
- Fees Exceed Costs
- Free Choice Feeds
- Minor Use or Minor Species
- Small Business

Significant Barrier to Innovation Waiver

FDA shall grant a waiver from or a reduction of one or more of the fees where FDA finds that:

- The product for which the waiver is being requested is innovative, and
- The fee would be a significant barrier to the requestor's ability to develop, manufacture, or market the innovative product or technology.

Fees Exceed Costs Waiver

FDA shall grant a waiver from or a reduction of one or more of the fees where FDA finds that:

- The fees to be paid by such person will exceed the anticipated present and future costs incurred by CVM in conducting the process for the review of new animal drug applications for such person.

Free Choice Feeds Waiver

FDA shall grant a waiver from or a reduction of one or more of the fees where FDA finds that:

- The new animal drug application or supplemental new animal drug application is intended solely to provide for use of the new animal drug in
  - a Type B medicated feed intended for use in the manufacture of Type C free-choice medicated feeds, or
  - a Type C free-choice medicated feed.

Minor Use or Minor Species Waiver

FDA shall grant a waiver from or a reduction of one or more of the fees where FDA finds that:

- The new animal drug application or supplemental new animal drug application is intended solely to provide for a minor use or minor species indication.

Small Business Waiver

FDA shall grant a waiver from an application fee where FDA finds that:

- The sponsor involved is a small business submitting its first new animal drug application to CVM for review.

Note:

- A "small business" is one that has fewer than 500 employees, including employees of affiliates.
- The waiver applies only to the first new animal drug application that the small business or its affiliate submits for review.

Summary of Waivers and Applicability to Fee Types

Waiver Type	Sponsor Fee	Establishment Fee	Product Fee	Application Fee
Barrier to Innovation	Yes[1]	Yes	Yes	Yes
Fees Exceed the Costs	Yes	Yes	Yes	Yes
Free Choice Feeds	Yes[1]	No	No	Yes
Minor Use Minor Species	Yes[1]	Yes	Yes	Yes
Small Business	No	No	No	Yes[2]

[1] All active INADs and NADAs must be covered by a waiver.
[2] First application only.

How to Request a Waiver

- Electronically
  - Create submissions using the eSubmitter tool and send via the FDA Electronic Submissions Gateway (ESG) NextGen
- Paper (via mail)

When to Request a Waiver

- Annual fees (sponsor, product, and establishment)
  - Waivers should be submitted at least 4 months prior to invoices being issued
    - Initial billing invoices issued at the end of December (request waiver by 9/1)
    - Clean-up billing invoices issued in November (request waiver by 8/1)
  - Waivers must be submitted no later than 180 days after the fee is due
    - For example, waivers are due July 30, 2025, for FY 2025 invoices
- One-time fees (application)
  - At least 30 days prior to submitting the application

Reference Links - ADUFA

- Main ADUFA page: https://www.fda.gov/industry/fda-user-fee-programs/animal-drug-user-fee-act-adufa
- ADUFA FY 2025 Fee Rates: https://www.fda.gov/animal-veterinary/cvm-updates/fda-announces-fy-2025-animal-drug-user-fee-rates-adufa-and-agdufa
- ADUFA Financial Reports: https://www.fda.gov/about-fda/user-fee-financial-reports/adufa-financial-reports
- ADUFA Performance Reports: https://www.fda.gov/about-fda/user-fee-performance-reports/adufa-performance-reports
- ADUFA Financial Plan: https://www.fda.gov/about-fda/user-fee-reports/user-fee-five-year-financial-plans

Reference Links – ADUFA Waivers

- GFI #170: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-170-animal-drug-user-fees-and-fee-waivers-and-reductions
- GFI #183: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-183-animal-drug-user-fees-fees-exceed-costs-waiverreduction
- CVM eSubmitter Resource Center: https://www.fda.gov/industry/fda-esubmitter/cvm-esubmitter-resource-center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Use of Foreign Data to Support Safety and Effectiveness

Courtney Flick, DVM
Ana Lazo, BS, RQAP
Brandi Robinson, MPH, CPH
Office of New Animal Product Evaluation, FDA CVM

Agenda

Use of Foreign Data
CVM's Expectations for Foreign Data Submissions
International Collaborative Review Opportunities

Use of Foreign Data

- Courtney Flick, DVM

What is Foreign Data?

- Data generated outside of the United States both by entities based within or outside of the United States.
  - Guidance For Industry (GFI) #265: Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs

Submission of Foreign Data

- Codified in Section 569B of the Federal Food, Drug, and Cosmetic Act, per Food and Drug Administration Safety and Innovation Act of 2012
- Accepted if **adequate under applicable standards**
- Applies to (A)NADA, CNADA, and (J)INAD files
- Must include both favorable and unfavorable data

Use of Foreign Data

- FDA accepts both previously conducted and prospective foreign data for target animal safety, for substantial evidence and reasonable expectation of effectiveness, and for human food safety technical sections.
  - May also be used to provide supporting information for safety and effectiveness, especially when bridging gaps in data.
- FDA considers whether the data fulfills regulatory requirements, both in terms of study conduct/ documentation and whether the data can inform a U.S. approval decision.

Target Animal Safety

- The types of studies and data requirements to demonstrate safety are the same regardless of foreign or US studies
  - Refer to GFI #185 (VICH* GL43) Target Animal Safety for Veterinary Pharmaceutical Products
- Recommend meet with CVM to discuss differences (husbandry, breed, etc.) at foreign sites prior to conducting study or submitting the data
- Refer to GFI #226: Target Animal Safety Data Presentation and Statistical Analysis for CVM requirements for data presentation and analysis

*VICH: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

Target Animal Safety Study Challenges

- Multiples of the dosing or study duration do not align with CVM recommendations
- Timing of necropsies is not appropriate
- Masking and randomization
- Regulatory compliance
- Statistical analysis is not appropriate

Examples of animal drugs approved with safety data from studies conducted outside of the U.S.

- Aquaflor® (florfenicol Type A medicated article) NADA 141-246
- AYRADIA™ (metronidazole oral suspension) NADA 141-572

Examples of animal drugs approved with safety data from studies conducted inside and outside of the U.S.

- Safe-Guard® AquaSol (fenbendazole) NADA 141-449
- Varenzin™-CA1 (molidustat oral suspension) CNADA 141-571
- UpCard®-CA1 (torsemide oral solution) CNADA 141-577

Human Food Safety

- Toxicology data generated in foreign countries following VICH Guidelines and OECD Test Guidelines, and/or in compliance with FDA Good Laboratory Practice (GLP), are acceptable.
- Residue chemistry data generated in foreign countries following VICH Guidelines and complying with FDA GLP standards are acceptable.

Effectiveness – GFI #265

- GFI #265: Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs
  - Provides guidance to animal drug sponsors on the approval process where the use of data from foreign investigational studies may be considered acceptable to support effectiveness requirements
  - How to obtain feedback from CVM
  - Acceptance of foreign data and international collaboration
- Foreign data may be **partially or fully acceptable** to support effectiveness requirements if the sponsor demonstrates that **conditions of use** are representative of U.S. practices.

Effectiveness

Address the following between the U.S. and each foreign site:

- Conditions of use of the investigational drug
- Standard of veterinary medical practice with respect to any differences that may impact the study
- Management & husbandry practices
- Animal species, breeds, or classes used in the study (including genetic differences)
- For antimicrobials: Bacterial strains, including target pathogen virulence, and target pathogen susceptibility (if applicable) to the investigational antimicrobial
- For antiparasitics: Parasitic strains, including source, age, and susceptibility (if applicable), and
- Any other relevant practices or conditions that could impact the study conduct or results.

Effectiveness (cont.)

- If differences exist:
  - Explain their **potential impact** on study conduct and,
  - Assess how they may influence **animal response to the drug**.
- CVM expects this information to be submitted either prior to the data submission in a meeting request or H submission, or with the study data.

For antiparasitics and antimicrobials, susceptibility, strains, and husbandry practices will likely vary across geographic locations, which may impact the acceptability of the data. For more information on antiparasitics, see GFI #90 (VICH GL7).

Effectiveness Challenges

- Sponsors submit the foreign data late in project development
- The indications are not aligned between regulatory agencies
- Final formulation differences
- Animal population diversity
- Raw data availability and study conduct issues

Examples of animal drugs approved with effectiveness data from studies only conducted outside of the U.S.

- SILEO (dexmedetomidine oromucosal gel) NADA 141-456
- Pexion™ (imepitoin tablets) NADA 141-509
- Banamine® Transdermal (flunixin transdermal solution) NADA 141-450

Examples of food animal drugs approved with effectiveness data from studies conducted inside and outside of the U.S.

- Longrange® (eprinomectin) NADA 141-327
- SAFE-GUARD AquaSol (fenbendazole oral suspension) NADA 141-449
- Rumensin® (monensin Type A medicated article) NADA 095-735

Examples of companion animal drugs approved with effectiveness data from studies conducted inside and outside of the U.S.

- Librela® (bedinvetmab injection) NADA 141-562
- AYRADIA™ (metronidazole oral suspension) NADA 141-572
- DuOtic™ (terbinafine and betamethasone acetate otic gel) NADA 141-579
- Credelio Quattro™ (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) NADA 141-581

CVM's Expectations for Foreign Data Submissions

- Ana Lazo, BS, RQAP

CVM Expectations

- Information about foreign data may be submitted in a meeting request for discussion with CVM, or in a technical section submission.
- When presenting foreign data, the following elements should be addressed:
  - Assure studies have (or will have) the same data qualities and study integrity standards as those expected from domestic studies
  - State the standard of conduct followed or intended to be followed and discuss the impact of the differences in the standards followed if different from FDA published standards (GLP, GCP)
- Explanation of how the study will fit within the overall development plan

Applicable Standards

1. Nonclinical Laboratory Studies (Safety):
   - Good Laboratory Practice (GLP) standards (21 CFR Part 58)
   - Include GLP compliance statement or explain non-compliance (See 21 CFR 514.1(b)(12)(iii)).
   - Quality Assurance Unit (QAU) required
2. Field Effectiveness Studies:
   - Conducted by qualified personnel (21 CFR 514.1(b)(8)).
   - Should follow GFI #85 / VICH GL9
   - QAU optional (highly recommended)
3. Laboratory Effectiveness Studies:
   - GCP principles apply
   - GLP not required, but good study conduct is expected
   - QAU optional (highly recommended)

Sponsor GLP Compliance Statement Expectations

- Affirm each study's compliance with 21 CFR § 58 (FDA GLP) or provide a brief statement of the reason for the noncompliance.
- Describe all deviations and GLP exceptions noted in the study director's FSR with the impact assessed.
- For studies conducted using standard other than FDA GLPs:
  - Describe how the study did not comply with FDA GLPs.
  - Describe how studies complied with the FDA GLPs and why the non-compliance to FDA GLPs did not affect the outcome of the study results.
- Be signed/dated by the sponsor representative(s) responsible for making these assurances.

Refer to Questions and Answer Document for the Data Quality Webinar Updated April 2021

Sponsor GLP Compliance Statement Challenges

- The Compliance Statement does not contain all items of noncompliance.
- For studies conducted using a standard other than FDA GLPs (e.g., OECD), the sponsor GLP compliance statement:
  - Does not always describe how the study complied with FDA GLPs
  - Provides information regarding the differences between the standard of conduct and 21 CFR Part 58; and does not include an assessment of the impact of any noncompliance to FDA GLPs

Raw Data Expectations

- All units of measurements should be consistent with the Imperial or International System of Units (SI) derivatives.
- Raw data can retain original units
  - All data for a specific variable should be consistently converted to the same unit of measure in the Final Study Report (FSR)

Use of Foreign Data – Privacy Concerns

- Drug companies are responsible for ensuring all data from foreign studies are compliant with local laws while still meeting the requirements for approval of new animal drugs in the U.S.
- For example: submissions do not always include CVs or training documentation (protocol, GLP/GCP, EDC system, etc.) for key study personnel.

Use of Foreign Data - Translations

- If any part of the application is in a foreign language, an accurate and complete English translation of each part that is not in English shall be appended
  - For example, translate the data directly on the data collection sheet or append a separate sheet with the translated data
- Certified translations are not required for data, study reports (GCP) and published literature; however, it is the sponsor's responsibility to verify the information for correctness

Draft GFI Translation of GLP Study Reports: Questions and Answers

- CDER Draft GFI
- Provides information to sponsors and nonclinical laboratories regarding the language translation of study reports for studies conducted in compliance with good laboratory practice (GLP) regulations (21 CFR part 58).
- This draft GFI states that GLP study reports should include a certified translation

Translation Challenges (GCP/GLP)

- All data are not translated from a foreign language to English. For example,
  - only portions of data on a study form are translated
  - study participant names and roles are not translated or included in the translations
- Foreign data are not recorded in the original language
- Foreign data are not translated by someone knowledgeable with the data and therefore translations may be inaccurate

Foreign Data and Bioresearch Monitoring (BIMO)

- As stated in CVM GFI #265 – FDA may conduct inspections in support of U.S. drug approvals.
- The BIMO program ensures data reliability and verifies compliance with the standard of conduct GCP and GLP for sponsors, clinical investigators and facilities outside the U.S. submitting data in support of a U.S. approval
  - For more information, refer to Bioresearch Monitoring Program (BIMO) Compliance Programs

How do sponsors increase the likelihood that effectiveness data generated for a foreign dossier is accepted as pivotal by CVM and can support substantial evidence?

- Present the data in context of the proposed indication, dosage regimen, and conditions of use being pursued in the U.S.

How do sponsors increase the likelihood that data generated for both a foreign dossier and CVM will be accepted?

- Discuss the study design with CVM, including how the proposed population is representative of the target population in the US.
- Submit a protocol for review.
- Consider one of the international regulatory collaboration options discussed later.

International Collaborative Review Opportunities

- Brandi Robinson, MPH, CPH

Foundation for Collaboration

- International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)
- Confidentiality Commitments
  - Established between FDA and regulatory counterparts in foreign countries
  - Available on the FDA website
  - Allow for exchange of non-public information

VICH Guidelines

- Founding members: Regulators and Industry from European Union, Japan, and the United States
- Provide harmonized technical requirements for development of data to demonstrate safety, effectiveness, and quality of a veterinary medicinal product in order to seek an approval or marketing authorization
- VICH Members agree to implement harmonized guidance as their own and to accept studies conducted following VICH guidelines

Collaborative Review Opportunities

- Simultaneous Review with Canada's Veterinary Drug Directorate (VDD)
- Parallel Scientific Advice with the European Medicines Agency (EMA)
- 5-way Collaborative Review Pilot
  - Australian Pesticides and Veterinary Medicines Authority (APVMA)
  - New Zealand Ministry for Primary Industries (NZ MPI)
  - United Kingdom Veterinary Medicines Directorate (VMD)
  - Veterinary Drugs Directorate (VDD)

Simultaneous Review with VDD

- Created under the Regulatory Cooperation Council (RCC) Agreement between the United States and Canada
- Opportunity to pursue approvals in the U.S. and Canada simultaneously **following CVM's phased review approach**
- Facilitates simultaneous new animal drug submissions in both countries
- Same fundamental data set

Simultaneous Review with VDD (cont.)

- If accepted, the sponsor submits the same information to both agencies at the same time
- CVM and VDD review submissions independently
- CVM and VDD discuss reviews of specific submissions before responding independently
- All applicable regulations and policies are followed in each jurisdiction and agencies' decisions may differ

Parallel Scientific Advice (PSA) with EMA

- Allows sponsors to receive feedback from CVM and the European Medicines Agency (EMA) at the same time and harmonized to the extent possible within their respective laws, regulations, and policies
- Requests should focus on specific questions or issues with the development of an investigational new animal product/veterinary medicinal product

Parallel Scientific Advice (PSA) with EMA (cont.)

- High quality submission
- Intention to authorize the product in both jurisdictions
- Specific questions for a development plan or study design
  - May include summaries of studies/data but no raw data for review
  - Example question topics include:
    - Effectiveness study inclusion criteria (patient population)
    - Effectiveness study endpoints
    - Use of adaptive designs
    - Manufacturing questions
- Procedure includes a trilateral meeting

5-way Collaborative Review Pilot

- Opportunity to submit a supplemental application for review by all 5 regulators: Australia, Canada, New Zealand, UK and the USA
  - Existing veterinary drug product that already has approval or marketing authorization in all 5 countries
  - Identical formulation and manufacturing, including source of the active ingredient
- Each country makes a sovereign decision on the application

Select Agency Resources- General

- Bioresearch Monitoring Compliance Programs
- Draft GFI Translation of GLP Study Reports: Questions and Answers
- Question and Answer Document for the Data Quality Webinar, Updated April 2021

Select Agency Resources- Target Animal Safety and Effectiveness

- CVM Policies and Procedures 1243.4068 Acceptability of Submissions Containing Foreign Data to Support Safety and Effectiveness
- GFI #265: Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs
- GFI #85 (VICH GL9): Good Clinical Practice (GCP)
- GFI #90 (VICH GL7): Effectiveness of Anthelmintics: General Recommendations
- GFI #185 (VICH GL43): Target Animal Safety for Veterinary Pharmaceutical Products
- GFI #226: Target Animal Safety Data Presentation and Statistical Analysis

Select Agency Resources- International

- Confidentiality Commitments
- FDA and European Medicines Agency Parallel Scientific Advice Program for Animal Drugs


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Morning Break

Morning session will resume at 11:00 am

Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs

Emily Smith, DVM
Office of New Animal Product Evaluation, FDA CVM

Learning Objectives

1) Understand regulatory definitions related to real-world data (RWD) and real-world evidence (RWE)
2) Understand the key questions to answer when evaluating whether RWD and RWE may be appropriate to support the approval of new animal drugs
3) Where to look for more information

Definitions: Law

Section 305 of the Animal Drug and Animal Generic User Fee Amendments of 2018 (FD&C Act)

Required FDA to issue Guidance "For purposes of assisting sponsors in incorporating … **real world evidence (including ongoing surveillance activities, observational studies, and registry data),** … into proposed clinical investigation protocols and applications for new animal drugs…"

- Focus is on **Effectiveness** and submissions to an **investigational new animal drug (INAD)** file, **new animal drug application (NADA),** and application for **conditional approval (CNADA)**

Definitions: Guidance

Guidance for Industry #266: "Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs"

Real-World Data (RWD): "are data routinely collected from a variety of sources relating to the health and productivity of animals, the delivery of veterinary care, or the management of livestock/animals for food."

Real-World Evidence (RWE): "is the clinical evidence of the effectiveness of a new animal drug derived from analysis of RWD."

Definitions: real-world data vs. clinical study data

Real-world data

- Data obtained during routine veterinary care and animal management (production), outside of a research setting
- Drug administered according to the veterinarian's clinical judgement

Clinical study data (research data)

- Data collected according to protocol-specified procedures, for research purposes
- Drug administered based on assignment of animal to a treatment group according to a research protocol

Key Questions

1. What is the regulatory question/purpose?
2. What sources of RWD are available?
3. Does the RWD have sufficient fitness for use (i.e., relevance and reliability)?
4. Is a study using RWD appropriate to answer the regulatory question?
5. What type of study (study design) is appropriate?
6. What should be included in the protocol?

What is the regulatory purpose?

Support product development plan

- Characterize dosage regimen and define conditions of use

Protocol development for a traditional clinical study

- Justify study elements (enrollment criteria, sample size, etc.)

Demonstrate reasonable expectation of effectiveness or substantial evidence of effectiveness

- Studies generating RWE

What sources of RWD are available?

- Health and management records
- Pharmacy records
- Disease surveillance programs
- Product and Disease registries
- Digital Health (and production)
- Insurance claims
- *[Pharmacovigilance Data]*

Does the RWD have sufficient relevance?

Is the information captured by the RWD source adequate for the regulatory purpose?

- Critical data elements captured in sufficient detail?
- Standardization of data collection?
- Representative animal population?
- Adequate number of animals?
- Supplemental data sources needed?

Does the RWD have sufficient reliability?

Determined by quality and integrity of the RWD and the source

- Evaluation of how the data are collected (data accrual)
- Quality control and quality assurance (QA/QC) processes throughout data lifecycle

Assessment of RWD reliability

High quality data are: **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal, and **A**ccurate (ALCOA)

Data integrity assessment for:

Completeness, Accuracy (e.g., consistency and plausibility), Provenance (record trail), and Traceability

Is a study using RWD appropriate to answer the regulatory question?

Considerations may include:

- Traditional clinical study design has ethical or feasibility issues with randomization
- Large treatment effect sizes expected (confounding and bias less likely to account for observed differences in treatment groups)
- Effectiveness based on objective and well-defined outcome (e.g., mortality)
- Disease has a predictable natural history

What Type of Study is Appropriate?

- Variety of study designs available, with variable reliance on RWD
  - Single arm (treatment group) study that uses RWD as external control arm (treatment arm is from clinical study data)
  - Non-interventional (observational) study

What should be included in the protocol? (Based on 21 CFR 514.117)

- Acceptable standard of conduct (e.g., GCP)
- Study objective
- RWD source(s) and a justification for its fitness-for-use (i.e., relevance and reliability)
- Procedures for data processing and preparation of the final RWD dataset
- Methods to control bias and confounding
- Data checks
- Statistical analysis plan
- Criteria to determine the effectiveness of the drug (basis of study conclusion)

Protocol: Study Objective

Population (target animal species/class)

Intervention (new animal drug and conditions of use as appropriate)

Comparator (control)

Outcome (endpoint specific to intended use)

Protocol: Preparing the RWD dataset

- Individual animal data extracted from RWD source and processed into a dataset for analysis (curation)
- Pre-specify and document data processing steps
- Considerations include:
  - Time frame for data extraction
  - Unstructured (requires transcription) vs. structured data
  - Linking sources (lab results and medical records)
  - Data standardization (terminology, formats, etc.)

Protocol: Identifying Sources of Bias

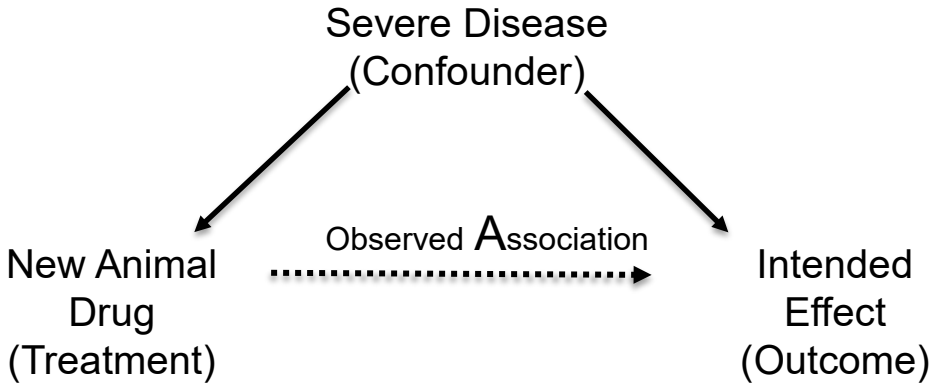
Bias: systematic error that leads to distortion of the true treatment effects

Examples:

- Selection bias: bias arising when study animals do not represent the target population
- Information bias: bias arising from errors in the data (measurement error)

Protocol: Identifying Confounding

Confounding: situation in which an independent factor (confounder) distorts the association between the treatment and an outcome



Protocol: Controlling Bias and Confounding

- Ensure data sources or databases are not selected, and specific analyses are not conducted, to favor certain conclusions
- Establish the protocol and analysis plan **prior to** conducting analyses
  - Identify appropriate comparators and statistical methods
  - Ensure masking during development and CVM review
- Use objective data when possible
- Conduct a robust data assessment

Protocol: Data Assessment

- Prespecify QA/QC plans
- Validate to source data
- Explain data corrections and assessment for duplicated data
- Data plausibility
- Completeness of data: Identify the factors that cause missing data

Protocol: Statistical Analysis Plan

- Hypothesis to be tested
- Define model(s) and method of estimation
  - Control confounding and/or bias
  - Address missingness
  - Quantify uncertainty
- Sensitivity analysis
  - Model assumptions
  - Impact of missing data
  - Unmeasured confounding

Protocol: Basis of study conclusion

- Criteria for concluding that the new animal drug is effective for the proposed indication based on:
  - Comparison between treated animals and control, or treated animals achieve the performance goal
  - Statistical significance
  - Interpretation of additional pre-planned statistical analyses
- Often requires close coordination between clinical and statistical reviewers

Summary

- RWD and RWE can be used to address a variety of regulatory questions
  - Early communication with CVM is encouraged
- Sources of RWD need to be reliable and contain the information to answer the regulatory question
  - RWD should be selected from all available sources to avoid selection bias.
- Protocols should be developed *a priori*
  - Address confounding factors and biases through study design and statistical analysis plan to derive RWE.

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References: FDA websites

FDA Real-World Evidence Page: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

CVM Guidance for Industry #266: Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs (October 2021) Available at: https://www.fda.gov/media/139953/download


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Q&A for Morning Session

Walt Ellenberg & CVM Panel

Lunch

Afternoon session will start at 1:00 pm

Makes a High-Quality Submission?

Laura Moussa, PhD
Jordan DeSilva, BS
Office of New Animal Product Evaluation
FDA CVM

Agenda

- Introduction
- Submission quality
- eSubmitter
- Raw data
- Good Documentation Practices
- Data capture
- Final study reports

Introduction: Why is quality important?

- The quality of a submission, including each component of its contents, directly impacts the efficiency with which CVM can review the information, make decisions, and provide clear, concise responses to sponsors.
- There are multiple aspects to quality, from study design to submission organization.
- Here, we will focus on the best practices in organization, using eSubmitter, providing copies of raw data, and good documentation practices.

SUBMISSION QUALITY

Submission quality: Organization

Your submission should be clear and organized, with an overview outlining the purpose of your submission. Reviewers need to be able to follow along with the submission.

For example:

- Use formatting to set the main point(s) apart by bolding, numbering or making a separate section of the document.
- Provide a table and/or outline to describe the study reports and amendments in the submission to help reviewers navigate the submission.
- Provide a ‘road map’ of your submission including an explanation of any amendments or deviations and how they did or did not impact the conduct of the study and accompanying results.

Submission quality: Best practices

- Include a history of relevant submissions reviewed by CVM (e.g., in the cover letter).
  - Reference the submission identifier(s) and date(s) [or letter date(s)].
- Provide document numbers, version numbers, page numbers, and effective dates on standard operating procedures (SOPs), protocols, etc.
  - Ensure version control.
- Include a complete glossary of acronyms or definitions early in the submission.
- For a technical section (TS) submission, include SOPs for critical procedures and ensure all referenced appendices are included with the final study report.
- You may request a meeting with CVM to discuss your submission prior to submission.

Submission quality: Consistency

- Check for consistency (e.g., product information, terminology, results) across the submission, including eSubmitter, the final study report, copies of raw data, etc.
  - If you find inconsistencies, investigate the source and provide an explanation.
  - If there are known inconsistencies, explain the differences and their impact.
    - » E.g., if the drug is proposed for oral administration (in eSubmitter) but the summaries of pilot work reflect intravenous administration.
- We may ask for an amendment, reset the clock, or refuse to review/refuse to file a submission:
  - if there are inconsistencies that are unexplained; or
  - if something is changed without explanation (e.g., inconsistencies across submissions).

Submission quality: Support and justification

- Provide a logical, coherent, well-supported justification to support the purpose of the submission.
- Explain any concerns or gaps, the supporting and non-supporting evidence, and draw a conclusion. Explain any issues that may have affected study conduct and data collection.
  - Address known gaps between the available information in your submission and the information recommended in the applicable guidance.
  - Otherwise, justify why you don't need to address these gaps for your specific product.
- Reference peer-reviewed literature or other high-quality sources of information.
  - Include copies of the referenced literature in the submission.
  - Guidance for Industry (GFI) #106 *The Use of Published Literature in Support of New Animal Drug Approvals*

Submission quality: Ensuring complete submissions

For your response to an incomplete letter:

- To ensure completeness of the response, we recommend that you reproduce each specific CVM question or concern and list your response following each question. For example:
  - **CVM question: Why is the sky blue?**
  - Sponsor response: *According to research by Dr. Hulbert (1953), Rayleigh scattering is…*
- Provide an adequate level of detail in the response, commensurate with the topic and level of concern.
- CVM may request an amendment, refuse to review, or incomplete the submission if you do not address each question.

Submission quality: Master files (MFs)

- Good communication between the sponsor and the MF holder is essential. Communicate with the holder of any referenced MF:
  - to confirm a letter of authorization (LOA) has been submitted to the MF,
  - to determine if the MF has previously been reviewed, and
  - to ensure that all outstanding deficiency comments have been addressed before making your chemistry, manufacturing, and controls (CMC) submission.
- Missing LOAs and unaddressed deficiencies in MFs can lead to the referencing submission being found incomplete.

Submission quality: Environmental Impact TS

- The conditions of use should be accurate and consistent.
- For investigational use of a drug, if the use conditions are still under development, a conservative estimation on range should be provided (e.g., if the dose is not certain, the highest tested dose in the investigational study should be provided).
- All questions in eSubmitter with blue dots should be answered fully and accurately.

Submission quality: Timeline impacts

Issue	Tool to address	What is the impact
Poor submission quality (incomplete on its face)	Refuse to review (RTR) or refuse to file (RTF)	Sponsor resolves issues and resubmits. Can cause significant delays.
Missing or inconsistent information	Minor amendment	Review process is delayed until information is received to allow review completion.
	Reset the clock	Submission requires major amendment to be complete. When it is received, the review clock starts from Day 0.
	Stop the clock (VIP only)	Sponsor submits requested information. Review clock is paused until the amendment is received.
	Incomplete letter	Additional review cycle(s) required.

Submission quality: Example - RTR

A sponsor submitted their CMC TS for the first time.

- The submission was 15 pages in length. It did not reference any master files; instead, the cover letter stated that the entirety of the drug substance and drug product CMC information was included in the submission.
- The submission did not include any information on the manufacturing facilities for either the drug substance or drug product.

IMPACT: The CMC TS was deemed incomplete on its face and CVM refused to review.

Submission quality: Example - incomplete letter

Human food safety (HFS) TS

- Residue chemistry studies: The final study report (FSR) does not accurately describe study activities and conduct. For example,
  - raw data on medicated feed consumption and start of withdrawal period not reported or matching description in FSR;
  - health status of animals in FSR not aligning with raw data;
  - additional analytical procedures used but not reported in FSR;
  - equipment failures not reported in FSR; or
  - multiple analyses of the same samples not reported in FSR.

IMPACT: In some cases, studies were repeated to achieve HFS TS complete. In other cases, additional review cycles were needed to reach information acceptable letters.

Submission quality: Example - reset the clock

Target animal safety (TAS) TS

- The sponsor submitted multiple laboratory studies to the TAS TS; however, no data from necropsy of study animals was included in the submission.
  - CVM requested a major amendment to include necropsy data.
  - The clock was reset on receipt of the amendment (+180 days).
  - The amendment contained the requested data. The reviewer was able to make a regulatory decision and complete the review.

IMPACT: The TAS TS was complete. Although the timeline was longer, an additional review cycle was not needed.

Submission quality: Example - stop the clock

A TS containing final product specifications was received for a product that was enrolled in the VIP. During the review, the reviewer noted that the test methods had not been validated.

- The review timeline was stopped to allow the sponsor to submit the method validation information.
- The sponsor spent considerable time and resources to create and execute a validation strategy. This was complicated by the inability to find commercial reference standards due to the biologic nature of the product.
- The sponsor submitted the requested information and the clock was restarted.

IMPACT: The review time was extended by the maximum amount of time allowed under stop the clock (180 days) rather than requiring an additional review cycle. The TS was found to be complete.

ESUBMITTER

eSubmitter: Basics

- Follow the appropriate eSubmitter template and eSubmitter User Guide.
- Ensure that the Responsible Official has signed the administrative cover sheet, rather than the person who was the submitter.
- Ensure that you have used the correct document type (GC file vs. G submission).
- Total submission size is limited to 10 GB (each individual file < 250 MB).
- Acceptable file types:
  - Comma Separated Values (CSV)
  - JPEG Image (JPG, JPEG)
  - MPEG Audio Stream Layer III (MP3)
  - MPEG-4 Video (MP4)
  - Extensible Markup Language (XML)
  - SAS Transport [XPT, XPORT (not CPORT)]
  - Portable Document Format (PDF)
  - Standard Text File (TXT)

eSubmitter: Compiling the report and attachments

- Read the prompts in eSubmitter.
  - Based on the input for some fields, additional questions or screens may populate.
  - Not answering the template questions can lead to confusion and delays.
- Include a table of contents (TOC) for attachments. List file names and include a detailed description of file contents to describe data element(s) in each file.
  - Make sure that the TOC addresses where key data elements are.
  - Organize the TOC to illustrate the file(s) necessary to review a specific variable (e.g., body weight), particularly when the data is spread over multiple files.
- Attaching hundreds of files can be confusing. Consolidate where possible.
- Include a Readme file for all programming and data files (e.g., SAS programs and SAS datasets) in a TS submission. See GFI #197 for more information.

eSubmitter: Attachment naming

- Use descriptive and unique filenames less than 100 characters in length.
  - This aids reviewers in locating information and helps prevent overwriting of files upon upload into review systems.
- Avoid spaces and special characters such as /, \, @, %, ;, non-English letters, and other non-alphanumeric symbols.

Example 1

Provide any additional information (e.g., literature articles, R&D reports).	
File Attachment 1	Baltimore study - raw data Site 1.pdf
File Attachment 2	Baltimore study - raw data Site 2.pdf
File Attachment 3	Baltimore study - raw data Site 3.pdf
File Attachment 4	Lit ref 1 - Rinderspacher 2012.pdf
File Attachment 5	Lit ref 2 - Massey 2015.pdf
File Attachment 6	Lit ref 3 - Massey 2021.pdf
File Attachment 7	Lit ref 4 - Chapman 2025.pdf

Example 2

3.10 Other Study Related Information	
Attach other study related information files for this study that have not previously been provided in this submission.	
File Attachment 1	2010Titleoftheartilec.pdf
File Attachment 2	Aldouos 2021 doi002305032912.pdf
File Attachment 3	Aldous 2024 doi1236648664.pdf
File Attachment 4	Level n gibberish is a Markov chain of order n-1..pdf
File Attachment 5	Massey,R etal 2011 Lookingforcracksintheceiling.pdf
File Attachment 6	Page 1 of 32.pdf
File Attachment 7	Page 10 of 32.pdf
File Attachment 8	Page 11 of 32.pdf
File Attachment 9	Page 12 of 32.pdf
File Attachment 10	Page 13 of 32.pdf
File Attachment 11	Page 14 of 32.pdf
File Attachment 12	Page 15 of 32.pdf
File Attachment 13	Page 16 of 32.pdf
File Attachment 14	Page 17 of 32.pdf
File Attachment 15	Page 18 of 32.pdf
File Attachment 16	Page 19 of 32.pdf
File Attachment 17	Page 2 of 32.pdf
File Attachment 18	Page 20 of 32.pdf
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File Attachment 24	Page 26 of 32.pdf
File Attachment 25	Page 3 of 32.pdf
File Attachment 26	Page 4 of 32.pdf
File Attachment 27	Page 5 of 32.pdf
File Attachment 28	Page 6 of 32.pdf
File Attachment 29	Page 7 of 32.pdf
File Attachment 30	Page 7 of 32_corrected.pdf
File Attachment 31	Page 8 of 32.pdf
File Attachment 32	Page 9 of 32.pdf
File Attachment 33	path serversharepointCFSLIBTT2010;.pdf

eSubmitter: PDF files

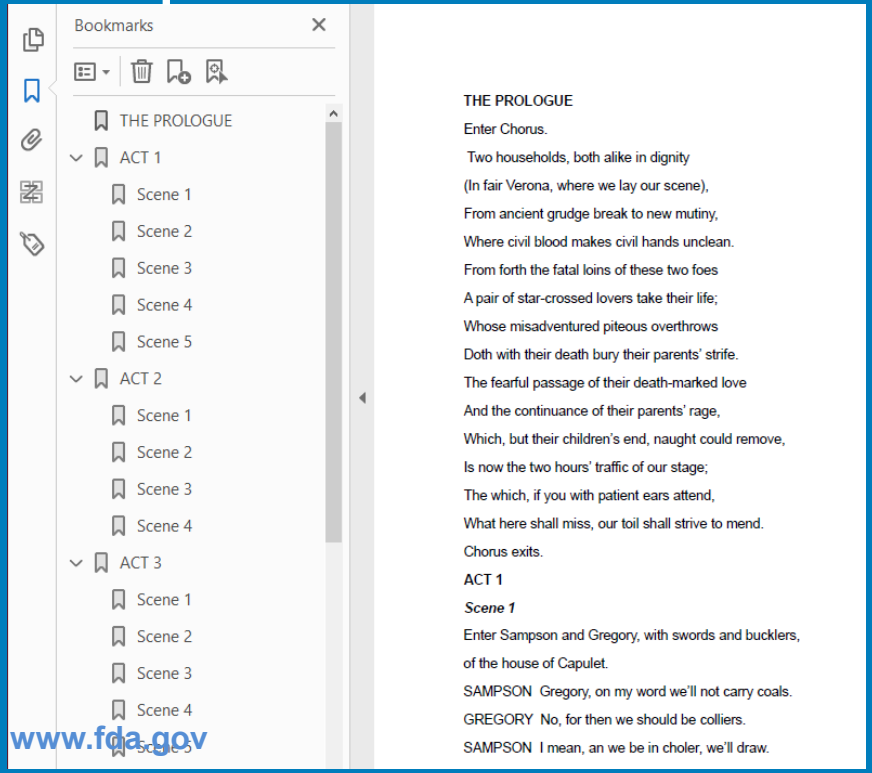
- Version 1.4-1.7, PDF/A-1, PDF/A-2 and beyond.
  - Should not be encrypted nor require additional software or plug-ins to be read, navigated, text-searched, text-selected, or printed.
  - Should not contain JavaScript, dynamic content that includes audio, video, or special effects and animations; attachments, 3D content; or annotations.
- As a best practice, it is recommended to run Optical Character Recognition (OCR) before attaching files.
- Hyperlinks between individual PDF documents are currently not supported. Any absolute links that reference across files will not work.

eSubmitter: PDF files and bookmarks

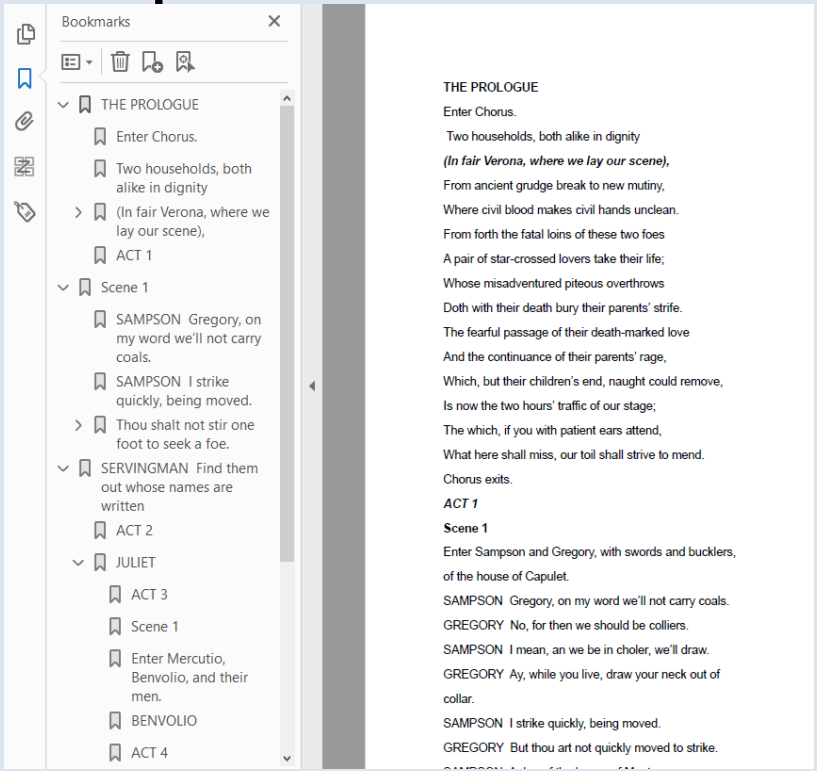
- We recommend that your PDFs:
  - have a table of contents,
  - provide bookmarks (internal only; bookmarks to other files will not work), and
  - include hypertext links for each item listed in the table of contents (including all tables, figures, publications, other references, and appendices).
- Bookmarks: hierarchy best practices
  - Bookmarks should follow the outline of the document and should correspond to the section headers and sub-section headers appropriately.
  - Bookmarks should not be automatically generated because this often leads to functionally useless bookmarks.

eSubmitter: PDF bookmark examples

Example 1



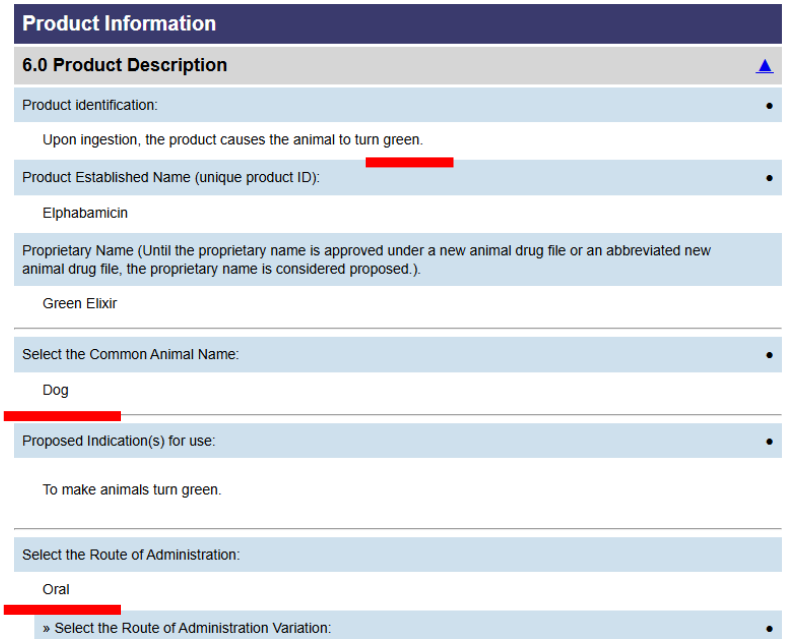
Example 2



eSubmitter: Consistency

- Do not include the same data in multiple locations.
  - E.g., if you create a separate PDF attachment containing your stability data tables, don't also put the stability data tables in your main Module 3 PDF.
  - Duplicating information causes the reviewer to spend extra time checking for consistency.
- Do not attach a PDF unless additional support is needed. If a PDF file is included, the information in the PDF should be consistent with those provided in the eSubmitter report (e.g., the conditions of use should be identical).
- Inaccurate information in eSubmitter results in additional time needed by reviewers to verify what information is correct. Amendments may be needed which cause additional time for sponsors and CVM reviewers.

eSubmitter: Consistency case study



Product Information

6.0 Product Description

Product identification:

Upon ingestion, the product causes the animal to turn green.

Product Established Name (unique product ID):

Elphabamicin

Proprietary Name (Until the proprietary name is approved under a new animal drug file or an abbreviated new animal drug file, the proprietary name is considered proposed.).

Green Elixir

Select the Common Animal Name:

Dog

Proposed Indication(s) for use:

To make animals turn green.

Select the Route of Administration:

Oral

» Select the Route of Administration Variation:

I. Introduction

This product was discovered in the laboratory of Dr. L. F. Baum at Shiz University. Research began in 2017, with a final formulation still under development

II. Product definition

The product is a subcutaneous injection that turns cats pink. The final dose is 400 mg/kg of the active ingredient dissolved in water for injection and various buffers.

III. Project summary

Dr. Baum is committed to ensuring that animals are able to change colors on demand. This work has been funded through various grants as well as crowdfunding to ensure the availability of color changing pets as quickly as possible. When most people think of color change, they think of octopuses or chameleons - but the ability to rapidly change color is surprisingly widespread. Many species of crustaceans, insects, cephalopods (squid, cuttlefish, octopuses and their relatives), frogs, lizards and fish can change color.

Coloration in animals is produced by reflection and scattering of light by cells and tissues, and by absorption of light by chemical pigments within cells of the skin. The melanophores play a crucial role in color change. They are large, star-like cells with long "arms" (dendrites) that extend towards the skin's surface. Color change occurs due to the movement of "packets" of melanin pigment (melanosomes) within the melanophores.

When melanin pigment is aggregated within the center of the cell, the skin appears very pale

eSubmitter: CMC

The question-based review (QbR) CMC TS eSubmitter template is designed to ensure all necessary information is provided by the sponsor.

- Answer all questions accurately so follow-up questions will be activated or inactivated appropriately.
- If you check a box to certify information is provided in Module 3, verify that the information actually exists in the corresponding section of your Module 3 PDF before submitting.
- If you get stuck, contact Division of Manufacturing Technology (DMT) for help rather than creating your own work-around that may inactivate crucial follow-up questions or sections.

eSubmitter:
CMC – ADMS Information

- CVM uses the Animal Drug Manufacturing System (ADMS) information in the eSubmitter template to do CGMP status checks and determine whether pre-approval inspections are needed. Missing/incorrect information can delay an inspection, which can delay completion/approval of the CMC submission.
- Common errors include:
  - Not providing supply chains for all applicable facilities.
  - Providing incorrect roles or qualifiers in supply chains.
  - Providing incorrect FDA Establishment Identifier (FEI) or Data Universal Numbering System (DUNS) numbers for facilities.

For questions about entering ADMS information, see https://www.fda.gov/animal-veterinary/resources-you/submitting-establishment-information-animal-drug-manufacturing-system-adms. If that doesn't answer your question, contact DMT for help.

eSubmitter: MF references

- CVM uses the information in the eSubmitter template to identify relevant MFs that need to be reviewed.
  - Missing/incorrect references can delay review of the MF, leaving less time to address problems in the MF via amendments.
  - If a referenced MF is found deficient because the problems can't be resolved in time, this could cause the submission to be incomplete.
- Common errors include:
  - listing an incorrect file type (VMF vs. DMF) or file number; or
  - not referencing MFs in resubmissions.

RAW DATA

Raw data: CVM's approach

- For new animal drug applications, FDA requires full reports of investigations which have been conducted to show a drug is safe and effective for use [section 512(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act)].
- CVM has provided information on raw data in draft GFI #287 *Raw Data for Safety and Effectiveness Studies*.

"We consider raw data the first permanent recording of an observation and, whether handwritten or electronic, should be attributable, original, contemporaneous, and legible."

- CVM expects the submission of copies of critical raw data with final study reports that support the approval of new animal drugs.
- CVM reviews copies of raw data to reconstruct the study and confirm the accuracy of the final study report.

Raw data: CVM's definitions

- For Good Clinical Practice (GCP) studies, CVM uses the definition provided in GFI #85.

  "Any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a study and are necessary for the reconstruction and evaluation of the report of that study. Raw data may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments."

- For Good Laboratory Practice (GLP) studies, CVM uses the definition of raw data provided in 21 CFR 58.3(k).

  "Any original worksheets, calibration data, records, memoranda and notes of first-hand observations and activities of a study that are necessary for the reconstruction and evaluation of the study. Raw data may include, but are not limited to, photographic materials, magnetic, electronic or optical media, information recorded from automated instruments, and hand-recorded datasheets."

Raw data: Collection

- Both the GLPs and GCPs state how raw data should be collected.
  - GLP: All raw data generated during the conduct of a study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the date of entry and signed or initialed by the person entering the data [21 CFR 58.160.130(e)].
  - GCP: Raw data whether handwritten or electronic, should be attributable, original, accurate, contemporaneous and legible (GFI #85, 8.3.1).
- If needed, ensure that raw data are translated to English.
  - Per 21 CFR 514.1(a) "If any part of the application is in a foreign language, an accurate and complete English translation shall be appended to such part. Translations of literature printed in a foreign language shall be accompanied by copies of the original publication."

Raw data: Study support

- CVM uses the data collected for a study to confirm that the study protocol was conducted accordingly and support the results and conclusion of the study.
  - Verify information in the FSR, adherence to relevant guideline(s).
  - Identify protocol or guideline deviations.
  - Provide audit data.
  - Verify statistical analyses.
- Raw data supports any conclusions drawn from the study. High-quality raw data are the strongest support for study conclusions.
- Only provide copies of raw data relevant to the FSR.
  - E.g., limit irrelevant or redundant email correspondence.

Raw data: Examples

- Examples of raw data:
  - Clinical and general health observations
  - Adverse events
  - Physical examinations and body weights
  - Dose preparation and administration
  - Instrument logs and maintenance records
- It is hard to analyze tables of data as PDFs. Where possible, please submit data and deviations as CSV or XML files.
  - Clinical pharmacology example: Individual animal blood concentrations may be submitted in .xml format, including columns with treatment group, subject, sex, dose (mg/kg), analyte sampling time (min/hr), and drug concentration (ng/mL).

Raw Data: Benefits of submitting

Example 1: No raw data

- The sponsor provided reports of the studies performed, but did not include copies of the raw data.
- The reports were high-level and did not include key details that impacted outcome (e.g., formulation, study population).
- Reviewers were not able to confirm that the results were accurate without this information.

IMPACT: The submission was found incomplete.

Example 2: Raw data

- The sponsor provided reports that contained summaries to support demonstration of effectiveness.
- The reports were high-level. An inconsistency was noted in the results.
- The copies of raw data that were included allowed the reviewers to resolve the inconsistency without the need for an amendment.

IMPACT: The TS was found complete.

Raw data: Importance of consistency

Laboratory dose confirmation study:

Protocol and FSR inconsistencies

- Protocol - Worm counts on Day 10.
- FSR stated that samples were recounted and verified 1 week later.
  - No protocol deviation provided.
- FSR included worm count data from counts on Days 15 and 20.

Raw data

- Original worm counts (Day 10) found by the reviewer in the raw data.
- Original counts indicated inadequate infection in the control group.
  - Invalid model?
  - Why were counts performed on days not specified by the protocol?

IMPACT: The inconsistencies resulted in a TS incomplete. This case took two additional review cycles to address these concerns and meet CVM acceptance of this study

GOOD DOCUMENTATION PRACTICES

What are Good Documentation Practices (GDPs)?

- GDPs are the guidelines that one follows in recording information in a legible, traceable and reproducible manner. GDPs are a systematic procedure of preparing, reviewing, approving, issuing, recording, storing and archiving of documents. GDPs describe standards by which documents are created and maintained.
- A key to GDPs is to consider these questions when you record your raw data:
  1. Is it attributable?
  2. Is it legible?
  3. Is it contemporaneous
  4. Is it original?
  5. Is it accurate?
  6. Is it complete?
  7. Is it permanent?

GDP: Purpose

- Ensures reliable, consistent transfer of information.
- Ensures product quality and safety.
- Complies with regulatory requirements.
- Fulfills the basic premise that good science is reproducible.
- Helps prevent dishonesty and fraud; and is essential for producing quality results.
- Provides control of processes and improves performance.
- Enables important messages to be communicated clearly and accurately.

GDP: ALCOA

- Raw data should include these attributes:
  - **A**ttributable
  - **L**egible
  - **C**ontemporaneous
  - **O**riginal
  - **A**ccurate
- Better known as ALCOA.
- If your raw data includes these attributes, they would likely be compliant with both GLPs and GCPs.

GDP: Attributes of ALCOA

- Each individual who recorded data is clearly identified.
- If someone other than the recorder conducted the observation or observed data point, then that should be documented. The person who did the task should review what was recorded for them by the recorder.
- Manually recorded data is recorded clearly and legibly in indelible ink.
- Data is accurately recorded at the time it was performed or observed, including the date and time.
- The data make sense and any metadata (e.g., units for values) are included and documented.
- Narrative documentation of study procedures, events, communication and notes to file should be clear and provide a complete, accurate description of each occurrence and be fully attributable.

GDP: Protocol amendments

- Official changes to the study protocol.
- GLP: 21 CFR 58.120(b) requires that “all changes in or revisions of an approved protocol and the reasons therefore shall be documented, signed by the study director, dated, and maintained with the protocol”.
- The protocol amendment would ideally be signed and effective prior to performing the changed study task.

GDP: Protocol deviations

- All deviations should be recorded, signed and dated by the investigator. Include the reason for the occurrence, corrective actions, and an assessment on the impact on the study.
- Deviations should ideally be recorded contemporaneous with the event.

GDP: Notes to file (NTF)

- Common issue: Written at the end or after study completion to document protocol requirements without supporting documentation.
  - Dosing procedure per the protocol required additional checks that product was administered. Months later, NTF was written to say the additional check was performed.
- If the NTF was written days or months later, is it contemporaneous?
  - No
- Was any supporting, contemporaneous documentation provided?
  - No
- It is helpful that compliance with the protocol was addressed but the delay in documentation adversely impacts the reliability of the NTF.

GDP: Error corrections

- The individual who made the mistake should line out the mistake by putting a single line through the entry, write the corrected information next to the entry, then initial and date the correction.
- All corrections should be clear and legible.
- Date of the correction should be the date the correction was made; not the date the error was made.
- Back-dating or post-dating of information is not allowed.
- If there is insufficient room to write the correction next to the entry, then the footnote method will be used to document the correction.

GDP: Error corrections (cont.)

Example of making a correction using a footnote:

1. Draw a single line through the mistake.
2. Add a footnote (a “1” with a circle around it) next to the mistake.
3. On the same page, find sufficient room to write the correction and draw the circled numeral you chose earlier.
4. Write the reason for change next to the footnote.
5. Initial and date the correction.

GDP: Error corrections (cont.)

- For electronic records, an audit trail may serve the purpose of traceability if the history can be retrieved and viewed as part of the current record.
- Any changes to the data, forms, records/documents after it has been signed and dated as reviewed, verified, or signed (wet ink or electronic signature), invalidates the signature. The document **should be reviewed, and/or verified again and re-signed.**
- Modification(s) to verified records should be limited to authorized individuals; documentation of modification to critical data should include a reason for the change.

GDP: Best practices

- Complete study documentation fully complies with the protocol and standard of conduct.
- All study documentation was appropriately maintained and will be able to maintain its integrity when archived.
- Unexpected events and deviations are fully described in the study documentation.
- Study documentation fully supports all statements and conclusions in the final study report.
- All study documentation possesses all the attributes of ALCOA.

GDP: Common errors

- Illegible and unclear documentation.
- Use of scrap paper or non-official forms in documentation.
- Failure to maintain original documentation (raw data).
- Obliterations or write-overs.
- Lack of corrections or excessive changes or corrections.
- Use of outdated or uncontrolled forms for documentation.
- Study procedures not initialed and dated by person performing the task.
- Incomplete study records or forms.
- Incomplete explanation of changes to data entries and how the correct data entry was confirmed.

GDP: Things to consider

- CVM does not expect perfect studies.
- It is a recommended practice to use notes to file to provide further clarification and not to document protocol requirements months later.
- It is recommended that Quality control (QC) procedures are in place to ensure data are reviewed in a timely manner to ensure quality and integrity.

GDP: Example scenario

- Event: There is bad weather at a site. Due to the effects of the weather event, personnel cannot make it to the site the next day. The following day personnel are on site and identify damaged pen fencing. Cattle are missing from the pen.
- Good documentation => As the protocol states study animals will be confined to pens for the duration of the study, a deviation is written the day animals are observed as missing. The deviation includes all relevant information.
- Deficient documentation => No deviation or explanation is written at the time of the event. There are unexplained missing entries on data capture forms for these animals for multiple days. Data starts being entered for these animals again in data capture forms, 3, 5, and 6 days later.

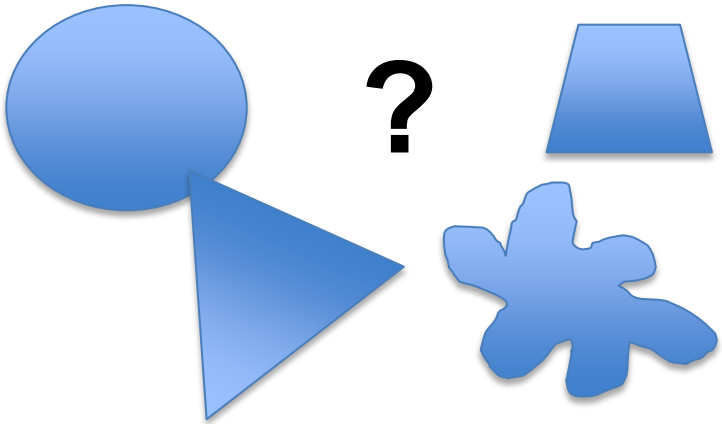
GDP: Good vs. deficient documentation

- Good documentation

  Small, manageable gaps in data, contemporaneous investigation and explanation, information aligns.

- Deficient documentation

  Large, unexplained gaps in data, no explanation, difficult to align information.

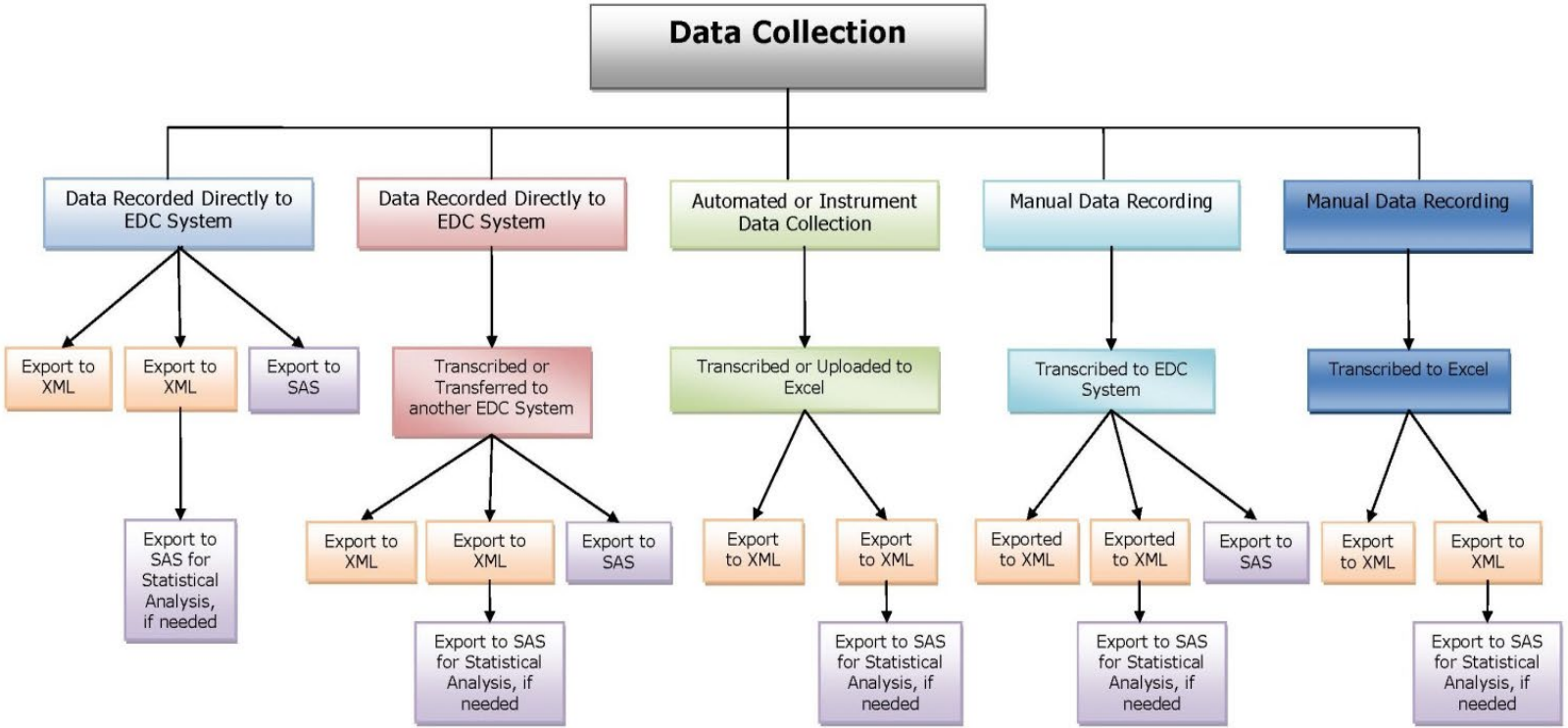


DATA CAPTURE

Data capture: Submitting documentation to CVM

- Two types
  - Manual Data Capture: Collected via handwriting with indelible ink on paper.
  - Electronic Data Capture (EDC): Collected into some type of computerized data capture system via an electronic device.
- Whether manual or electronic:
  - Data should possess the attributes of ALCOA.
  - Any changes should be clearly denoted, legible, and attributable.
  - CVM should be assured of the veracity and integrity of the data from collection to submission to CVM.
- Sponsors should clearly identify which data was collected manually versus electronically and provide assurance of the accuracy of any transcription of data.

Data capture: Methods for data collection submitted to CVM



Data capture: Things to consider

- Raw data collected in an EDC system should mimic how raw data are collected on paper.
  - The EDC system should meet 21 CFR Part 11 compliance.
  - EDC systems should be validated.
  - Equipment utilizing EDC systems to document output should be validated and calibrated, as appropriate.
- Individuals recording data should be appropriately trained and ensure that all data generated adheres to good documentation practices, or when it does not, is documented as a deviation.
- Each sponsor should evaluate the needs for their study, select appropriate equipment and systems, and validate those equipment for their needs.

Data capture: 21 CFR Part 11

- EDC is required to be compliant with Part 11.
  - Clearly state in the final study report that all EDC systems have been validated for use and meet 21 CFR Part 11 compliance.
  - Also address in the submission that the data files submitted to CVM as electronic data had to be exported and/or converted to a format to be submitted via eSubmitter.
- Compliance must be maintained throughout the data lifecycle and should be considered during your validation process. Be sure that you are thinking of the following:
  - data generation;
  - changes to the data;
  - submission to CVM; and
  - archival.

Data capture: Best practices for submitting copies of raw data

- For multi-site field studies, organizing raw data in “books” or files (pdfs) by site is helpful. Particularly when the documents included in these files are consistently organized for each case and at each site. For example:
  - All site XYZ raw data is saved as, “XYZ raw data_file 1_Study ABC-123.pdf”.
  - Each sequentially numbered file contains the same bookmarks and same documents:
    - Case ID
      - » Owner consent form
      - » Physical examination form
      - » Quality of Life questionnaire
  - This organization strategy is consistently applied for raw data for all sites.

Data capture: Best practices for submitting copies of electronically captured raw data

- The data and key associated metadata should be submitted.
  - Exported directly from the source EDC system and provided in XML format.
  - If the raw data cannot be directly exported from the original EDC system in XML format, then describe the process and controls in place for the transformation or manipulation of data to the final XML format.
  - If raw data was originally captured on paper and transcribed into the EDC system, then a copy of the paper document should be submitted in PDF format.
- Audit trails
  - Should be linked to the original data points and the data modified, operator ID, time/date stamp, and reason for change should be recorded.
  - Provided in XML format.
  - Contents should also be described in the ReadMe file.

Data capture: Best practices for submitting copies of electronically captured raw data (cont.)

- Final Study Report
  - Name of EDC system(s) used and the data collected by each system.
  - Statement on each EDC systems validation status.
  - Clear identification on which study data were collected manually vs. electronically as well as which study data were collected manually and transcribed into the EDC system.
  - Information on the archiving and retention of the electronically captured raw data.

Data capture: Best practices for submitting copies of electronically captured raw data (cont.)

- ReadMe file (see GFI #197 for specifications)
  - Lists and describes each data and program file.
  - Describes the audit trail file listing and contents if submitted separately from the data files.
- Describe the systems used to generate XML files for the submission.
  - Validation status
  - How data integrity was maintained:
  - » from collection to submission.
  - » when information is converted between formats.
- Describe the controls in place after data was exported to prepare for submission to CVM.

Data capture: GFI #197 *Documenting electronic data files and statistical analysis programs recommendations*

- Convert raw data files to XML files prior to performing analysis using the converted XML files.
  - Document how XML files were converted (e.g., SAS program, R code) and describe what software was used.
- Check whether programs are executable.
- Ensure all files are submitted, including macros.
- Correctly name variables in data files.
  - Only use alphanumeric or underscore characters.
  - Do not include special characters, including dashes and periods.
  - The first character cannot be a number.

Data capture: GFI #197 recommendations

- Documentation of data manipulation and derivation:
  - If data were deleted or modified due to errors, duplicates or deviations, document it in FSR and note the manipulation in analysis program.
  - If certain variables were derived, include documentation.
    - » E.g., A portion of the intestine sample was examined for endo-parasite count. The original count of parasites from that portion should be recorded and submitted in raw data, and the factor that the original count should be multiplied by to derive the parasite count for each animal should be documented in the analysis program and in the FSR.

Data capture: Top findings in studies using EDC

1. Unexplained time discrepancies observed when comparing the audit trail date and time stamps to the protocol and other study documentation.
2. Lack of a description of quality control procedures used if data was transcribed into the EDC system.
3. Entry errors and discrepancies indicating a lack of training on use of the EDC system.
4. User roles do not include descriptions of what information each role can access to maintain masking.

Data capture: EDC system (EDCS) raw data – Case study #1

- Two animals from the same household were enrolled in a clinical field study.
  - "animal dosing_form 1.xml" indicates animal 12-xy received the IVP and animal 13-xy did not.
  - "owner communications_site xy.xml" indicates animal 12-xy did not receive the IVP, but animal 13-xy did.
- This impacts the assessment for inclusion in the safety population.
- This suggests poor record keeping or oversight by the study Investigator and/or Monitor.
- Outcome: amendment request for clarification.

Data capture: EDCS raw data – Case study #2

- In the clinical field study, one animal was not enrolled according to “enrollment.XML”; however, the same animal was recorded as receiving a dose of the Investigational Veterinary Product (IVP) on “animal dosing form 1.XML”.

- This impacts the assessment for inclusion in the safety population.
- This suggests poor record keeping or oversight by the study Investigator and/or Monitor.
- Outcome: amendment request for clarification.

Data capture: EDCS raw data – Case study #3

- Two animals from the same household were enrolled in a clinical field study (CB111 and CB112).
- The protocol states that animals in the same household will receive the same treatment.
  - "animal dosing.xml" indicates that animal CB111 received the control product (CP), whereas animal CB112 received the IVP.
- Protocol deviation if the xml data are accurate.
- This impacts the assessment for inclusion in the safety and effectiveness populations for the study.
- This suggests poor record keeping or oversight by the study Investigator and/or Monitor.
- Outcome: amendment request for clarification; may exclude cases from the analysis.

Data capture: EDCS raw data – Case studies

- In each case, the inconsistencies should have been noticed and investigated prior to submission to CVM.
- The submission should contain documentation to explain these discrepancies.
- Otherwise, if the raw data is incongruous, CVM will need to rely on review of the raw data to reconstruct what happened. If this is not feasible, an amendment request is necessary.
- If the circumstances are not explainable, the cases could be excluded from the analysis.

FINAL STUDY REPORTS

Final study reports (FSRs)

- A FSR summarizes the conduct and findings of a study.
- Most standards of conduct define the contents of the FSR. The most commonly used standards of conduct for studies submitted to CVM are:
  - 21 CFR Part 58 Good Laboratory Practice
  - Guidance for Industry #85 (VICH GL9) *Good Clinical Practice*
- FSRs are submitted to CVM with copies of critically important raw data. Raw data expected to be submitted varies. General guidelines are provided in eSubmitter, CVM Policy and Procedure documents, GFI #287 *Raw Data for Safety and Effectiveness Studies*, and other publicly available resources provided by CVM.
- Raw data expectations for specific studies and projects can be discussed with CVM.

FSR: Contents

The FSR should:

- should fully and accurately reflect the study and its compliance with the final, signed protocol and the standard of conduct; and be an accurate representation of all raw data.
- clearly state the standard of conduct.
- accurately reflect the conduct of the study.
- accurately and completely reflect the data generated during the study.
- be consistent.
- fully address any issues that may have impacted the outcome of the study.
- explain irregularities, significant events, and deviations and any impact on the study.
- describe amendments.
- contain signed contributor reports.

FSR: Best Practices

- Information to include in the FSR:
  - Personnel names, study role, masking status
  - Key study dates or timeline
  - Field studies: number of enrolled animals in safety and effectiveness populations by study site
  - Dosing as individual case listings (companion animals)

FSR: Common deficiencies

- Does not accurately reflect the raw data.
- Missing or not signed contributor reports.
- All required contents per the standard of conduct not included
- Does not accurately describe the QC procedures in place for the transfer of data to a contributing scientist (or necessary personnel).
- Deviations not reported to the study director and impacts on the study not addressed.
- Analysis validation plans not defined or described in the protocol.
- EDC systems not clearly defined or listed.
- Data transcribed into an EDC system not clearly identified in the FSR or submission.

FSR: Common deficiencies (cont.)

- How ALCOA was maintained.
- Archival of data collected using an EDC system not reported.
- Validation and or calibration of equipment not described.
- Incomplete or incorrect data or calculations in FSR data tables.
- Inconsistencies across the FSR:
  - Data in table is inconsistent or disagrees with data in text.
  - Terminology.
- Cases erroneously included or excluded from the safety and/or effectiveness analysis without explanation (i.e., after agreement at an inclusion/exclusion meeting).
- Lack of identification and explanation for changes.

FSR: Common deficiencies (cont.)

- Lack of identification of a specific case(s) involved in a particular part of the study (e.g., a list of cases removed from the study, list of cases that died and were necropsied).
- Poor animal accountability description in the FSR.
- Contains an inaccurate Quality Assurance (QA) Statement.
- Does not document that the QA Unit is conducting protocol required phase inspections.

FSR: Case study of EFF TS submission

The FSR for the pivotal effectiveness study, Study ABC_123, had numerous discrepancies, gaps in documentation, and gaps in data and study integrity.

- Statements in the FSR did not accurately reflect the raw data or were incorrect.
- The names of key study personnel listed in the FSR were inconsistent with the personnel identified in the raw data.
- Procedures described in the FSR were inconsistent with the raw data (e.g., dose preparation, randomization, post-treatment observations and examinations).
  - These were not documented as protocol deviations.
- Results described in the FSR were inconsistent with the raw data (e.g., abnormal health observations).

FSR: Case study for field safety and effectiveness study

In the FSR, an animal with a clinically relevant adverse event (AE) was not discussed, though the AE was included in a table appended to the FSR.

- Animal received a dose of the Investigational Veterinary Product (IVP) and later that day experienced the AE.
- Owner removed consent and the animal was removed from the study.
- The animal was not included in the safety population; therefore, the AE was not part of the sponsor's safety assessment, and no explanation was provided to support this decision.

This is an unexplained gap that may result in additional review time needed and possibly an amendment request.

FSR: Case study for field safety and effectiveness study (cont.)

Outcome – CVM determined that the AE was possibly associated with the use of the IVP and was included in the Freedom of Information Summary and labeling.

Additional recommendations related to AEs:

- Use terminology consistently (e.g., convulsion or seizure).
- Check for over- or undercounting the adverse event rate based on use of overlapping terminology (e.g., counting “loose” stool and “soft” stool separately).
- The FSR should be checked multiple times for consistency with the associated tables and raw data.
  - Discuss all AEs relevant to the known toxicity profile of the IVP (e.g., hepatotoxicity, neurotoxicity), regardless of the animal or incident rate of the AE.
  - Discuss all serious AEs in the FSR.

References

- Guidance for Industry (GFI)
  - GFI #85 Good Clinical Practice
  - GFI #106 The Use of Published Literature in Support of New Animal Drug Approvals
  - GFI #197 Documenting Electronic Data Files and Statistical Analysis Programs
  - GFI #287 Raw Data for Safety and Effectiveness Studies
- Good Laboratory Practices (GLPs)
- Computerized Systems Used in Clinical Trials
- Data Quality Resources Webpage
- eSubmitter User Guide
- Animal Drug Manufacturing System (ADMS)


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Afternoon Break

Session will resume at 2:45 pm

Adaptive Study Designs

For Effectiveness Studies

Anthony Parker, MS, PhD

Office of New Animal Product Evaluation, FDA CVM

Outline

- Introduction to adaptive study designs
- Regulatory considerations and challenges
- Decision-making processes for developing and implementing adaptive study designs
- Summary
- Appendix A - example

INTRODUCTION TO ADAPTIVE STUDY DESIGNS

Guidance for Industry #268

- Key Guidance for Industry (GFI) regarding the use of adaptive and other innovative designs in animal drug development can be found in GFI #268 “Adaptive and Other Innovative Designs for Effectiveness Studies of New Animal Drugs,” published by CVM in October 2021.

What Are Adaptive Designs?

- **Adaptive design** (defined in GFI #268)**:** A clinical effectiveness study design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the study.

Why Use Adaptive Designs?

- Design adaptations can improve efficiency of studies by saving time, money, and resources, as well as supporting the reduction principle for animal use.
  - A study with interim analyses (IA) could stop early for effectiveness or lack of effectiveness (futility).
- An adaptive design can provide ethical advantages over a non-adaptive design.
  - The ability to stop early can reduce the number of animals exposed to the unnecessary risk of an ineffective treatment.

REGULATORY CONSIDERATIONS AND CHALLENGES

Transparency

- Adaptive designs and other innovative methods intended to support effectiveness determinations should be consistent with regulatory requirements (21 CFR 514.4).
  - How such designs are planned and executed should be well-defined and pre-specified.

Regulatory Considerations

- Adequately control the chance of erroneous conclusions and minimize the risk of statistical and operational biases.
  - Statistical bias
    - ❖ Selection bias, sampling bias, etc.
  - Operational bias
    - ❖ Knowledge of accumulating data and the adaption rule (e.g., sample size re-estimate, randomization ratio change) can affect the course and conduct of a trial, and the behavior of its sponsor, investigators, and participants.

Communication with CVM

- Early communication with CVM is encouraged to discuss plans for adaptive study designs.
  - Discussion
    - ❖ Information to support protocol submission or meeting request (H Submission)
    - ❖ Meeting request (Z Submission: Early Information [EI], Presubmission Conference [PS], ONAPE Other [OO])
    - ❖ General Correspondence [GC]: submission not related to a specific INAD
  - Informal Communication via eSubmitter (Z submission)
    - ❖ Quick questions and updates related to a particular INAD for which a sponsor meeting is not needed.

Adaptive Study Design Recommendations

- GFI #268 provides general recommendations intended to enhance the validity and interpretability of confirmatory studies.
- The methods are also applicable to exploratory studies, with fewer restrictions.

Types of Studies

- Exploratory studies
  - Intended to generate new hypotheses (*a posteriori*).
  - Typically, restrictions are less stringent; studies may be smaller and more flexible.
  - Inferential statistics may or may not be employed.

Types of Studies (cont.)

- Confirmatory studies
  - Intended to test the validity of an already formed hypothesis (*a priori*).
  - Typically based on previous studies or knowledge and are designed to confirm an existing result or theory.
  - Statistical methods should be pre-specified.

DECISION-MAKING PROCESSES FOR DEVELOPING AND IMPLEMENTING ADAPTIVE STUDY DESIGNS

Study Integrity

- Adequate procedures are needed to protect study integrity.
  - The protocol should clearly explain the process used to evaluate interim data and justify how/why certain decisions will be made (e.g., sample size re-estimation, dropping of ineffective treatments).
  - The protocol should also specify how the results will be communicated to the sponsor and clinical investigators to minimize bias and protect masking.
    - ❖ Personnel with detailed knowledge of the accumulated data related to interim results should be limited.

Planning - 1

- Adaptive study design proposals should address the following elements:
  - How the proposed adaptive study fits the product development plan, and why it is beneficial,
  - The type of adaptation(s) proposed, and the timing and number of the adaptation(s),
  - The operating characteristics of the design and the analytical methods or simulations used to explore these characteristics.

Planning - 2

- Details of an adaptive design should be completely pre-specified in the protocol.
- CVM strongly recommends that the sponsor obtain protocol concurrence prior to conducting the study.

Planning - 3

- Pre-specified details of an adaptive design should include:
  - Number and timing of interim analyses (IA),
  - Type and algorithm of adaptations,
  - Type I, Type II error control and bias control,
  - Statistical analysis plan (SAP) to guide when and how adaptations should be made, based on interim results,
  - Flexibility in study design to address unforeseen issues.

Two Frequently Used Adaptive Designs

- Group Sequential Design (GS)
  - To allow for early stopping of a study based on accumulating data, either for effectiveness or futility
- Sample Size Re-estimation (SSR)
  - To adjust the planned sample size based on accumulating data to account for uncertainty in initial assumptions about the effect size or other parameters

Group Sequential Design

- Group sequential (GS) design allows for one or more prospectively planned interim analyses of the outcomes that use treatment group information, with prespecified criteria for stopping the study.
- Benefit: provide ethical and efficiency advantages by reducing the expected sample size and duration of clinical studies.

Group Sequential Design (cont.)

- GS design considerations
  - Multiple statistical hypothesis tests for effectiveness (e.g., IA) will inflate the overall Type I error.
  - Timing of IA
    - ❖A minimum sample size needed for generalizability of effectiveness results, for inferential value and independent substantiation of evidence, as well as a reliable evaluation of safety.

Sample Size Re-estimation (SSR) - 1

- SSR is a study adaptation to prospectively modify sample size based on interim analysis results.
- Benefit: help avoid under-powering a study
  - Underpowered studies: fail to detect a real and important effect because of insufficient sample size.

Sample Size Re-estimation (SSR) - 2

- May use treatment information (blinded vs. unblinded)
  - Blinded
    - E.g., to monitor the total event rate in oncology studies
    - Generally believed to have limited or no effect on overall Type I error
  - Unblinded
    - E.g., to estimate the treatment effect
    - Overall Type I error may be inflated

Sample Size Re-estimation (SSR) - 3

- SSR design considerations:
  - Control of errors and biases
    - ❖Overall Type I error control
    - ❖“Over-powering” a study
    - ❖Study conduct and integrity
  - Timing of adaptation(s): balance amount of information vs. potential benefit to remainder of study

Assumptions for Established Statistical Methods

- GS designs require the independent increment property so that the test statistic follows a Brownian process.
- Commonly used statistical methods for SSR, including the conditional power method, are based on the conditional invariance principle.

Applying Established Statistical Methods

- Established statistical methods may be directly applicable to studies with simple random samples where the experimental units are mutually independent, e.g., a study with central randomization (no random effect for site).

Studies with Central Randomization

- CVM may accept a justification for central randomization (CR) along with appropriate strategies to minimize variability across sites.
- The acceptability of a CR should be evaluated from both clinical and statistical perspectives.
- Proposals for using CR will be evaluated by CVM on a case-by-case basis at the protocol stage.

Special Features of Animal Clinical Studies

- Confirmatory field effectiveness studies typically include:
  - Multiple sites with treatment assignment randomized by site
  - An analysis with mixed models which may include site and site-by-treatment interactions as random effects

Applying Established Statistical Methods to Typical Animal Clinical Studies

- The assumptions of established statistical methods are violated in clinical studies with site stratified randomization, e.g., animals from the same site before and after interim analysis are not independent.
- Simulation may be the only method to demonstrate the control of the overall Type 1 error rate.

Simulations - 1

- Essential simulation elements to support adaptive study design proposal:
  1. Does the submission clearly state the simulation's objectives?
  2. Does the submission clearly articulate the adaptation algorithms and operating characteristics that will be evaluated?
  3. Are all the choices of parameters within the simulation submission justified?
  4. Does the simulation explain all assumptions and details of the interim analysis?

Simulations - 2

- Essential simulation elements (cont.):
  5. Does the submission specify how the interim analysis will be conducted and how it will influence decision making?
  6. Are there any “hidden” assumptions or steps the CVM reviewers may not be able to identify?
  7. Is the simulation code legible for CVM reviewers?

Simulations - 3

- Simulation results may demonstrate that the study design is a good “fit” for its purpose.
- Further, sharing the code used in the simulation with CVM will allow reviewers to confirm its accuracy and assess whether the overall Type 1 Error rate is properly controlled.

Example SSR Adaptive Design

- See Appendix A to these slides for a detailed example of how to approach and plan for an adaptive study design with a sample size re-estimation in a study randomized by site.

SUMMARY

Summary

1. While there are challenges in regulatory considerations, decision-making, and presenting interim results, adaptive designs can provide a flexible and efficient way to assess the effectiveness of animal drugs.
2. Adequate procedures are needed to protect the study integrity.
3. Because of the special features of animal clinical studies, established statistical methods may not be directly applicable. Simulations may be an option to demonstrate the operating characteristics, e.g., type I error control, meet desired levels for the proposed study design.
4. Early communication with CVM is strongly encouraged.

APPENDIX A

EXAMPLE: SSR ADAPTIVE DESIGN WITH RANDOMIZATION BY SITE

Simple SSR Adaptation Example

- This is an example of simulation steps for a study with a binary endpoint (e.g., success or failure), randomization by site, and with one interim analysis (IA) for unblinded SSR.

Simulation Steps

Step 1: Data generation

Step 2: Interim analysis (IA)

- Step 2a: Criteria to determine when to perform IA
- Step 2b: Algorithm of SSR applied in IA

Step 3: Post-interim analysis decisions

Step 4: Computation of operating characteristics

Step 1: data generation

- The following key parameters should be provided:
  - Expected success rates for control and investigational veterinary product (IVP) across a reasonable wide range
  - Nuisance Parameters:
    - ❖Variance of site and site-by-treatment across a reasonable wide range
    - ❖Specify how each variance realization will be simulated
  - Covariates:
    - ❖Study covariate parameters within a reasonable range

Step 1a (cont.)

- In the data generation step, the statistical model should be specified.
  - Statistical model example for binary data (success vs. failure)
    - ❖Incorporate site and site-by-treatment variability
    - ❖Use logit scale to simulate data

Step 1b (cont.)

- In the data generation step, other critical simulation details should be provided:
  - Number of iterations per scenario (≥ 10,000)
  - Planned and maximum sample sizes
  - Randomization ratio
  - Number of sites and evaluable cases per site
  - The strategy for completing enrollment after IA
    - ❖Adding more sites and/or more subjects in existing sites
    - ❖Proportion of low vs. high enrollment sites

Step 1c (cont.)

- Recommended Elements
  - Simulate realistic enrollment to account for overrun:
    - ❖Associate each enrollment sample with:
      - ➢ Enrollment time
      - ➢ Time to primary endpoint assessment
      - ➢ Overall time to endpoint evaluation

Step 2

- Step 2a: Criteria to determine interim analysis (IA) timing
  - Perform IA when a certain proportion of planned samples have completed the primary endpoint assessment
  - Consider the number of sites eligible for IA analysis

Step 2 (cont.)

- Step 2b: Algorithm of SSR at IA
  - The statistical model used at IA
  - The test statistic used for SSR calculation
  - The method to determine SSR (e.g., conditional power, predictive probability, etc.)

Step 3

- Possible Actions
  - Stop for futility
  - Continue to planned sample size
  - Continue to updated sample size

Step 3a (cont.)

- Stop for futility
  - Futility Criteria
    - ❖Binding futility
      - ➢ The study should always stop if the futility criteria are met.
      - ➢ The clinical study must follow the same rule if binding futility is used in the simulation

Step 3b (cont.)

- Stop for futility (cont.)
  - Futility Criteria (cont.)
    - ❖Non-binding futility
      - ➢ The futility stopping criteria are guidelines that may or may not be followed.
      - ➢ Futility stop will not be implemented in the simulation to assure the simulated type I error rate represents the largest rejection rate under the null, overall possible design modifications.
  - Recommendation
    - ❖Use non-binding futility for broader applicability

Step 3: Post-Interim Analysis Decisions

- Possible Actions
  - Stop for futility
  - Continue to planned sample size
  - Continue to updated sample size
- Final Analysis
  - Specify the statistical model to be used

Step 4

- Post-Simulation Analysis
  - Specify the method for computing operating characteristics
- Key Metrics
  - **Alpha Level:** Define the significance threshold
  - **Overall Type 1 Error Rate:** Calculate error rates
  - **Power Estimates:** Determine the study's power

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Thank you!


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Q&A for Afternoon Session

Walt Ellenberg & CVM Panel

Closing Remarks

- Slides and Video will be available online and, in the Docket,
- Questions received during this meeting will be submitted to the Docket
- Additional questions may be submitted to the Docket
- Video recording from 2024 is available via: CVM Public Meeting: First Annual Animal Drug User Fee Educational Conference - 07/17/2024 | FDA
- Thank you for your participation


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