



From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process

STARTING POINT: An idea

FINISH LINE: An approved animal drug on the market

Many of us may not be familiar with the path to the finish line, so let's break it down to see how an animal drug makes the journey from being an idea to a product on the market.



Helpful Definitions

Drugs

To understand the journey, we need to understand the term “drugs.” The Federal Food, Drug, and Cosmetic Act (FFDCA) defines the term “drugs” as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.”

In plainer language, a drug (the “article”) is something that treats a disease or changes the structure or function of the body. Some drugs, such as insulin, do both — treat a disease and change the structure or function of the body. Insulin given to a cat with diabetes treats a disease (diabetes mellitus) and changes the cat's body by allowing cells to take up glucose, commonly called “blood sugar,” from the blood. Other drugs only change the structure or function of the body. For example, in the routine animal husbandry practice called “heat synchronization,” a compound is given to a group of cows to make them ovulate at the same time. Although this compound is not treating a disease in the cows, it is still a drug because it changes how their bodies function.

FFDCA – Federal Food, Drug, and Cosmetic Act
FDA – Food and Drug Administration
CVM – Center for Veterinary Medicine
ONADE – Office of New Animal Drug Evaluation
OMUMS – Office of Minor Use and Minor Species Animal Drug Development
NADA – New Animal Drug Application

The FFDCA gives the U.S. Food and Drug Administration (FDA) the legal authority to approve and regulate drugs for both people and animals. If a drug is for use in animals, it is called a new animal drug. New animal drugs are approved and regulated by FDA's Center for Veterinary Medicine (CVM).

CVM is made up of six offices that work together to approve new animal drugs and monitor the drugs after they are on the market. The Office of New Animal Drug Evaluation (ONADE) is the “pre-approval office,” meaning that it is the lead office for reviewing the information about a new animal drug before it is approved. The new animal drug can be for companion (pet) animals, such as dogs, cats, and horses; or for food-producing animals, such as cattle, pigs, and chickens. A new animal drug can also be for minor species, like fish, ferrets, and goats; or for minor uses in a major species, like a rare disease in horses. If the drug is for a minor species or a minor use in a major species, the Office of Minor Use and Minor Species Animal Drug Development (called “OMUMS” for short) is also involved in the review process.

Drug Sponsor

Now, let's define "drug sponsor." A drug sponsor is the entity responsible for collecting all the information about a new animal drug and submitting this information to CVM for review.

Who can be a drug sponsor? Any organization, or even one person, can be a drug sponsor. For example, scientific research groups; government agencies, such as the U.S. Department of Agriculture; and academic organizations, such as colleges and universities, can all be drug sponsors. But typically, drug sponsors are pharmaceutical companies.

Together, CVM and the sponsor guide the drug through the approval process.

Approved New Animal Drug

We also need to understand what it means for a drug to be an approved new animal drug. An approved animal drug is one that has gone through the New Animal Drug Application (NADA) process and has received CVM's stamp of approval. Just as high school seniors who want to attend college must go through the college application process, drug sponsors who want to make and sell animal drugs must go through the NADA process. A high school senior uses a college application to formally ask a school for acceptance. The college application tells the senior's story, including all the information about the student's extra-curricular activities and grades in high school. Likewise, a drug sponsor uses a NADA to formally ask CVM to approve a new animal drug. The NADA tells the drug's story and contains all the information about the drug.

CVM's approval of the NADA means the animal drug is safe and effective if it is used according to the label.

"Safe" includes safety:

- To the animal; and
- Of food products made from the treated animal, if the drug is for use in food-producing animals.

"Effective" means the drug consistently and uniformly does what it is supposed to do.

CVM's approval also ensures that the drug's strength, quality, and purity are consistent from batch to batch, and that the drug's labeling is appropriate and truthful.

Two other important factors that CVM considers during the NADA process are:

- The drug's impact on the environment; and
- The safety of the people who will give the drug to the animal or who may come in contact with the drug.



Besides the standard NADA process, two additional pathways to the marketplace are available for some animal drugs for minor species or minor uses in a major species. These two pathways are conditional approval and indexing. Learn more about minor species, minor uses, conditional approval, and indexing by visiting the following websites:

<http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm189540.htm>; and <http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/default.htm>.

Common Misconceptions

Now, we need to clear up some common misconceptions about the drug approval process.

Misconception: The drug approval process starts with CVM.

Truth: The drug approval process starts with the drug sponsor. The sponsor conducts initial research on a potential new animal drug, and if the research is promising, the sponsor contacts CVM to initiate discussions about the drug and the approval process.

Misconception: CVM tells the drug sponsor which new animal drugs to research and develop.

Truth: The drug sponsor decides which new animal drugs to research and develop for possible approval. CVM and the sponsor discuss what information is needed to get a drug approved.

Misconception: CVM tests a new animal drug for safety and effectiveness.

Truth: The drug sponsor is responsible for testing a new animal drug for safety and effectiveness. CVM reviews the results of the testing to decide if the drug is safe and effective and if the approval requirements are met.

A Brief Summary of the Drug Approval Process

- The drug sponsor collects information about the safety and effectiveness of a new animal drug. The sponsor may need to conduct studies to get this information. For any studies that are performed, the sponsor analyzes the results.
- Based on the collected information, including any study results, the sponsor decides if there is enough proof that the drug is safe and effective to meet the requirements for approval.
- The sponsor submits a New Animal Drug Application (NADA) to CVM. The NADA includes all the information about the drug and the proposed label.
- A team of CVM personnel, including veterinarians, animal scientists, biostatisticians, chemists, microbiologists, pharmacologists, and toxicologists, reviews the NADA. If the CVM team agrees with the sponsor's conclusion that the drug is safe and effective if it is used according to the proposed label, the NADA is approved and the drug sponsor can legally sell the drug.

Longer Version

The Beginning: The Idea

The journey to drug approval begins with the drug sponsor having an idea about a new compound. Perhaps this new compound has certain qualities that may make it a useful drug to treat bovine respiratory disease (BRD) in cattle. The sponsor researches and develops the new compound and conducts initial ("pilot") studies on it for a specific use (called an "indication") in a specific animal species (called the "target animal species"). In the example above, the indication is for the treatment of BRD and the target animal species is cattle. If the results of the pilot studies are promising and there is a potential market for the drug, the drug sponsor contacts CVM to officially start the drug approval process.

CVM – Center for Veterinary Medicine
ONADE – Office of New Animal Drug Evaluation
INAD – Investigational New Animal Drug
ADUFA – Animal Drug User Fee Act
NADA – New Animal Drug Application

The First Steps: Open Communication

The key to a smooth journey to drug approval is open and early communication between the drug sponsor and CVM. The drug sponsor initiates this communication by contacting ONADE to open an INAD file, discuss ADUFA fees, and discuss the development plan for the new animal drug. The sponsor may contact ONADE simply to share scientific information about a new animal drug.

INAD stands for Investigational New Animal Drug. Typically, the drug sponsor opens an INAD file in the beginning of the drug approval process. The sponsor then uses the file as a way to correspond with CVM throughout the journey. For example, the sponsor uses the INAD file to notify CVM before:

- Shipping the investigational drug from state to state or to a location outside the United States so it can be used in studies. The sponsor must meet certain legal requirements to ship the investigational drug; and
- Using food products, such as meat, milk, and eggs, made from food-producing animals treated with the investigational drug. If the drug sponsor wants food products made from treated animals to enter the food supply, the sponsor must ask CVM for permission to slaughter the animals and use the food products.

Before granting permission, CVM makes sure that food made from treated animals is safe for people to eat.

ADUFA stands for the Animal Drug User Fee Act of 2003. Under ADUFA, drug sponsors must pay CVM a “user fee” to review each NADA. A similar “user fee” system was created in 1992 for drug sponsors that make and sell drugs for people. Learn more about ADUFA by visiting the following website:

<http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/default.htm>.

A development plan discussion is usually held early in the drug approval process. As part of the development plan, ONADE and the drug sponsor discuss, and generally agree on, the information needed to get the drug approved, including the number and types of studies that may be required and the overall design of each study.

The Puzzle Pieces

Let’s think of the drug approval process as a puzzle. Before starting the puzzle, the drug sponsor has to figure out the dosage form of the drug and the dosage regimen that will be on the drug’s label.

The dosage form is the drug’s physical form when it comes out of the manufacturing facility. There are several categories of dosage forms, including oral and injectable. Tablets and capsules are two types of an oral dosage form. A drug that is injected under the skin, into muscle, or into a vein is an injectable dosage form. A solution is a common type of an injectable dosage form.



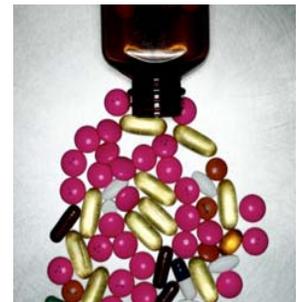
The dosage regimen includes:

- How much of the drug to give (the dose);
- How often to give it (the frequency);
- How long to give it (the duration); and
- How to give it (the route of administration). Various routes of administration include injecting the drug under the skin, into muscle, or into a vein; giving the drug by mouth; or applying the drug topically to the skin.

The Major Technical Sections

The five major technical sections are the biggest pieces of the drug approval puzzle:

- Target Animal Safety;
- Effectiveness;
- Human Food Safety;
- Chemistry, Manufacturing, and Controls; and
- Environmental Impact.



Target Animal Safety

The drug sponsor must show that the drug is safe to the target animal species when it is used according to the label. To prove the drug’s safety, sponsors typically conduct a target animal safety study in a small number of healthy animals.

The two goals of a standard target animal safety study are:

- To identify any harmful side effects of the drug; and
- To establish a margin of safety for the drug. The margin of safety is usually determined by testing the drug at higher-than-labeled doses for a longer-than-labeled time period in the target animal species. The drug’s margin of safety is like a “cushion” or “safety net” to make sure the drug will be safe when it is used in animals that may be sick or sensitive to the drug.

During the study, safety information on the drug is collected by:

- Examining the animals;
- Observing their behavior;
- Looking at their bloodwork results; and
- Looking at their tissues and organs both grossly (with the naked eye) and under a microscope.

For some drugs, there may be additional safety questions that may not be answered in a standard target animal safety study. For example, if the drug might be used in pregnant females, CVM may ask the sponsor for information on the safety of the drug in breeding animals. CVM may sometimes ask the sponsor to conduct a special case study, for example, a study done in a specific dog breed that may be extra-sensitive to the drug. An injection site irritation study is a common special case study that CVM usually requires for a drug that is injected into a food-producing animal. This type of study shows how injecting the drug affects the skin and muscle of treated animals.



Safety information on the drug is also collected during any effectiveness studies that are conducted.

Effectiveness

The drug sponsor must show that the drug works in the target animal species when it is used according to the label. One way for sponsors to prove that the drug is effective is by conducting a field study. In a field study, all the animals in the study have the disease or condition that the drug will be used for. For example, if the drug will be used to treat urinary tract infections (UTIs) in dogs, a dog must have a UTI to be in the field study. The goal of the field study is to make sure the drug will do what it is supposed to do when it is used under normal (“field”) conditions and according to the label.

Human Food Safety

Food products made from treated animals must be safe for people to eat. To show that the food products are safe, a drug sponsor usually conducts what are called human food safety studies.

When a food-producing animal is treated with a drug, chemical residues of the drug may be present in or on food products made from that animal. Chemical residues include small amounts of leftover drug, or parts of the drug that are not completely broken down by the animal’s body. One goal of the human food safety studies is to make sure the level of chemical residues in or on food made from treated animals will not harm people.

All animals normally have bacteria in and on their bodies. When an animal is treated with a drug, all the bacteria in and on that animal are also exposed to the drug. Some of the exposed bacteria may become resistant, meaning that the drug, and possibly similar drugs, will no longer work against those bacteria.

CVM – Center for Veterinary Medicine
ADI – Acceptable Daily Intake

Drug resistance in people and animals is a growing public health concern, particularly resistance to antimicrobial drugs. Antibacterial drugs, commonly called antibiotics, are one category of antimicrobial drugs. Antibiotic-resistant bacteria that enter the food supply may add to drug resistance in people. A second goal of the human food safety studies is to minimize the number of antibiotic-resistant bacteria that enter the food supply in or on food products made from treated animals.

There are four slices of the human food safety puzzle piece:

- *Toxicology*: By looking at information about the drug, toxicologists at CVM determine the “acceptable daily intake,” or “ADI.” The ADI is the largest amount of the drug that will not harm people if they ingest that amount every day.
- *Residue Chemistry*: Using the ADI, residue chemists at CVM set the tolerance for the drug, which is the level of chemical residues allowed to be in or on food products made from treated animals. Eating food that contains even the full amount of chemical residues allowed by the tolerance will not exceed the ADI.

Based on the tolerance, the residue chemists set the withdrawal time. The withdrawal time is the time from when the animal was last treated with the drug to when the animal can be slaughtered for food or the animal's milk can go to market. The withdrawal time allows for the drug (or parts of the drug) to get to levels in the animal's body that are at or below the tolerance. If the withdrawal time is followed, food products made from the treated animal are safe for people to eat.

- *Microbial Food Safety:* To determine if an antibiotic can be safely used in food-producing animals, CVM's microbiologists first look at the drug's ability to cause bacteria to become resistant. Second, the microbiologists look at the impact of that resistance on public health.
- *Regulatory Method:* CVM's scientists make sure appropriate and accurate testing methods were used by the drug sponsor in the human food safety studies.

Chemistry, Manufacturing, and Controls

In the Chemistry, Manufacturing, and Controls (CMC) technical section, the drug sponsor describes the plan for making the drug. This plan includes:

- What ingredients will be used to make the drug;
- Where the ingredients will come from;
- Where the drug will be made;
- How it will be made;
- How it will be packaged;
- How it can be stored (under what conditions); and
- How long it can be stored (this is important in determining the drug's expiration date).



A big portion of the CMC puzzle piece is looking at what tests the drug sponsor will use to make sure the drug is high-quality and safe. Another important part is deciding when FDA's investigators should inspect the manufacturing facilities where the drug is made. When an inspection is needed, FDA's investigators work with scientists at CVM to make sure the manufacturing facilities are using the correct equipment and methods to consistently produce a high-quality and safe drug.

Environmental Impact

Under the National Environmental Policy Act (NEPA), CVM must consider how the environment will be affected by an animal drug after it is approved. To do this, CVM requires that drug sponsors prepare an Environmental Assessment (EA). An EA describes how much drug is expected to get into the environment and its potential effects on the environment.

NEPA – National Environmental Policy Act
CVM – Center for Veterinary Medicine
EA – Environmental Assessment
FONSI – Finding of No Significant Impact
EIS – Environmental Impact Statement
CE – Categorical Exclusion

EAs are available to the public at the following website:

<http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/EnvironmentalAssessments/default.htm>.

If CVM decides that the drug will not have a significant impact on the environment based on the information in the EA, CVM writes what is called a "Finding of No Significant Impact," or "FONSI" for short. If CVM decides that the drug will have a significant environmental impact, CVM writes an Environmental Impact Statement (EIS).

Both FONSI and EISs are available to the public at the following website:

<http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/EnvironmentalAssessments/ucm072419.htm>.

A drug sponsor may ask CVM for a waiver from having to prepare an EA. This waiver is called a "categorical exclusion," or "CE" for short. A CE means that the drug falls into a legally-defined category that is unlikely to cause a significant environmental impact. If CVM grants a CE, the sponsor does not have to prepare an EA.

Two examples of when CVM typically grants a CE are:

- A drug for companion animals, like cats and dogs. Because a drug for companion animals is given to one animal at a time (as opposed to a herd or flock of animals), not much of the drug is likely to get into the environment; and
- A slight change to an already-approved animal drug if the change will not greatly increase how much drug is used or how much will get into the environment.

The Minor Technical Sections

The two minor technical sections are smaller pieces that fit into the puzzle after the five bigger pieces are complete or almost complete. These are:

- All Other Information; and
- Labeling.

All Other Information

The All Other Information technical section includes all information about the drug that was not part of the five major technical sections. The drug sponsor typically collects this information from:

- Published scientific literature;
- Foreign experience, if the drug is approved in a country outside the United States;
- Medical experience in people, if the drug is approved for use in people; and
- Studies that were conducted by the drug sponsor but not included in the five major technical sections.

Labeling

The term “labeling” includes all the information on the:

- Immediate container – this is the container that the drug itself comes in. Vials, bottles, syringes, and packets are immediate containers. For a drug that is in animal feed, the immediate container is the feed bag.
- Package insert – this is usually attached to the immediate container. The package insert is typically written for veterinarians who will prescribe or give the drug to animals.
- Outer packaging – this is what the immediate container comes in. For example, if a vial is packaged in a carton, the carton is the outer packaging.
- Shipping label – this is put on the larger container that is shipped from the manufacturing facility to identify the container’s contents. For example, the container may hold 12 cartons, with each carton holding one vial.
- Client information sheet – this is written for pet owners and animal producers to let them know what to expect when giving the drug to their animals, including what side effects to look for. Not every approved animal drug has a client information sheet.



In the Labeling technical section, CVM looks at the complete labeling in its final form. CVM makes sure the labeling provides all the necessary information to use the drug safely and effectively, including the risks associated with the drug. CVM also makes sure the labeling is not false or misleading.

The Last of the Puzzle Pieces

The Freedom of Information Summary

The Freedom of Information (FOI) Summary is a public document describing the safety and effectiveness

information that supports CVM’s decision to approve the new animal drug. It includes summaries of any studies that were done and explains the basis for CVM’s approval.

FOI – Freedom of Information
CVM – Center for Veterinary Medicine
NADA – New Animal Drug Application

Electronic copies of the FOI Summaries for approved animal drugs are located online at the following website:
<http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm>.

If an electronic copy of the FOI Summary is not available online, a hardcopy can be requested in writing. For more information on how to make a written request to CVM for an FOI Summary, please see the following website:

<http://www.fda.gov/RegulatoryInformation/FOI/HowtoMakeaFOIRequest/default.htm>.

The End: The Puzzle is Complete!

The NADA is approved if the information submitted by the drug sponsor:

- Meets the requirements for approval; and
- CVM is satisfied that the drug is safe and effective if it is used according to the label.

After the drug is approved, a notice of approval is published in the FEDERAL REGISTER. The new animal drug has now completed its journey through the approval process, and the drug sponsor can legally sell the drug.



Generic Animal Drugs

After an approved brand name animal drug has been on the market for a specific number of years, another drug sponsor can start the approval process for a generic copy. Rather than a New Animal Drug Application, drug sponsors of generic animal drugs submit an Abbreviated New Animal Drug Application (ANADA) to CVM. The application is “abbreviated” because generic copies of brand name animal drugs go through a shortened drug approval process. This shortened approval process was established in 1988 by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA).

For a generic animal drug to be approved, the information in the ANADA must show that the generic copy is identical to the approved brand name drug in:

- Active ingredient;
- Strength;
- Dosage regimen; and
- Dosage form.

ANADA – Abbreviated New Animal Drug Application
CVM – Center for Veterinary Medicine
GADPTRA – Generic Animal Drug and Patent Term Restoration Act
AGDUFA – Animal Generic Drug User Fee Act

The information in the ANADA must also show that the generic copy is:

- Consistently made from batch to batch; and
- Bioequivalent to the approved brand name animal drug. This means that the generic drug is absorbed by and acts the same way in the animal’s body as the approved animal drug.

Also, the labeling for the generic copy must match the labeling for the approved brand name animal drug, although the generic copy may use a different trade name.

Similar to the “user fee” system for brand name animal drugs, drug sponsors for generic animal drugs must pay CVM a fee to review each ANADA. The “user fee” system for generic animal drugs was established in 2008 by the Animal Generic Drug User Fee Act (AGDUFA).

Learn more about GADPTRA and AGDUFA by visiting the following websites:

<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ActsRulesRegulations/ucm049100.htm>; and

<http://www.fda.gov/ForIndustry/UserFees/AnimalGenericDrugUserFeeActAGDUFA/default.htm>.

CVM's Stamp of Approval

Whether the drug is a brand name animal drug or a generic copy, CVM's stamp of approval stands for safety and effectiveness when the drug is used according to the label. The rigorous journey through the drug approval process protects the health of both animals and people by assuring that only safe, effective, and high-quality animal drugs make it to the market, while unsafe animal drugs and those that do not work are kept off.

