U.S. FOOD & DRUG ADMINISTRATION

Third Annual Animal Drug User Fee Educational Conference:

Public Meeting

July 7, 2026
Docket No. FDA-2024-N-2602

Opening Remarks and Meeting Overview

Krystyna Reign, MBA, DCPM

Moderator

Branch Chief, Project Management Branch
Division of Business Information Science and Management
Center for Veterinary Medicine

Points to Consider

- MS Teams Webinar platform chat, cameras, and microphones are disabled
- Agenda timeline to be followed as closely as possible
- All in-person attendees to wear a name tag
- Refreshments are available at Café Mack (outside the Wiley building)

Points to Consider (cont.)

- Meeting materials will be available:
  - Event page: https://www.fda.gov/animal-veterinary/news-events/workshops-conferences-meetings
  - Docket: FDA-2024-N-2602 at www.regulations.gov

Agenda

Start Time	Presentations
8:00 a.m.	Registration
9:00 a.m.	Opening Remarks & Meeting Logistics
9:05 a.m.	Welcome
9:15 a.m.	Overview of Regulatory Pathways
9:30 a.m.	Indexing for Minor Use/Minor Species (MUMS) & Conditional Approval (CA)
10:05 a.m.	Expanded Conditional Approval (XCA) & Reasonable Expectation of Effectiveness (RXE)
10:35 a.m.	Break (10 min)
10:45 a.m.	Real World Example of Regulatory Flexibility During a Public Health Emergency
11:00 a.m.	Animal Biotechnology Products & the Veterinary Innovation Program (VIP)
11:35 a.m.	Protocol Quality & Best Practices
12:20 p.m.	Break (10 min)
12:30 p.m.	Q&A Session (20 min)
12:50 p.m.	Closing Remarks
1:00 p.m.	Conference Adjourns

Q&A Format

- Q&A panel session to begin at approximately 12:30 PM and answer questions as time allows
- Attendees may submit questions via the QR code until 12:10 PM
- All questions are anonymous
- All other questions will be retained and submitted to the Docket for consideration at future meetings

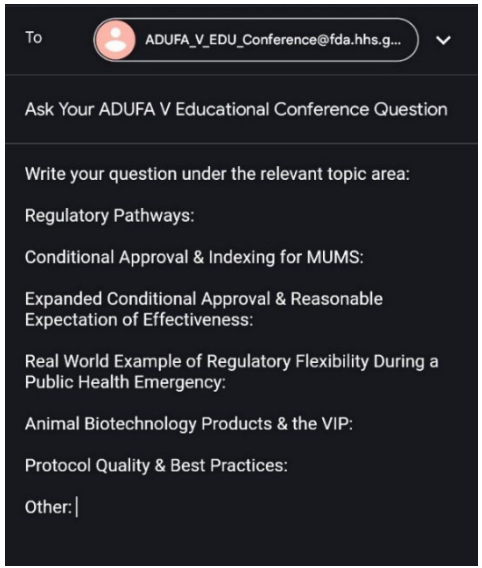
Questions?

- **Scan the QR Code or send an email to**

  ADUFA_V_EDU_Conference@fda.hhs.gov

Submitting Questions Via Email

Attendees can ask questions either by scanning the QR code or by sending an email to: ADUFA_V_EDU_Conference@fda.hhs.gov



When submitting questions via email, please indicate the relevant topic area.

Welcome

Dr. Timothy Schell

Director

Center for Veterinary Medicine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Overview: Regulatory Pathways

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July 7, 2026

Regulatory Pathways

- Indexing
- Conditional Approval
  - Minor Use in a Major Species and Minor Species (MUMS)
  - Expanded Conditional Approval (XCA)
- Veterinary Innovation Program (VIP)
- Priority Zoonotic Animal Drug (PZAD) Designation
- Emergency Use Authorization (EUA)

Conditional Approval

- Available for:
  - Minor Use in a Major Species and Minor Species (MUMS) indications
  - Expanded Conditional Approval (XCA) for certain non-MUMS indications
- All technical sections completed to the full approval standard except Effectiveness
  - Reasonable expectation of effectiveness (RXE) rather than substantial evidence of effectiveness (SEE)
- Conditional approval is valid for 1 year; can be renewed for up to 4 additional 1-year terms while working to complete SEE

Veterinary Innovation Program (VIP)

- Available to developers of IGAs (intentional genomic alterations) in animals, ACTPs (animal cells, tissues, and cell- and tissue-based products), and gene-therapy products
- Benefits:
  - Increased communication
  - Stop the clock

Priority Zoonotic Animal Drug (PZAD) Designation

- PZAD designation must meet two criteria:
  1. Does the new animal drug have the potential to prevent or treat a zoonotic disease in animals, including a vector-borne disease?
  2. Does the zoonotic disease have the potential to cause serious adverse health consequences for, or serious or life-threatening disease in, humans as defined in 21CFR 312.300(b)(1)?
- After receiving designation:
  - All subsequent submissions are afforded expedited review
  - Stop the clock
  - Pre- and post-review feedback

Emergency Use Authorization (EUA)

- Only authorized temporarily for public health emergencies by HHS Secretary
- Main benefit - Emergency use of certain unapproved new animal drug products and unapproved uses of approved new animal drug products
- Legal standards differ for EUAs than product approvals
- Benefits may include:
  - Increased communication
  - Modified CVM review timelines

References

- Guidance for Industry (GFI) #61, Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species
- GFI #261, Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs
- GFI #283, Priority Zoonotic Animal Drug Designation and Review Process
- VIP website: https://www.fda.gov/animal-veterinary/development-approval-process/vip-veterinary-innovation-program

Thank You!


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Indexing Program:

An Alternative Legal Marketing Pathway for Animal Drugs for Minor Species

Lucy Lee DVM, MPH
Office of Minor Use and Minor Species Animal Drug Development (OMUMS)
CVM | U.S. FDA
July 7, 2026

Learning Objectives

- ❑ Define major and minor species
- ❑ Understand what indexing is and why it exists
- ❑ Understand the steps to get a drug indexed
- ❑ Identify an indexed drug product on the market
- ❑ Understand the similarities between legal marketing statuses
- ❑ Know what resources are available for information and how to contact us

Definitions

- **Major Species -** cattle, pigs, chickens, turkeys, dogs, cats, and horses
- **Minor Species -** all animals (other than humans) that are not major species
- **Minor Use -** The intended use of a drug in a major species for an indication that occurs infrequently or in limited geographic areas and in only a small number of animals annually in the United States

The Minor Use & Minor Species Animal Health Act of 2004

- Establishes an Office to oversee the development of MUMS drugs.
  - **OMUMS**
- Provides incentives to encourage drug approval.
  - **Designation Program**
- Allows early marketing to recoup investment costs.
  - **MUMS Conditional Approval Pathway**
- Provides an alternate legal pathway to market drugs for certain minor species.
  - **Indexing Program**

OMUMS Mission

To improve access to safe and effective animal drugs for all underserved animal populations

What is indexing?

- It is an alternative to the FDA drug approval process.
  - For non-food minor species only
  - Target animal safety and effectiveness via risk-benefit analysis by an outside expert panel
- It provides a legal marketing status in the U.S.
- It is not an FDA approved drug.
- A 3-step process:
  - Step 1- Submit a request for determination of eligibility
  - Step 2- Submit information for the outside expert panel
  - Step 3- Submit a request for addition to the Index

What is the Index?

- "The Index" stands for **The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species**
  - A list of indexed drugs
  - An index listing refers to each indexed drug entry on the Index
- FDA website: https://www.fda.gov/animal-veterinary/minor-useminor-species/index-legally-marketed-unapproved-new-animal-drugs-minor-species

A Step-By-Step Guide – Using a Fictional Example

- Name of the drug company: Pharmazoo
- Active ingredient: hippodrug
- Name of drug: ZooMed (hippodrug injectable solution)
- Indication: For the treatment of excessive drooling
- Species: Hippotomuses
- Route of administration: Intramuscular

Pre-Submission Meeting

- Optional, but highly recommended
- Indexing regulations: 21 CFR Part 516 Subpart C
- CVM #201 Small Entity Compliance Guide for The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species

- ✓ **<u>Step 1</u>:** Submit a request for determination of eligibility for indexing (21 CFR 516.129)

Your request should provide information to address each of the following criteria:

1) Identification of the minor species or groups of minor species for which the new animal drug is intended;
2) Information regarding drug components and composition;
3) A statement of the intended use(s) of the new animal drug in the identified minor species or groups of minor species;
4) A statement of the conditions of use associated with the stated intended use(s) of the new animal drug, including the proposed dosage, route of administration, contraindications, warnings, and any other significant limitations associated with the intended use(s) of the new animal drug;
5) A brief discussion of the need for the new animal drug for the intended use(s);
6) An estimate of the anticipated annual distribution of the new animal drug, in terms of the total quantity of active ingredient, after indexing;
7) Information to establish that the new animal drug is intended for use:
   (i) in a minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food-producing animals; or
   (ii) in a hatchery, tank, pond, or other similar contained man-made structure in an early non-food life stage of a food-producing minor species, and information to demonstrate food safety in accordance with the standards of section 512(d) of the FD&C Act and 21 CFR 514.111 (including, for an antimicrobial new animal drug, with respect to antimicrobial resistance);
8) A description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of the new animal drug sufficient to demonstrate that the requestor has established appropriate specifications for the manufacture and control of the new animal drug and that the requestor has an understanding of current good manufacturing practices (CGMPs);
9) Either a claim for categorical exclusion under 21 CFR 25.30 or 25.33 or an environmental assessment (EA) under 21 CFR 25.40;
10) Information sufficient to support the conclusion that the new animal drug is safe under section 512(d) of the FD&C Act with respect to individuals exposed to the new animal drug through its manufacture and use; and
11) The name and address of the contact person or permanent resident U.S. agent.

Summary of Step 1

- Provide basic information about the drug
- Propose the target animals or groups of animals State the intended use of the drug in those animals
- Provide a summary of the manufacturing process
- Address environmental safety and human user safety
- Include contact information

- ✓ **Step 2**: Propose a qualified outside expert panel that will review target animal safety and effectiveness information (21 CFR 516.141)

Information regarding your selection of the qualified outside expert panel should include:

- Propose a list of at least three panel members.
- A curriculum vitae (CV) or similar document for each of the panel members.
  - Ensure the panel, as a whole, is qualified by training and experience to review all available target animal safety and effectiveness information for the proposed intended use.
- Conflict of interest information for each panel member.
  - Panel members cannot be an employee of the FDA and must not have a financial conflict of interest (or an appearance of a conflict of interest).

- ✓ **Step 3**: Submit a request for addition to the Index (21 CFR 516.145)

Your request for the addition of a new animal drug to the Index should provide information to address each of the following requirements:

1) A copy of FDA's determination of eligibility issued under 21 CFR 516.137;
2) A copy of FDA's written determination that the proposed qualified expert panel meets the selection criteria provided for in 21 CFR 516.141(b);
3) A written report that meets the requirements of 21 CFR 516.143;
4) A proposed index entry that contains the information described in 21 CFR 516.157;
5) Proposed labeling, including representative labeling proposed to be used for Type B and Type C medicated feeds if the drug is intended for use in the manufacture of medicated feeds;
6) Anticipated annual distribution of the new animal drug, in terms of the total quantity of active ingredient, after indexing;
7) A written commitment to manufacture the new animal drug and animal feeds bearing or containing such new animal drug according to current good manufacturing practices;
8) A written commitment to label, distribute and promote the new animal drug only in accordance with the index entry;
9) The name and address of the contact person or permanent-resident U.S. agent; and
10) A draft FOI summary which includes the following information:
    i. A general information section that contains the name and address of the requestor and a description of the drug, route of administration, indications, and recommended dosage;
    ii. A list of the names and affiliations of the members of the qualified expert panel, not including their addresses or contact information;
    iii. A summary of the findings of the qualified expert panel concerning the target animal safety and effectiveness of the drug;
    iv. Citations of all publicly-available literature considered by the expert panel;
    v. For an early non-food life stage of a food-producing minor species animal, a human food safety summary.

Summary of Step 3

- Provide the qualified expert panel's final written report
- Propose draft labeling
- Signed commitment to manufacture the drug product according to current good manufacturing practices
- Signed commitment to label, distribute, and promote the new animal drug only in accordance with the index listing
- Submit a draft Freedom of Information (FOI) Summary
- Include contact information

Example - ZooMed is now an indexed drug…

- Add ZooMed to the Index on the FDA website
  - The index listing will include basic information about the company, the drug, the date of entry, and a copy of the Freedom of Information (FOI) summary and drug product labeling.
- ZooMed can now be legally marketed in the U.S. based on the index listing.

What's next?

- Post-market Requirements (21 CFR 516.165)
  - Report Adverse Drug Events
  - Annual Drug Experience Report
- Promote and advertise in accordance with the Index listing
  - Extra-label drug use is prohibited for indexed drugs
- If the same drug, in the same dosage form, for the same intended use is FDA approved, the Index listing must be removed (21 CFR 516.167)

How to Recognize Indexed Drugs

- Drug label includes a 6-digit Minor Species Index File (MIF) number.
  - Example: "MIF 900-0XX"
- Drug label includes required labeling statements regarding the legal marketed status.
  - “LEGAL STATUS—In order to be legally marketed, a new animal drug intended for a minor species must be Approved, Conditionally Approved, or Indexed by the Food and Drug Administration. THIS PRODUCT IS INDEXED—MIF #. Extra-label use is prohibited.”

Similarities Between the Legal Marketing Statuses

- All:
  - Go through a pre-market process that includes FDA review of information related to the safety, effectiveness, and manufacturing
  - Are monitored by the FDA once drugs are marketed
    - Approved drugs: inspection, annual reports, promotion, and advertising
    - Conditional approval: annual renewal process
    - Indexed drugs: eligible for inspection, annual reports, promotion, and advertising
  - Report adverse drug events electronically at https://www.fda.gov/animal-veterinary/report-problem/how-report-animal-drug-and-device-side-effects-and-product-problems

Additional Resources and When to Contact Us

- Indexing regulations: 21 CFR Part 516 Subpart C
- GFI #201 SECG for The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species
- For general information about indexing, please visit the FDA website: https://www.fda.gov/animal-veterinary/minor-useminor-species/drug-indexing
- For any questions, please contact us: AskCVM@fda.hhs.gov.


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Conditional Approval

Understanding the Basics and Strategic Advantages

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July 7, 2026

Legal Authority

Federal Food, Drug, and Cosmetic Act (FD&C Act)
Section 571

- MUMS Conditional Approval (2004)
  - Minor Uses in major species
  - Use in Minor Species

- Expanded Conditional Approval- XCA (2018)

What is NOT Eligible?

A product cannot receive conditional approval if:

- It is contained in, or is a product of, a transgenic animal
- The sponsor previously filed a conditional approval application for a product with the same drug, dosage form, and intended use (whether or not conditionally approved)
- The sponsor obtained the application or data from someone who previously filed for conditional approval of the same drug, dosage form, and intended use
- **For XCA pathway only:** The product contains an antimicrobial active ingredient

Additional Eligibility Consideration

Existing Approved Products:

An application for conditional approval will be denied if another product with the same drug, dosage form, and intended use has already been approved

UNLESS the conditional approval applicant can demonstrate that the sponsor of the approved product is unable to assure availability of sufficient quantities to meet market needs.

Example Scenarios for Conditional Approval

- Product addresses an unmet animal or human health need
- Drug is intended to address an emerging disease situation
- Preliminary data demonstrates promise, but pivotal studies are needed

More Time for Effectiveness Studies

For example, if…

- Long-term effectiveness studies would delay access to the drug
- Field effectiveness studies require multiple seasons/production cycles
- Technical or biological barriers to completing effectiveness studies

Additional Development Advantages

- Flexibility in study design and timing

  E.g., Real-world data collection during conditional period
- Ability to refine product labeling based on field experience
- Maintains development momentum

Business Advantages

Commercial Benefits may include…

- Earlier market entry - potentially years ahead of full approval
- Revenue generation supports continued development costs
- Competitive positioning in marketplace
- Establishes market presence and brand recognition
- Additional incentives for MUMS

MUMS Incentives

- Eligible for waivers from user fees
  - Application fee (for MUMS indication)
  - Product and establishment fees (for products marketed solely for MUMS indications)
- With MUMS Designation:
  - 7 years of exclusive marketing rights upon conditional approval
  - Eligibility for MUMS grant program to support development costs

Minor Species

Why Conditional Approval is Ideal:

- Small patient populations may require multiple years to gather a robust data set
- Critical therapeutic gaps in minor species can be alleviated during product development

Minor Use in Major Species

Strategic Opportunities:

- Uncommon diseases in cattle, swine, poultry, horses, dogs, cats
- Regional or seasonal disease challenges
- Emerging diseases with limited prevalence
- Specific life stages or production phases

Conditional Approval Requirements

- **Reasonable expectation of effectiveness**
- Target animal safety
- Chemistry, manufacturing, and controls
- Environmental impact
- Human food safety (for food-producing species)
- Labeling and all other information

Reasonable Expectation of Effectiveness (RXE)

- RXE may include:
  - pilot studies in the target species,
  - studies in the published literature,
  - foreign studies, or
  - extrapolation of data from effectiveness studies for other similar species, related diseases, or related dosage forms.
- The legal requirements for demonstrating RXE are found in section 571(a)(2)(B) of the FD&C Act.
- Evidence to support RXE may include studies that also contribute to substantial evidence of effectiveness that is required for full approval. (See GFI #61)

Timeline for Full NADA Completion

- Full NADA must (by statute) be submitted no later than 180 days prior to the termination date of the last conditional approval period
  - ~4.5 years from the date CA was granted
  - This applies even for administrative NADAs

- The CA will be terminated if substantial evidence of effectiveness is not demonstrated within the time frame mandated

Resources and Next Steps

Available Support:

- Office of New Product Evaluation Project Managers
- Pre-submission Conference with CVM
- Office of Minor Use and Minor Species Animal Drug Development
- MUMS Designation (if applicable)
- Guidance for Industry #61 (MUMS)
- Guidance for Industry #261 (XCA)

Additional Resources

- Section 571 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- P&P 1243.5704: Process for Eligible Sponsors to Obtain Conditional Approval
- P&P 1243.5706: Meeting to Discuss Post-Approval Responsibilities for Sponsors of Conditional Approvals
- P&P 1243.5708: Procedure for Sponsors to Maintain Conditionally Approved Products and Obtain Full Approval
- CVM webpage “Conditional Approval Explained: A Resource for Veterinarians”

Expanded Conditional Approval and Reasonable Expectation of Effectiveness

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July 7, 2026

Expanded Conditional Approval

- In 2004, the Minor Use and Minor Species (MUMS) Animal Health Act was enacted, allowing for the conditional approval (CA) of drugs intended for use in minor species or minor uses in major species.
- In 2018, the reauthorization of the Animal Drug User Fee Act (ADUFA) also amended section 571 of the Federal Food, Drug, and Cosmetic Act to expand eligibility of conditional approval to include certain non-MUMS products.
- Guidance for Industry (GFI) Documents:
  - GFI #61: Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species
  - GFI #261: Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs

Eligibility for Expanded CA

Serious or life-threatening disease or condition **OR** **Unmet animal or human health need**

- A disease or condition associated with mortality or morbidity that has substantial impact on day-to-day functioning in the target animal; or
- A zoonotic disease or condition in animals and that presents a risk of a serious or life-threatening disease or condition to human beings; or
- A disease or condition that causes wide-spread morbidity in food-producing animals that presents a risk of regional or national disruption to food production.

- A disease or condition whose treatment, control, or prevention is not adequately addressed by *available therapy.*
  - Available therapy does not exist for the same intended use proposed for the drug, or
  - The drug is reasonably expected to provide a *meaningful advantage* over available therapy.
- This is a disease or condition that affects individual or defined groups of animals or humans, or a condition that more broadly affects animal or human health.

Note: Transgenic animals and drugs containing an antimicrobial active ingredient are not eligible for expanded conditional approval.

Eligibility for Expanded CA pt. 2

Complex or particularly difficult study or studies

a. The nature of the disease or condition makes it unusually difficult to enroll enough animals.

b. The need for an unusually large number of animals or the need for use of advanced or complicated tests.

c. It is necessary to develop and qualify effectiveness endpoints (e.g., biomarkers).

d. The need to develop and validate or qualify novel methods to evaluate effectiveness (e.g., diagnostic tests).

e. The endpoint is a delay in progression of a chronically progressive disease or condition where the effectiveness evaluation will take an extended period of time (typically a year or more).

f. There is a need to evaluate the treatment of a disease or condition over an extended period time (typically a year or more).

g. The drug will be indicated for mitigating transmission of a zoonotic disease from animals to humans and it is necessary to conduct a study(ies) to evaluate the human aspect of effectiveness.

Determination of Eligibility

- G submission, subclass code “DE”.
- Eligibility is based on the **indication** and the **study design** to support substantial evidence of effectiveness (SEE).
  - CVM should agree to the indication prior to receipt of the DE submission.
  - Sponsor should have an idea of the general study design to support SEE.
  - Changes to the indication or study design affect eligibility.
- The submission should address how the proposed drug/indication qualify for expanded CA.
- The submission should identify the specific factors that make the study complex or particularly difficult.

Determination of Eligibility pt. 2

- Outcome of the submission:
  - Eligible or ineligible
  - Incomplete
- The study protocol and/or submitted data should be consistent with the conditions described in the DE submission.
- Eligibility is reassessed upon receipt of the conditional new animal drug application.

Expanded CA Products

App Number	Product	Indication/Species	Basis of Eligibility
141-567	PANOQUELL®-CA1 (fuzapladib sodium for injection)	For the management of clinical signs associated with acute onset of pancreatitis in dogs.	Serious and life-threatening, unmet need. Difficulty in diagnosing the disease.
141-571	Varenzin™-CA1 (molidustat oral suspension)	For the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats.	Serious and life-threatening, unmet need. Long study duration to establish effectiveness.
141-577	UpCard®-CA1 (torsemide oral solution)	For use with concurrent therapy with pimobendan, spironolactone, and an angiotensin converting enzyme (ACE) inhibitor for the management of pulmonary edema in dogs with congestive heart failure caused by myxomatous mitral valve disease (MMVD).	Serious and life-threatening. Diagnosis of the disease requires the use of advanced and complicated tests.

Note: New world screwworm approvals will be discussed separately.

Expanded CA Products pt. 2

App Number	Product	Indication/Species	Basis of Eligibility
141-578	FIDOQUEL™-CA1 (phenobarbital tablets)	For the control of seizures associated with idiopathic epilepsy in dogs.	Serious and life-threatening, unmet need. Unpredictability of the occurrence or outcome of the disease, and the need for use of advanced or complicated tests.
141-604	felycin®-CA1 (sirolimus delayed-release tablets)	For the management of ventricular hypertrophy in cats with subclinical hypertrophic cardiomyopathy (HCM).	Serious and life-threatening, unmet need. Nature of the disease or condition makes it unusually time consuming or difficult to enroll sufficient numbers of eligible animals and requires the use of advanced diagnostic tests.

Refer to the Freedom of Information Summaries found in the Animal Drugs @ FDA Database.

https://animaldrugsatfda.fda.gov/adafda/views/#/search

Fully Approved Expanded CA Products

App Number	Product	Indication/Species	Basis of Eligibility
141-273 (141-556)	Vetmedin® (pimobendan)	For the delay of onset of congestive heart failure in dogs with Stage B2 preclinical myxomatous mitral valve disease.	Serious and life-threatening, unmet need. Long study duration to establish effectiveness.
141-615 (141-544)	KBroVet® (potassium bromide chewable tablets)	For the control of seizures associated with idiopathic epilepsy in dogs.	Serious and life-threatening, unmet need. Unpredictability of the occurrence or outcome of the disease, and the need for use of advanced or complicated tests to diagnose idiopathic epilepsy.

Reasonable Expectation of Effectiveness

- Reasonable expectation of effectiveness (RXE) of the new animal drug for the proposed intended use may include pilot studies, published literature, foreign data, or data in other species or dosage forms.
- CVM will review the protocol for a prospective study used to support RXE.
- Evidence to support RXE may include studies that also contribute to SEE required for full approval.

RXE Examples

PANOQUELL®-CA1 (fuzapladib sodium for injection)

- Multi-site pilot field study in 61 client-owned dogs with acute onset pancreatitis.
- Dogs received either a non-final formulation of fuzapladib sodium (n=31) or vehicle control (n=30) by intravenous (IV) injection once daily for 3 days.
- The difference in group mean modified canine activity index (MCAI) scores between Day 0 and Day 3 was evaluated.
  - The MCAI score includes seven areas of clinical relevance to dogs with acute onset of pancreatitis: activity, appetite, vomiting, cranial abdominal pain, dehydration, stool consistency, and blood in the stool.
- On Day 3 of the study, the treatment group had an improved mean MCAI score compared to the control group.

RXE Examples pt.2

Varenzin™-CA1 (molidustat oral suspension)

- Multi-site pilot study in 21 client-owned cats with naturally occurring nonregenerative anemia associated with CKD.
  - Cats received either molidustat oral suspension (n=15) or a vehicle control (n=6) orally once per day for 28 days.
  - On Day 28, success was defined as either a relative increase in hematocrit (HCT) of > 25% above baseline or an absolute increase in HCT of ≥ 4% points above baseline.
  - Half of the cats (7/14; with 1 cat excluded) in the treatment group were considered successes compared to only 16.7% of control cats (1/6).
- Eight cats were enrolled in an 8-week continuation phase of the study.
- Using the same success criteria as that used during the effectiveness phase, most cats in the continuation phase were successes on Day 56 (75%; 6/8) and Day 84 (62.5%; 5/8).
- The margin of safety study (at 0.5 and 1X) and a pharmacokinetic/ pharmacodynamic study (at 1 and 2X) showed all cats had an increase in HCT, some of which were quite dramatic (HCT > 60%).
- In an interim safety analysis of the ongoing field effectiveness study, most cats in an unmasked phase of the study had an increase in HCT or PCV while on treatment and a decrease of HCT/PCV when off treatment.

RXE Examples pt.3

UpCard®-CA1 (torsemide oral solution)

- Multi-site European field study in client-owned dogs that had experienced at least one episode of pulmonary edema due to congestive heart failure (CHF).
- This study was used to support registration of a tablet formulation in Europe, and a subset of the effectiveness population was selected that met the inclusion criteria to support the proposed US indication.
- Dogs diagnosed with MMVD that were clinically stable and had received furosemide tablets twice daily for at least 10 days prior to Day 0 were included in the analysis for RXE.
- Starting on Day 0, dogs either continued with twice daily furosemide (n=36) tablets or were transitioned to torsemide tablets (n=25) once daily.
- Effectiveness was evaluated on Day 84. A dog was considered to have a successful response to treatment if pulmonary edema and/or pleural effusion or ascites had not worsened compared to Day 0.
- The success rates were 96.0% (24/25) for the torsemide group and 80.6% (29/36) for the furosemide group.

RXE Examples pt.4

FIDOQUEL™-CA1 (phenobarbital tablets)

- A systematic review of published literature was performed to evaluate and summarize the available information on the effectiveness of phenobarbital in dogs when used for controlling seizures associated with idiopathic epilepsy in dogs. Publications included:
  - Two current clinical consensus statements on seizure management in dogs, published by the American College of Veterinary Internal Medicine (ACVIM) and the International Veterinary Epilepsy Task Force.
  - Six published clinical studies, including four randomized, prospective, comparator studies in dogs with seizures.
- To bridge safety data from the published literature, FIDOQUEL™-CA1 was compared, and found to be similar, to the commercially available oral formulations of phenobarbital with qualitative and quantitative comparisons of the formulations and dissolution data.
- FIDOQUEL™-CA1 was determined to have comparable *in vivo* bioavailability and pharmacokinetic performance in dogs to the commercially available oral formulations of phenobarbital included in the published literature used to demonstrate safety.

RXE Examples pt.5

felycin®-CA1 (sirolimus delayed-release tablets)

- Two-site exploratory pilot field study in 43 client-owned cats with subclinical HCM with echocardiographic findings of left ventricular (LV) hypertrophy (maximum wall thickness ≥ 6 mm).
- Cats received felycin®-CA1 at 1X the label dose (n=15), felycin®-CA1 at 2X the label dose (n=15), or a placebo control tablet (n=13) orally once weekly for 180 days ± 10 days.
- An exploratory analysis was conducted and maximum wall thickness (MWT) of the LV on Day 180 was selected as the effectiveness endpoint.
- On Day 180, the MWT of the LV in cats in the 1X group decreased by a mean value of 0.17 mm compared to baseline. In contrast, the MWT increased by a mean value of 0.94 mm and 0.50 mm in the placebo group and the 2X group, respectively.

- Mouse Model Literature:
  - Two studies evaluated the effects of sirolimus when administered in a mouse model of hypertrophy.
  - Sirolimus delayed the development of hypertrophy when given prior to aortic banding and was associated with improvement of hypertrophy when given after aortic banding.
- Human Literature: A study in human transplant recipients showed greater improvement in patients receiving sirolimus in measures of hypertrophy.

XCA Full 512(b) Approvals

Vetmedin®

- Vetmedin® (pimobendan)
  - Approved on April 30, 2007 (NADA 141-273) for the management of the signs of mild, moderate, or severe congestive heart failure in dogs due to MMVD or dilated cardiomyopathy (DCM).
- Vetmedin®-CA1
  - CA on June 16, 2022 (application number 141-556) for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical myxomatous mitral valve disease (2019 ACVIM Consensus Statement).
- Vetmedin® supplemental application was approved on December 12, 2025

KBroVet®

- KBroVet®-CA1 (potassium bromide chewable tablets)
  - CA on January 14, 2021 (application number 141-544) for the control of seizures associated with idiopathic epilepsy in dogs
- KBroVet® NADA approved on January 9, 2026

Vetmedin®-CA1 RXE

- Evaluation of Pimobendan in Dogs with Cardiomegaly Caused by Preclinical Mitral Valve Disease – EPIC. (Study No. 2009045)
  - Long-term (over 4 years), multi-center international field study in client-owned dogs with cardiomegaly secondary to Stage B2 preclinical MMVD.
  - Dogs received either Vetmedin®-CA1 (n=182) or a vehicle control chewable tablet (n=181).
  - The primary endpoint was the development of left-sided congestive heart failure or death due to cardiac disease.
  - RXE was determined based on the length of time from first treatment to when the dog reached the primary endpoint.
  - The median time to the primary endpoint was 1,228 days in the Vetmedin®-CA1 group compared to 761 days in the control group, a difference of 467 days (15.6 months).

Vetmedin® SEE

- Study No. 2009045 (EPIC study) supported this indication when evaluated in conjunction with Study No. 2019035.
- A Pivotal, Clinical Field Study Evaluating the Effectiveness of Pimobendan in Delaying the Onset of Congestive Heart Failure (CHF) in Dogs with ACVIM Stage B2 MMVD. (Study No. 2019035)
  - A multi-site single-arm field study that enrolled a subset of dogs (n=161) with more advanced ACVIM Stage B2 preclinical MMVD (dogs with a left LA/Ao ratio ≥1.8).
  - All enrolled dogs were treated with Vetmedin® and the effectiveness of Vetmedin® was compared to a subset of the control group enrolled in Study No. 2009045 (EPIC Study) that met the enrollment criteria for Study No. 2019035.
  - The primary endpoint was treatment success at 365 days, defined as the absence of radiographic evidence of CHF and no significant progression of clinical signs requiring additional therapy.
  - Of the 125 dogs, 99 (79.2%) successfully completed the study without disease progression, while 26 were classified as treatment failures due to developing CHF, cardiac-related death, or other advancing clinical signs.
  - The study's success criteria were met, as the lower bound of the 95% confidence interval for the success rate (70.3%) was well above the pre-specified threshold of 54%.

KBroVet®-CA1 RXE

- RXE was supported by real world data (RWD), including a retrospective evaluation of medical records of client-owned dogs that were previously treated with potassium bromide (KBr) to control their idiopathic epilepsy.
- To be included, the dogs must have received only KBr to control their seizures at the same daily dose for at least 60 days.
- Fifty-one eligible cases were identified, with 27 cases included in the evaluation of both safety and effectiveness and 24 cases included only in the safety evaluation.
- Effectiveness was evaluated by comparing change in seizure counts, seizure event days per month, and seizure severity scores in the 30-day period before starting KBr therapy to a 30-day period of steady state KBr dosing.
- Descriptive statistics were used to characterize effectiveness outcomes, clinical findings, and adverse events (a hypothesis-based statistical analysis was not performed).
- Based on the effectiveness parameters, 67% (18/27 dogs) were treatment successes and 33% (9/27) were treatment failures.

KBroVet® SEE

- SEE was also supported by RWD, including the retrospective study used to support RXE, and an additional retrospective study that evaluated the medical records of an additional 46 client-owned dogs treated with KBr monotherapy for management of canine idiopathic epilepsy.
- Treatment success for an individual dog was defined as a 50% or greater reduction in seizure frequency measured during the 30-day period of steady state KBr dosing compared to the 30-day baseline period before initial treatment with KBr.
- Results of the study showed that compared to baseline, 40 out of 46 evaluable cases experienced at least a 50% reduction in seizure frequency.
- The retrospective study results were also used in conjunction with published literature to support the safety of KBroVet®.

Limitations

- Field Safety
  - In certain circumstances, CVM may need additional field safety information to issue a technical section complete for Target Animal Safety (e.g., Varenzin®-CA1).
- Final Formulation
  - For certain products, changes in manufacturing can result in major product differences; therefore, data to support RXE may need to be collected with the final formulation (e.g., monoclonal antibodies and gene therapy products).
- Timing
  - The full NADA must be submitted no later than 180 days prior to the end of the fifth year of the CA period.
  - Sponsors should plan accordingly to ensure that the study will be complete, and the data can be prepared for submission in time to prevent termination of the CA.


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Break (10 minutes)

Questions?

- Scan the QR Code or send an email to ADUFA_V_EDU_Conference@fda.hhs.gov

Real World Example of Regulatory Flexibility During a Public Health Emergency

Anna O'Brien, DVM
Division of Food Animal Drugs
Food Animal Branch 1
Office of New Animal Product Evaluation
CVM | U.S. FDA
July 7, 2026

First Animal Public Health Emergency

- On August 18, 2025, the U.S. Department of Health and Human Services (HHS) declared a public health emergency regarding New World Screwworm (NWS), due to its potential threat to national security and animal health. This declaration enables the FDA to authorize emergency use of animal drugs (unapproved product or unapproved use of an approved product) to combat NWS myiasis, a parasitic infestation affecting livestock and pets.

Emergency Use Authorization (EUA)

Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that:
  - the product **may be effective** in diagnosing, preventing, or treating the serious or life-threatening disease or condition; and
  - the known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product; and
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

How We Used EUA

Product	Species
Credelio (lotilaner) chewable tablets	Dogs
Credelio CAT chewable tablets	Cats
Ivomec (ivermectin) injectable solution	Cattle
NexGard (afoxolaner) chewable tablets	Dogs
NexGard COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution)	Cats
F10 Antiseptic Wound Spray with Insecticide (benzalkonium chloride, polyhexanide and cypermethrin topical solution) and F10 ointment	Cattle, Horses, Minor Species of Hoof Stock, Raptors, Wild Birds, Pet Birds, Captive Wild, Exotic, and Zoo Mammals
Negasunt powder	Cattle, Swine, Goats, Sheep, Horses, Donkey, Domestic Hybrid Equids, Captive Wild, Exotic, and Zoo Mammals
Dectomax (doramectin) injection	Dairy Cattle, Horses, Swine, Sheep, Deer

Priority Zoonotic Animal Drug (PZAD) and Expanded Conditional Approval (XCA)

- GFI 283 Priority Zoonotic Animal Drug Designation and Review Process
- GFI 261 Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs

How We Used PZAD and XCA

Product	Species
Dectomax-CA1 (doramectin injection) injectable solution	Cattle
Exzolt Cattle-CA1 (fluralaner) topical solution	Cattle
Credelio Quattro-CA1 (lotilaner, moxidectin, praziquantel, pyrantel) chewable tablets	Dogs

New World Screwworm: Information for Veterinarians

New World Screwworm: Information for Veterinarians | FDA
https://www.fda.gov/animal-veterinary/safety-health/new-world-screwworm-information-veterinarians


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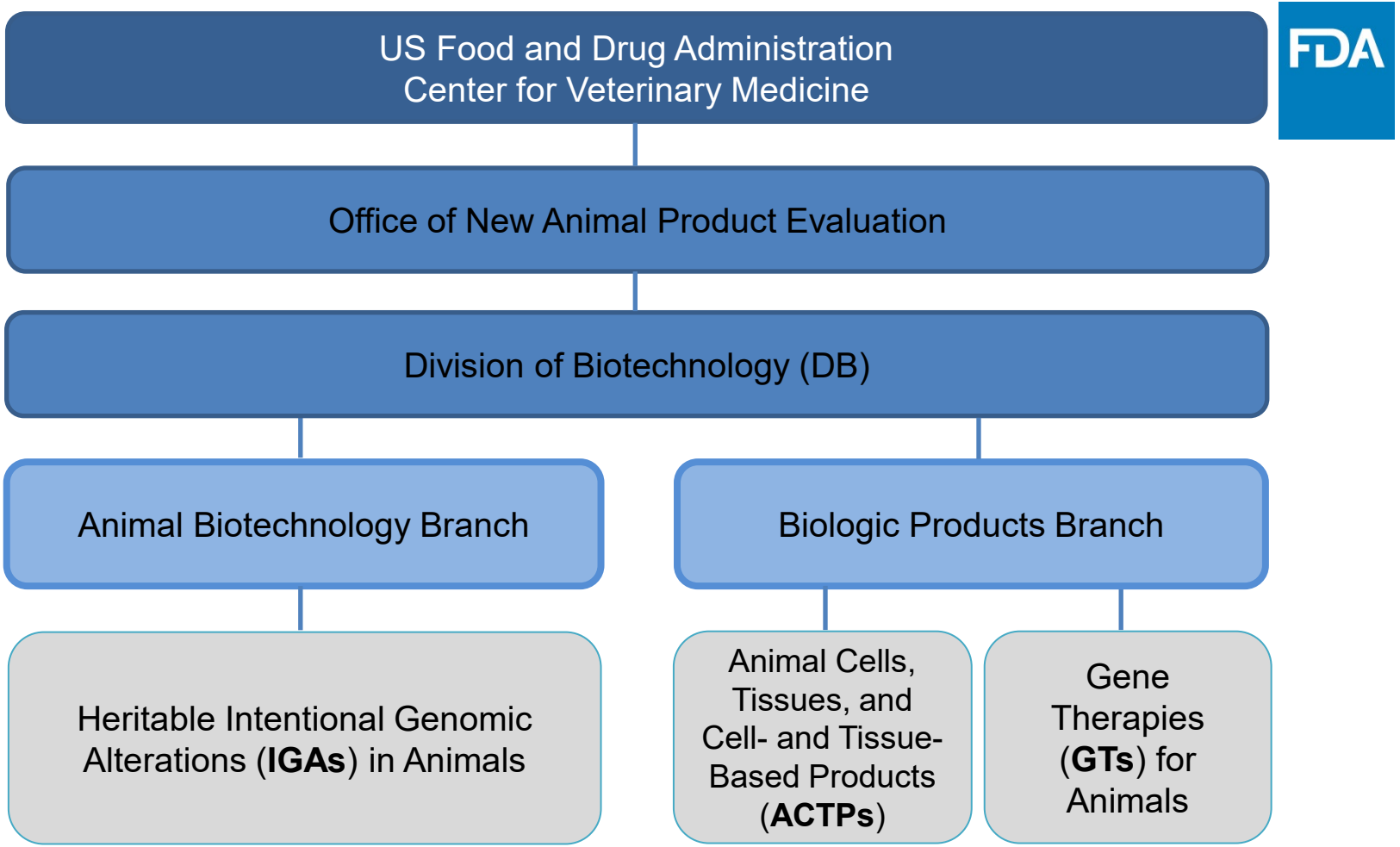
Animal Biotechnology Products and the Veterinary Innovation Program (VIP)

Carlo Mercado, PhD
Jennifer Peters-Hall, PhD
Office of New Animal Product Evaluation
CVM | U.S. FDA
July 7, 2026

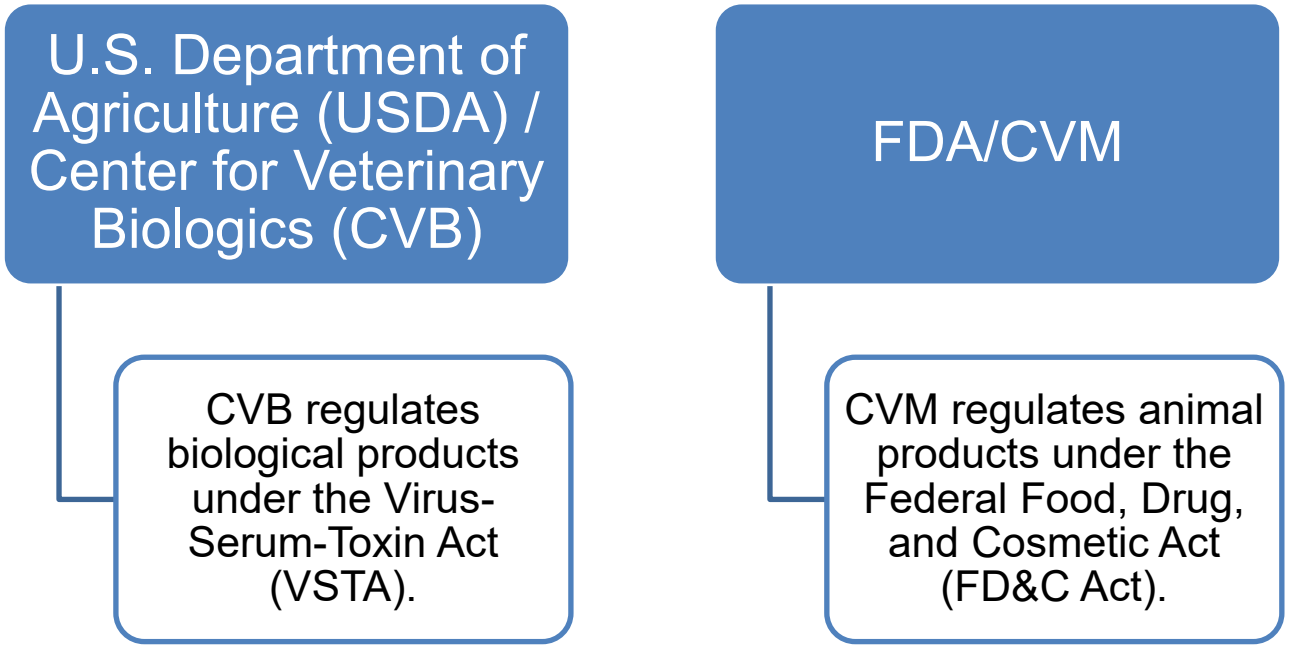
Overview

- **Introduction to Animal Biotechnology Products**

- **The Veterinary Innovation Program (VIP)**
  - Overview
  - Benefits
  - VIP in Action


US Food and Drug Administration
Center for Veterinary Medicine
Office of New Animal Product Evaluation
Division of Biotechnology (DB)
Animal Biotechnology Branch
Biologic Products Branch
Heritable Intentional Genomic Alterations (IGAs) in Animals
Animal Cells, Tissues, and Cell- and Tissue-Based Products (ACTPs)
Gene Therapies (GTs) for Animals

Regulation of Animal Biologicals

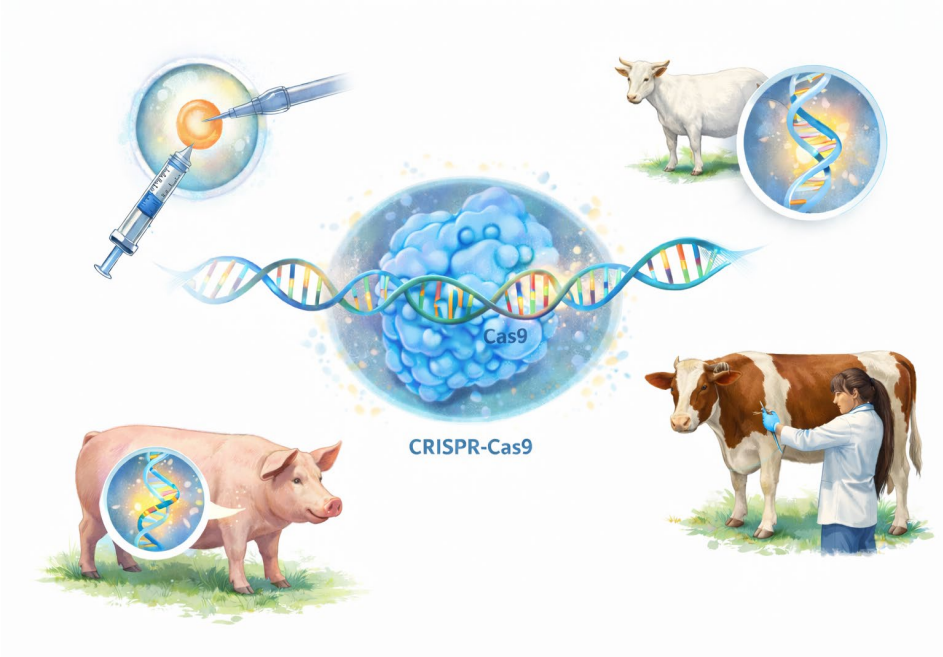


This presentation applies to products under FDA regulation.

What is an IGA?

- A **heritable** change introduced into the animal's genome using molecular technologies [e.g., recombinant DNA (rDNA), CRISPR-Cas, etc.].

- Includes random or targeted DNA sequence changes (e.g., nucleotide insertions, substitutions, or deletions) that are *inherited through the germline*.



What is an ACTP?

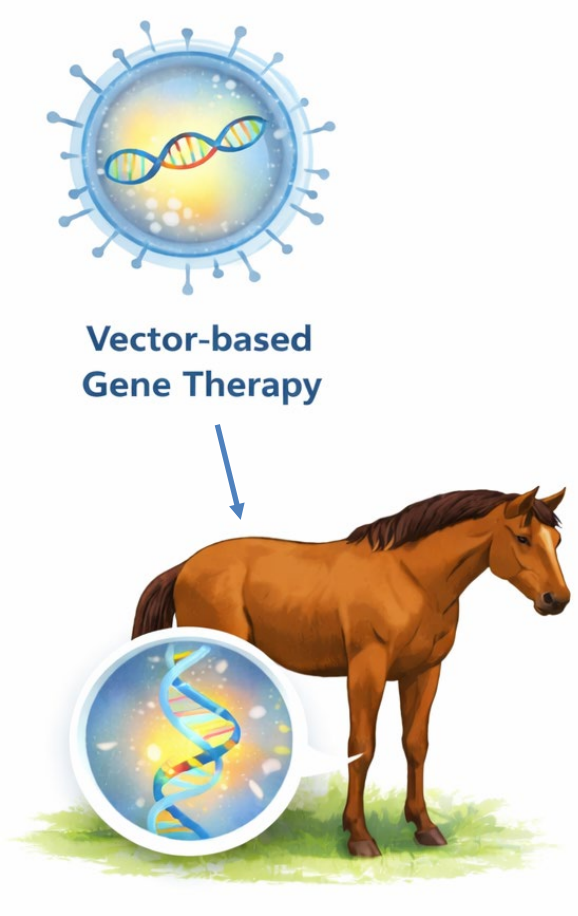
- Articles containing, consisting of, or derived from cells or tissues that are intended for implantation, transplantation, infusion, or transfer into an animal recipient.

- Includes mesenchymal stem cells, placental tissues, pancreatic islet cells, bone marrow, blood-derived products, etc.

What is a GT?

- A product intended to mediate a **non-heritable** genetic change, which modifies or manipulates the expression of a gene or alters the biological properties of living cells by introducing a new or modified gene.

- Includes nucleic acids (e.g., plasmids), genetically modified microorganisms (e.g., viruses, bacteria, fungi); *ex vivo* genetically modified cells, etc.



Potential Uses of Animal Biotechnology Products

Heritable IGAs in animals	ACTPs	GTs in animals
• 'Biopharm' animals • Improvements to agriculture • Human health claims	• Regenerative medicine • Restore lost function • Replace or repair damaged tissue	• Inactivating or replacing disease causing genes • Introducing a new or modified gene

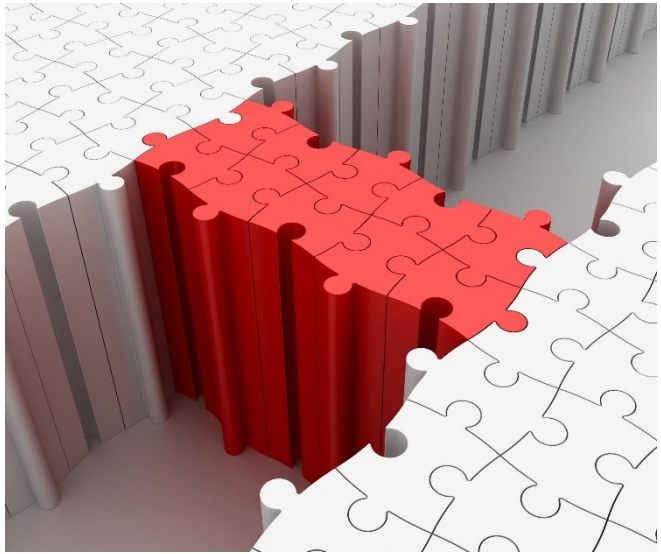
Oversight Objective

For FDA approval, developers of Animal Biotechnology products must demonstrate:

- **Safety** to the animal
- **Safety** to anyone that consumes food from the animal
- **Effectiveness** (product does what it is supposed to do)

Novel Scientific and Regulatory Questions

- Rapidly evolving scientific fields = Limited precedent and knowledge surrounding safety/effectiveness
- New segment of industry for developing novel classes of products



THE VETERINARY INNOVATION PROGRAM (VIP)

The **VIP** reflects CVM's commitment to supporting innovation in animal biotechnology.

(est. 2018)

FDA

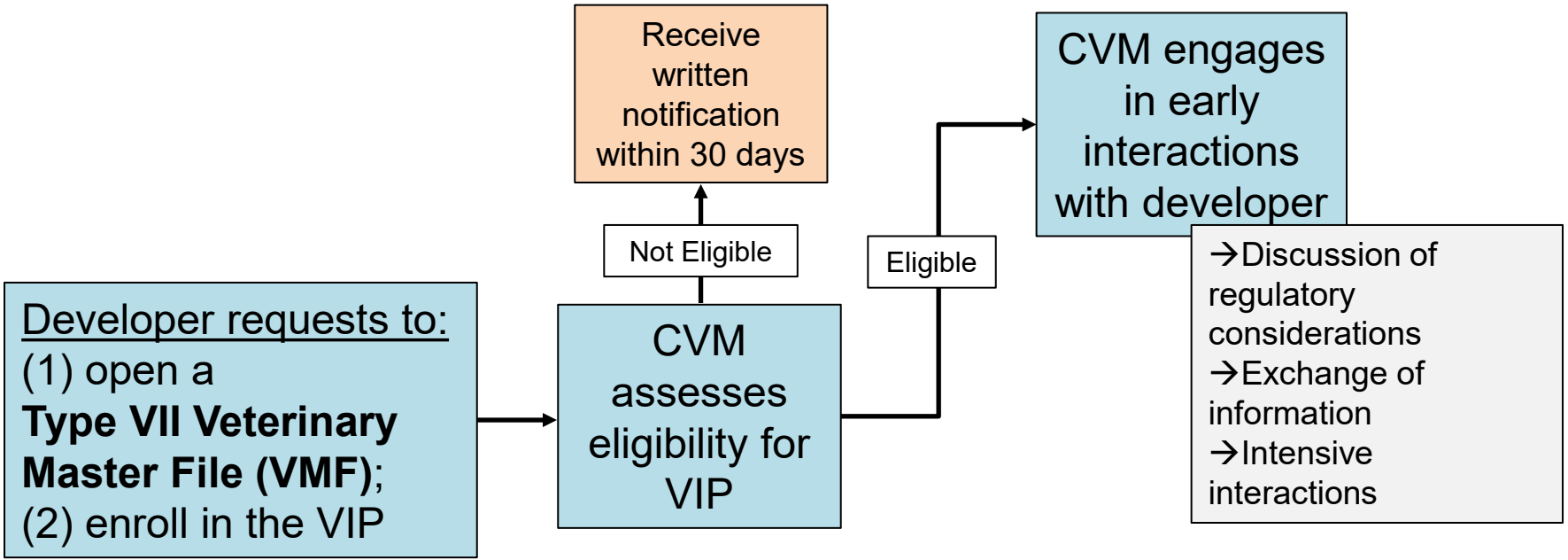
What products are eligible?

Available for animal biotechnology products (IGAs, ACTPs, GTs) that provide a benefit to human or animal health, food production, or animal well-being.

Purpose of the VIP

- Provide greater certainty in the regulatory process
- Encourage development and research
- Support an efficient pathway to market

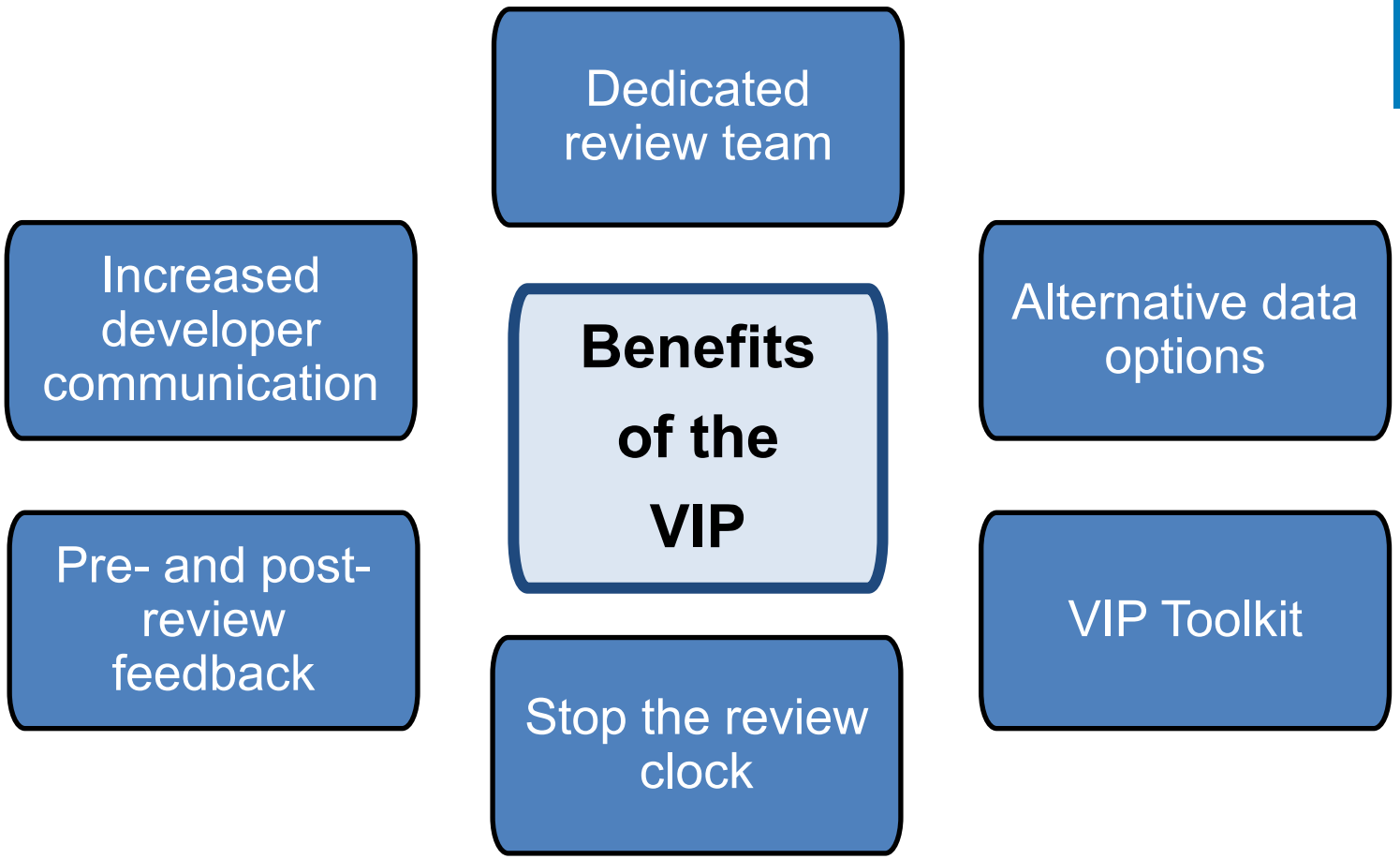
Early Interaction Workflow

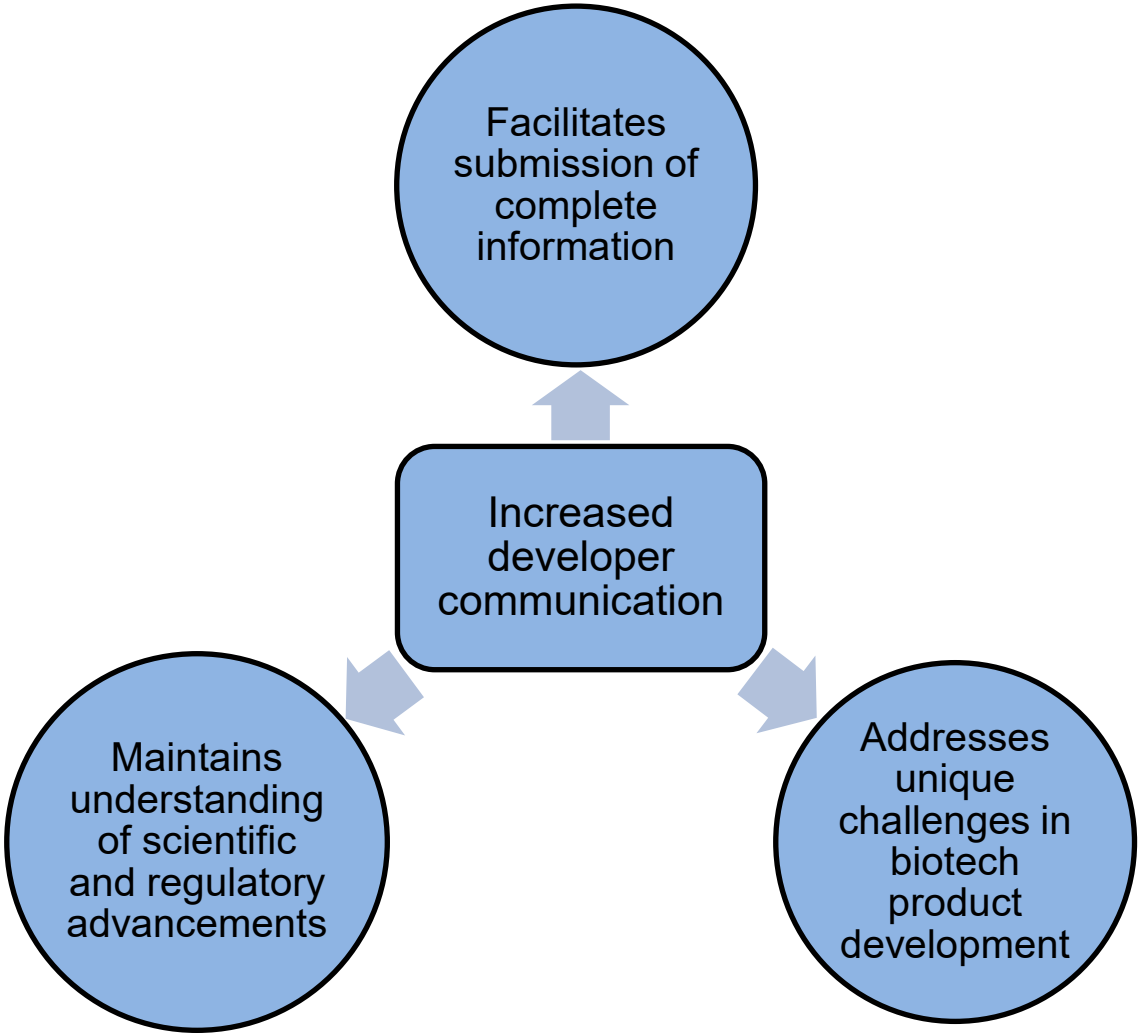


Type VII Veterinary Master File

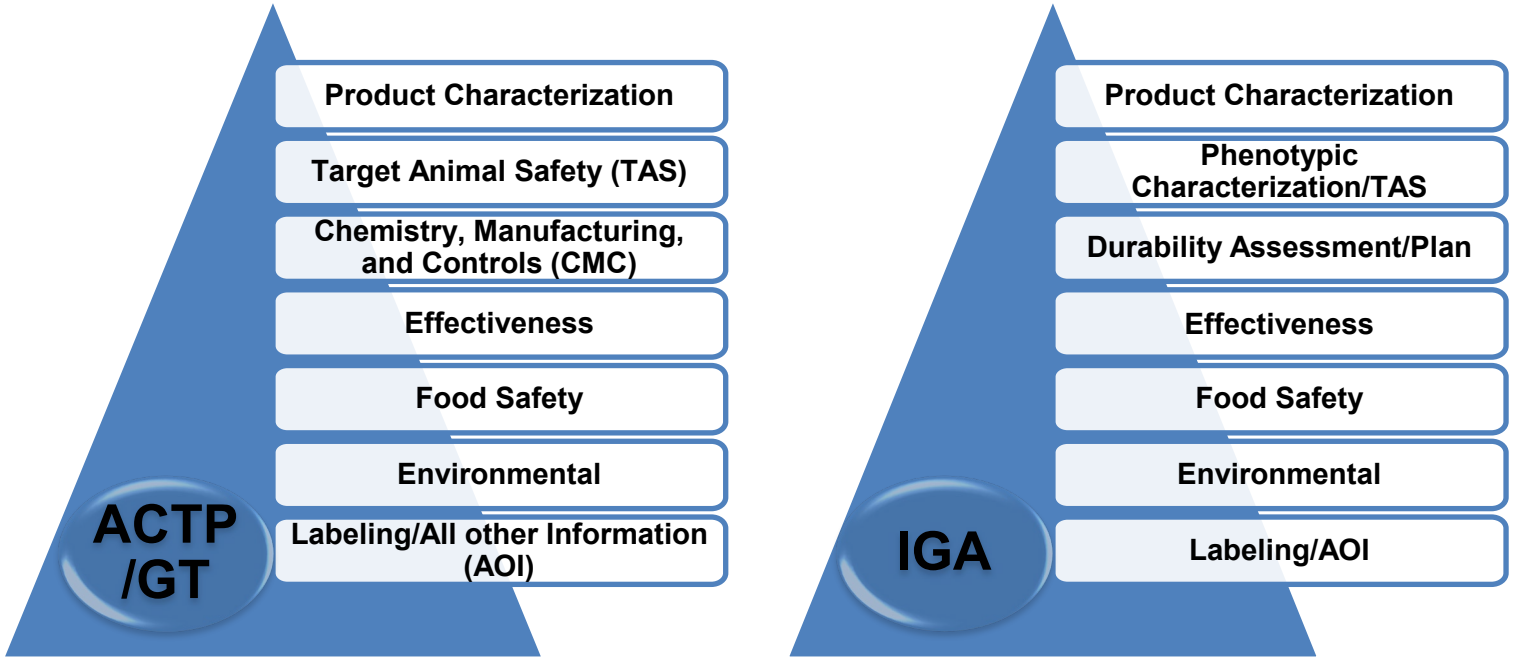
- Non-binding meetings
- Pre-investigational development (PID) information
- VIP aligns review times for early product development with the review times for similar activities under an investigational file (INAD)

Type VII VMF Submission Type	VIP Fast-Step Review Time	Non-VIP Review Time
Establishing a File (A-0000)	100 days	180 days
New Facility/Product	100 days	180 days
Shipment Notice	50 days	180 days
Reporting a New Study	50 days	180 days
Annual Report	100 days	180 days


Dedicated review team
Increased developer communication
Benefits of the VIP
Alternative data options
Pre- and post-review feedback
VIP Toolkit
Stop the review clock


Facilitates submission of complete information
Increased developer communication
Maintains understanding of scientific and regulatory advancements
Addresses unique challenges in biotech product development

Phased Review of Animal Biotechnology Products



Pre-Review Feedback

Informal high-level feedback on the organization and general contents of draft submissions.

Intended for…

- Outlines and table of contents
- Specific questions on examples of info to be included
- Examples of data presentation (formatting, level of detail, file format, etc.)
- Descriptions of methods for data analysis
- Identifying missing data or items requiring justification

Not intended for…

- Evaluation of entire submissions
- Questions on the acceptability of specific information
- Questions on the overall development plan
- Review of data

Post-Review Feedback

Feedback intended to clarify CVM letter comments.

Purpose

- Developer and CVM discuss letter comments
- Facilitate comprehensive response
- Highlight important issues and gain an understanding of product development challenges

Process

- Meeting shortly after incomplete letter is issued
- Entire review team participates
- Discussion limited to letter contents (i.e., new proposals or questions should be discussed in a separate meeting)

Stopping the Review Clock

- Where appropriate, CVM may stop the clock to provide preliminary feedback regarding incomplete or insufficient elements of a submission

- Goal is to decrease number of review cycles

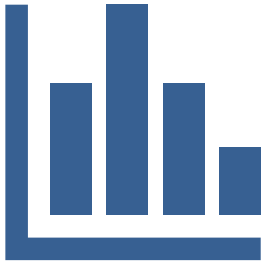
CVM considers whether the information requested…

1. can be generated in no more than 180 days;
2. can be reviewed within the remaining review time; and
3. could result in a complete submission (technical section or module)

Alternative Data Options

- Where appropriate, CVM may accept alternative strategies for generating data or the submission of different types of data

- CVM encourages developers to meet and discuss possible approaches to product-specific unique regulatory considerations



VIP and the Product Lifecycle for Approval

Pre-investigational development (PID):

- Developer requests to open a file and enroll in VIP
- CVM opens Type VII VMF
- Developer qualifies for VIP; receives ***VIP toolkit***
- CVM and developer engage in ***early interactions***

Investigational review:

- When ready, developer opens investigational (INAD) file
- Cross-disciplinary ***review team*** assembled
- Intensive interaction and review process benefits (***pre-*** and ***post-review feedback***; ***stop the clock***; ***alternative data options***)

Approval:

- CVM provides ***hands-on assistance*** with:

(1) Post-approval obligations (establishment registration, listing product)

(2) Other requirements (labeling, durability, comparability)

Sponsor requests approval of application (NADA)

Post-approval:

- CVM provides ***hands-on assistance*** with post-approval reporting (i.e., minor changes in stability, manufacturing changes, comparability, morbidity and mortality data, and adverse events)

How VIP Benefits Apply to the Approval Process

Developer Opens VMF or INAD File

Early Interactions

- PID Meetings
  - Discuss approval process
  - Discuss product-specific characterization and manufacturing

Pre-review Feedback

- Cross-disciplinary review team
- Provide high-level non-binding feedback on product development and submission drafts
- Written response or meeting response with meeting summary

Example Situations for Pre-review Feedback

- **Submission drafts:** technical section and module drafts, protocols, prior approval manufacturing supplements under an NADA

- **Discussions regarding product development:** e.g., identity/potency assays, reagents, study design, genome editing strategy, cloning/breeding strategy, off-target identification methods, alternative data options

Example Situations for Alternative Data Options

- Data to support multiple donors/cell lines in a single approval (e.g., single batches each from multiple donors/cell lines)
- Data to support multiple genetic alterations in a single approval (e.g., multiple combinations of gene knockouts for a xenotransplantation product)
- Data generated through collaboration across institutions (e.g., potency assay data generated from academic institution; validation data generated from contract research organization)
- Data from a limited number of animals (e.g., effectiveness study in laboratory animals vs. multi-site clinical field study) or generations/lineages of animals

How VIP Benefits Apply to the Approval Process

Sponsor Submits Data/Information to Support Approval

Review team convenes and meets up to 3 times to discuss acceptable/unacceptable items

If review team decides to stop the review clock, letter with unacceptable items transmitted to sponsor

Sponsor has up to 180 days to submit amendment in response to stop the clock letter comments

While review clock is stopped, sponsor can request a meeting or pre-review feedback

Review clock restarted when stop the clock amendment received, review team completes review, and transmits decision letter

For incomplete/unacceptable submissions, post-review feedback meeting may be offered to sponsor

Example Situations for Stop the Clock

Examples of information or data that can be generated while the clock is stopped:

- Additional data that address an issue AND can be generated in the 180-day resubmission timeframe (e.g., assay feasibility data, additional sequencing data)
- Draft a new proposal to address requested information (e.g., conduct a risk analysis, develop a new method to assess an aspect of donor eligibility)
- Address an inadequate method/assay validation (e.g., missing specific parameters, additional samples needed, etc.)

Current Biotech Approvals

Name	Traits	Purpose	Approval Date
AquAdvantage Atlantic Salmon	IGA results in Atlantic salmon that reach market size more quickly than non-IGA farm-raised Atlantic salmon	Food	**2015**
SBC LAL-C Chicken	IGA produces a recombinant form of human lysosomal acid lipase protein in egg whites for treatment of patients with lysosomal lipase deficiency	Biopharm	**2015**
LFB R69 Rabbit	IGA produces human recombinant Factor VII zymogen in rabbit milk for the treatment of patients with hemophilia A or B disorders	Biopharm	**2018**
GalSafe™ Pig*	IGA results in non-detectable levels of alpha-gal sugar on cell surfaces to be used for food and as a source of human therapeutics	Food/ Biopharm	**2020**
PRRSV-resistant Pig*	IGA confers resistance to porcine reproductive and respiratory virus (PRRSV)	Food	**2025**

Products enrolled in VIP

Summary

- The VIP provides enhanced support for eligible animal biotechnology products that benefit human and animal health, food production, and animal well-being
- The VIP offers a variety of benefits that encompass intensive interactions and increased communication with dedicated review teams
- >50 products currently enrolled in the VIP

Resources

- CVM Animal Biotechnology Products
  - https://www.fda.gov/animal-veterinary/development-approval-process/biotechnology-products-cvm-animals-and-animal-food

- Veterinary Innovation Program (VIP) and VIP Plus
  - https://www.fda.gov/animal-veterinary/biotechnology-products-cvm-animals-and-animal-food/vip-veterinary-innovation-program
  - https://www.fda.gov/animal-veterinary/biotechnology-products-cvm-animals-and-animal-food/vip-plus

U.S. FOOD & DRUG ADMINISTRATION

Protocol Quality and Best Practices

Cheryl Johnson, DVM
Veterinary Medical Officer
Division of Companion Animal Drugs
Office of New Animal Product Evaluation
CVM | U.S. FDA

July 7, 2026

Importance of the Protocol

- Provides a clear, understandable plan for a study to ensure study repeatability and maintain data quality
- Ensure that studies are adequate and well-controlled to meet the regulatory requirements
- Can be submitted to CVM for review

Statutory Definitions of Studies 1

- Adequate and well-controlled studies (21 CFR §514.117)
  - "The primary purpose of conducting adequate and well-controlled studies of a new animal drug is to distinguish the effect of the new animal drug from other influences, such as spontaneous change in the course of the disease, normal animal production performance, or biased observation. One or more adequate and well-controlled studies are required to establish, by substantial evidence, that a new animal drug is effective."

Statutory Definitions of Studies 2

- Adequate and well-controlled studies (21 CFR §514.117)
  - "Adequate and well-controlled studies, in addition to providing a basis for determining whether a new animal drug is effective, may also be relied upon to support target animal safety. The report of an adequate and well-controlled study should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present."

Substantial Evidence Definition

- Substantial evidence (21 CFR §514.4)
  - "Substantial evidence shall include such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect."
  - Evidentiary standard applied to effectiveness for full approval, and, for combination new animal drugs, to the demonstration that each active ingredient contributes to the product.

How to develop a high-quality protocol

- Early development discussions
- Recent updates to protocol review process
- Overall protocol quality
- Common issues and non-concurrence items
- Raw data H submissions

Early Development Discussions

- General Correspondence or GC (pre-INAD/Investigational New Animal Drug)
- Under the INAD (Early Information or Pre-submission Conference)

GC (Pre-INAD) meetings

Early, high-level meetings

- Questions regarding a novel indication (suitability of and how to support it)
- May help determine the appropriate indication
- Opportunity to discuss novel products, receive early feedback from CVM, and identify any concerns regarding development
- Opportunity to discuss proposals for novel evaluations or study designs (biomarkers, surrogate endpoints, unique statistical analyses, multiple or composite endpoints, etc.)

GC meetings (cont.)

Other concepts to be discussed under an GC meeting could include:

- General questions about the path to approval for a specific product
- Summary discussion of existing data and if it may support approval
- Opportunity for a conversation and exchange of ideas

No review of data or reaching agreements during these meetings

Early INAD Conversations

- Held under the INAD file
- Appropriate before a Pre-submission Conference to discuss early elements such as
  - Dose or dosing schedule
  - Indication
  - Effectiveness evaluations (novel evaluations or interim analyses)
  - Possibility of eligibility for Conditional Approval
- Early discussions can provide feedback to help refine the product development plan and prepare sponsors for the Pre-submission Conference
- Proposals can be supported by pilot data and/or literature
- No binding agreements

Early submission of data

- Summaries of pilot data may be submitted under an INAD file as an H submission (data submission) or under the A-0000 (Early Information)
- Data used to inform future meeting discussions including Pre-submission Conferences
- Allows CVM time to understand your product and provide the most specific answers to your questions
- Submit an overview document detailing your proposals and development plan

Early submission of literature as data

- It is the sponsor's responsibility to explain how submitted literature supports their proposals
- Articles are clearly applicable to the proposed product (clear references for each point)

Pre-submission Conference (PSC)

- Held at the stage when a sponsor has a complete development plan for all major technical sections
- Final or nearly final dose and indication
- Complete proposal to demonstrate safety and effectiveness
  - For products pursing conditional approval, this includes Reasonable Expectation of Effectiveness and Substantial Evidence of Effectiveness

PSCs (continued)

- Complete proposals allow for discussion of unique aspects, such as:
  - Real World Data/Real World Evidence
  - Data collected in foreign countries and studies proposed to be conducted outside of the US
  - Literature to support safety or effectiveness
  - The use of specific scoring systems
  - Multiple, composite, or multi-component endpoints
  - Adaptive study design proposals
  - Biomarkers or surrogate endpoints

PSCs (cont.)

- Manufacturing discussions may be held with other technical sections or under a separate meeting, but the sponsor should have a complete proposal at this stage
- Will also discuss which data is recommended to be submitted prior to protocol submission (data submitted under an H submission)
  - This is generally data to justify specific study design proposals or any proposed major deviations from standard guidance (fed/fasted data, pilot effectiveness data, pharm/tox data, etc.)

Updates to Protocol Review Process

Principles of Protocol Review

- Internal document written to incorporate the following:
  - feedback from stakeholders
  - routine re-evaluation of office policies
  - results of internal audit of protocol letters
- Purpose: to focus protocol review on the adequacy of critical science and regulatory compliance elements of study design, execution plans, and analysis, not general improvement of the protocol
- The principles were implemented by a working group through revisions of the Review of Protocols P&P, as well as concurrence and nonconcurrence letter templates

Updates to Review of Protocols P&P (1243.4060)

New “Elements of Protocol Review” section outlines that CVM will **not:**

- provide editorial comments unless they impact a critical study element
- provide comments regarding compliance with the stated standard of conduct (GLP, GCP, etc.)
- provide comments regarding the inclusion of verbiage to address a variety of potential occurrences
- comment on data capture forms unless the issue identified compromises the scientific or regulatory validity of the study
- provide comments regarding the creation of the final study report
- require training records, curriculum vitae, or the names of study director/investigators at the protocol review stage
- require attachment of all study standard operating procedures (SOPs) to a protocol

Updates to Protocol Concurrence Letters

- Protocol concurrence means we fundamentally agree with your proposed design, execution, and analyses and represents a commitment that we will not later alter our perspectives on these issues unless public or animal health concerns appear that we did not recognize at the time of the protocol assessment
- Concurrence does not guarantee that data obtained will support an approval
- We strongly recommended sponsors submit protocols to us for review and concurrence, but this is not a requirement

Updates to Protocol Concurrence Letters (continued)

- Scope of comments in protocol concurrence letters is limited to minimize confusion and promote consistency
- Protocol concurrence letter will only include:
  - Reminders on specific items for the data package or corresponding technical section
  - Reminders regarding drug development process
  - General reminders or observations, not related to the current protocol, that we would like the sponsor to consider for future protocols

Updates to Protocol Non-concurrence letters

- Sent when CVM does not concur with the protocol design, execution plans, or data analyses and/or we lack sufficient information to reach a decision
- Can include comments on non-critical aspects of the protocol that are not adequate, missing, or unclear, but are not required for protocol concurrence

Protocol Quality

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July 7, 2026

Protocol Quality (cont.)

- The protocol should clearly describe how study activities are to be carried out (including data analysis)
- Communicating with CVM early and often improves chances of single cycle protocol concurrence but is not a substitute for CVM protocol review

Protocol Quality (continued)

- Ensure recommended supporting information is provided before submitting a protocol
  - Justification for key design elements (novel endpoints, study population, major deviations from published guidance)
- Protocol should be consistent with the agreed upon development plan
- Sponsor is responsible for ensuring protocol compliance with the intended standard of conduct

Protocol Components –Part 1

- Study objective(s)
- Study population
  - Enrollment, inclusion, and exclusion criteria
  - Source
- Treatment and control groups
- Experimental unit
- Sample size and justification
- Housing and animal husbandry
- Concurrent medications
- Duties of study personnel

Protocol Components – Part 2

- Randomization and masking procedures
  - Masked vs. unmasked activities and personnel associated with each
- Schedule of study events
- Description of study design and experimental model
- Dosing information
  - Dose, route of administration, dosing procedure, post dosing observation and re-dosing if vomiting is observed
- Pre and post treatment observations and data collection
- Statistical analysis plan (that matches the study design)
- Success criteria for effectiveness studies

Protocols Components: To Be Determined

- It is acceptable for some elements of the protocol to not yet be determined at the time of CVM review:
  - Study Site(s), investigator(s) and study personnel
  - Final details of electronic data capture (EDC) form and EDC system layout
    - All data to be collected should be clearly described
  - Subcontract laboratories (bioanalytical, pathology)

Protocol Components: Sometimes Included

- Depending on the specific study, additional elements may be needed to allow CVM to adequately understand the study:
  - Tools to be used in the study
    - Owner or investigator scoring rubrics
    - Specialized sampling methods
  - Certain SOPs critical to understanding the study conduct
    - If actual SOPs are not available, then key elements of the procedures covered by those SOPs should be included in the protocol
  - Owner instruction sheets
  - Informed consent forms - included for all studies that enroll client-owned animals

Effectiveness Study Protocols

- Effectiveness studies are typically conducted in accordance with Good Clinical Practice (GCP) guidance (CVM GFI# 85).
- Outcome Measurement:
  - Does the endpoint match the indication?
  - Does the study population reflect the target population for the proposed indication?
  - Is the analysis model appropriate to the endpoint?
- Use of foreign data: refer to 2025 ADUFA V Education Conference presentation on the subject and CVM GFI # 265 Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs
- Interim analysis, multiple endpoints, and adaptive designs
  - Inclusion of these approaches present additional statistical considerations
  - Discussion with CVM prior to protocol submission is recommended

Effectiveness Study Protocols: Secondary Endpoints

- Inclusion of secondary endpoints and/or analysis may be acceptable
- Results are not automatically reported on labeling or in the Freedom of Information (FOI) Summary
- To be considered for inclusion, those results should:
  - Use analysis that meets the same standards as primary endpoints
  - Be used in reaching agency conclusions and/or provide information important to the user for the safe and effective use of the product
- If multiple analysis are planned, the potential for multiplicity concerns should be considered so primary outcomes are not adversely impacted

Target Animal Safety (TAS) Study Protocols

- TAS studies are nonclinical laboratory studies typically conducted under Good Laboratory Practice (21 CFR Part 58)
- Based on GFI#185: (VICH GL43) Target Animal Safety for Veterinary Pharmaceutical Products
- Additional Guidances are available for specific situations, e.g.,:
  - GFI # 49 for bovine mastitis
  - GFI #281 for canine infectious otitis externa topical drugs
- Deviations from recommendations in the Guidances can be acceptable, but may necessitate scientific justification

Target Animal Safety: Additional Studies

- Safety in reproducing animals - required for systemically absorbed drug intended for use in breeding animals
- Safety in neonatal animals - account for the immature physiological systems of newborn animals, including incomplete blood-brain barrier development, reduced hepatic metabolic capacity, and altered renal clearance
- Mammary gland safety - to evaluate the safety of drugs intended for intramammary use in lactating or non-lactating animals
- Avermectin products - studies in known sensitive dogs may be necessary

Target Animal Safety: Unique Considerations

These should be discussed in a PSC as previously mentioned

- Pharmacology: helps design safety studies (food effect, compressed study design, timing of safety assessments and necropsy, and a dose interval for single administration products)
- Immunogenicity: unique aspect of protein and other immunomodulatory products, generally recommend banking plasma samples for potential anti-drug antibody (ADA) assays
- Known toxicity: may necessitate modifications to the dosage levels or duration of drug administration in the target animal safety study based on data

Common Issues and Non-concurrence Items

- Common Response to Protocols with Non-concurrence Issues
- Non-concurrence Issues
  - Overall Quality
  - Masking
  - Randomization
  - Analysis Model/Study Design Mismatch
  - Other Examples

Responses to Protocols with Non-concurrence Issues

- Amendment: very minor additions or corrections identified early in review, overall protocol is otherwise clear and acceptable
- Non-concurrence
  - Shortened Review Time (SRT): offered when protocol is generally acceptable and only straight-forward corrections or additions are needed
  - Standard Review Time: Significant omissions, errors, or missing justifications. Also appropriate when substantial redesign of the protocol is needed or the sponsor may choose one of several options

Common Non-concurrence Issues:
Overall Quality

- Inconsistencies across protocol sections or between protocol and data capture forms
- Poor organization
- Inadequate details
  - Missing site-specific SOP (e.g., no detail for parasite counting methods)
  - Inclusion/exclusion criteria

Common Non-concurrence Issues: Masking

- Inadequate description of the bias control procedures (e.g., insufficient details on which study roles are masked, and which study roles are unmasked)
- Masking not maintained before database lock
- Unmasked study personnel conducting masked activities (e.g., making observations or collecting data)

Common Non-concurrence Issues: Randomization

Inadequate information on

- how experimental unit will be randomized to treatment groups, cages/pens, or rooms
- order animals/groups will undergo procedures
- methods (i.e., computer programs) used in the randomization

Common Non-concurrence Issues:
Analysis Model/Study Design Mismatch

- Blocking factors not included in analysis model
- Multiplicity adjustment not considered as part of the analysis plan:
  - Multiple treatment groups comparisons in one study are involved
  - Multiple confirmatory subgroup analysis in one study
  - Multiple primary endpoints will be tested and the drug will claim effectiveness when at least one test shows significance
  - Adaptive design involves interim analysis

Common Non-concurrence Issues: Other

- Unclear on whether data will be collected on paper or in electronic data capture system
- Information that reveals the treatment group assignment of the animals is on data capture forms
- Unclear/inconsistent timing of evaluations. Consider a table of scheduled events in addition to text. Specify am/pm

Common Non-concurrence Issues: Other (cont.)

- Failure to include the informed consent form for studies that enroll client-owned animals
- Submitting a protocol without previously submitting critical supporting data (i.e. to support a compressed dosing schedule)
- Insufficient detail on data to be collected to support safety and effectiveness endpoints

Raw Data Agreement H Submission

- Definition
- Key Features & Review Time
- Criteria & Timing
- Possible Outcomes

Definition

- A voluntary submission (code: H-RD) that allows sponsors to confirm their agreement with ONAPE's list of expected raw data and study documents to be submitted before conducting for target animal safety or effectiveness studies.

- P&P1243.4095: Review of Raw Data Agreement H Submission For Target Animal Safety and Effectiveness Studies (December 11, 2025).

Key Features & Review Time

Key Features of eSubmitter for the H submission:

- Limited to Target Animal Safety and Effectiveness studies
- Question-based format in eSubmitter
- Aligned with data descriptions in the P&P (Appendices 1, 2, and 3)
- Review Time: 100 days

Criteria & Timing

ONAPE will only review a Raw Data H submission if all of the following criteria are met:

- The associated target animal safety or effectiveness study protocol has been submitted for review in advance of conducting the study
- The review of the associated protocol submission is pending
- The associated protocol's submission number is clearly identified in the Raw Data H submission

Possible Outcomes

Refuse to Review (RTR):

- If the associated protocol submission is unacceptable and receives a final action of RTR, then the H submission will receive a final action of RTR.

Review Ended Early:

- If there is protocol non-concurrence where revisions may impact the raw data and study documents to be collected, the H review is terminated, and an Acknowledgment Letter is issued with comments included where possible.

Review Completed:

- If there is protocol concurrence, or non-concurrence with SRT and the revisions will not impact the raw data to be collected, then the H raw data submission review is completed, and an Acknowledgment Letter is issued with all applicable comments included.

Selected Resources/References: General

- CVM Drug Development Resources for Animal Drug Sponsors
  - https://www.fda.gov/animal-veterinary/resources-you/drug-development-resources-animal-drug-sponsors
- First Annual Animal Drug User Fee Educational Conference (2024)
  - https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/cvm-public-meeting-first-annual-animal-drug-user-fee-educational-conference-07172024
- Second Annual Animal Drug User Fee Educational Conference (2025)
  - https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/cvm-public-meeting-second-annual-animal-drug-user-fee-educational-conference-07152025

Selected Resources/References: P&Ps

- 1243.3024 Scheduling and Holding Meetings with Outside Parties
- 1243.4060 Review of Protocols
- 1243.4092 H Submissions Preceding Meetings and Protocols
- 1243.4095 Review of Raw Data H Submission For Target Animal Safety or Effectiveness Studies

Selected Resources/References: CVM GFIs

- #56: Protocol Development Guideline for Clinical Effectiveness and Target Animal Safety Trials
- #215: Target Animal Safety and Effectiveness Protocol Development and Submission
- #85: Good Clinical Practice
- #185 (VICH GL 43): Target Animal Safety for Veterinary Pharmaceutical Products
- # 266: Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs
- #267: Biomarkers and Surrogate Endpoints in Clinical Studies to Support Effectiveness of New Animal Drugs
- #268: Adaptive and Other Innovative Designs for Effectiveness Studies of New Animal Drugs
- Human Food Safety (115, 116, 141,147, 148, 149, 159, 160, 205, 206, 207, 208, 232, 257)


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Second Break (10 minutes)

Questions?

- Scan the QR Code or send an email to ADUFA_V_EDU_Conference@fda.hhs.gov

Q&A

Closing Remarks

- Slides will be available online and in the Docket
  - Event page: https://www.fda.gov/animal-veterinary/news-events/workshops-conferences-meetings
  - Docket: FDA-2024-N-2602 at www.regulations.gov
- Questions received will be retained for future meetings
- Questions may also be submitted to the Docket
- Thank you for your participation


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