

The Altascientist

SCIENTIFIC JOURNAL

MANUFACTURING CONSIDERATIONS FOR ANIMAL HEALTH PRODUCTS

Manufacturing requirements for human and veterinary prescription drugs share a common foundation in Good Manufacturing Practices (GMP) and Quality by Design (QbD) principles, covering products such as capsules, tablets, injectables, ophthalmic products, creams and gels, and spray-dried dispersions. The main differences in end-product requirements stem from species-specific physiology, public health considerations, and regulatory frameworks.

Human drug manufacturing focuses on producing safe and efficacious medicines for a single species with relatively predictable physiology. Veterinary drug manufacturing must account for diverse species, including ruminants, monogastric livestock, poultry, aquaculture species, and competition animals. Species-specific gastrointestinal physiology, metabolic rates, feeding behavior, and husbandry practices influence formulation design, dosing strategies, and manufacturing controls. A CDMO with experience in both human and animal health manufacturing delivers a solid foundation of understanding these core principles, and expertise in animal-specific considerations, both regulatory and logistical.

In this issue, we explore some of the species-specific considerations that drive efficient, effective manufacturing of veterinary products for the U.S. market, and provide a case study for the manufacture of an injectable veterinary product.

MANUFACTURING CONSIDERATIONS FOR VETERINARY DRUG PRODUCTS

Quality Systems



Human drug manufacturing requires extensive documentation, deviation management, and lifecycle validation. Veterinary products follow similar principles but may allow flexibility depending on species risk, dosage form, and intended use. For instance, drug products for food-producing animals face stricter controls due to residue and public health concerns. The specific requirements for each program are determined in close alignment with expert CDMO partners.

Facility and Equipment Requirements

Both human health and veterinary drug development require:

- Controlled environments, such as cleanrooms, controlled temperature/humidity, and HEPA-filtered air to protect the product from contamination and variability.
- Qualified equipment that safeguards against process failures, incorrect dosing, mechanical contamination, and data errors.
- Cleaning validation to control any risk of chemical, microbial, and allergen contamination.
- Cross-contamination controls, including segregation, dedicated equipment or fully validated cleaning methods, air handling separation, and workflow design.

Manufacturing facilities for veterinary products often handle a broader range of APIs (anthelmintics, antiparasitics, hormones), requiring tailored containment strategies. EMA and VICH guidelines emphasize GMP for veterinary APIs, including quality systems and contamination control measures.

Requirement	Primary Risk Controlled	Result
Controlled Environments	Microbial/particulate contamination	Keeps product clean and stable
Qualified Equipment	Process variability and mechanical contamination	Ensures consistent, accurate manufacturing
Cleaning Validation	Residue and chemical carryover	Prevents unintended ingredients in the next batch
Cross-Contamination Controls	Mixing of products or potent compounds	Ensures products do not contaminate each other, and protects patients and operators

Process Validation

Veterinary products follow similar principles to human drug validation guidance (FDA's Process Validation Guidance of 2011) but may justify reduced validation for lower risk dosage forms or legacy products, depending on regulatory justification.



Raw Materials and APIs

Veterinary APIs follow VICH GL10 and the newer VICH GL60 draft guidance, which aligns veterinary API GMP with international standards and ensures quality and purity of APIs used in veterinary medicinal products.

Microbiological Control

Sterile human and veterinary products require strict microbiological controls and validated sterility assurance strategies. Manufacturing requirements depend on factors such as product type, route of administration, and sterilization approach. For products suitable for terminal sterilization, controlled manufacturing environments can be combined with a validated terminal sterilization process to achieve the required sterility assurance.

Pharmacovigilance

Human pharmacovigilance systems are extensive. Veterinary pharmacovigilance additionally monitors:

- Food safety
- Environmental impact
- Antimicrobial resistance

Table 2. Key Manufacturing Differences

Manufacturing Element	Human Health	Animal Health
Sterility Requirements	Strict, Annex 1/FDA aseptic guidance	Similar, but risk-based adjustments allowed for some species/routes
Process Validation	Full lifecycle validation	Risk-based; may be reduced for low risk dosage forms
Formulation Flexibility	Limited	High (palatability, boluses, long-acting injectables, feed premixes)
Cross-Contamination Controls	Very strict	Strict, but broader range of APIs handled
Pharmacovigilance	Human safety focus	Includes food safety, environmental impact, AMR monitoring

SPECIES-SPECIFIC FORMULATION CONSIDERATIONS



Ruminants vs. Monogastrics

Ruminants (e.g., cattle, sheep) have a multi-compartment stomach with microbial fermentation, which affects drug stability and absorption. Monogastrics (e.g., pigs, canines, felines) have simpler GI tracts, similar to humans, allowing more conventional oral formulations. VICH guidelines include species-specific efficacy and safety recommendations that influence formulation design.

Ruminants (Cattle, Sheep, Goats) Have:

- A large forestomach (rumen) with microbial fermentation
- High fluid turnover
- Long retention times
- Microbial degradation of many APIs



Common formulation strategies include:

- Rumen bypass coatings for drugs or nutrients degraded by rumen microbes, such as:
  - Enteric-coated monensin boluses
  - Protected amino acids (methionine, lysine)
- Density-controlled intraruminal boluses designed to remain in the reticulorumen for months, such as:
  - Anthelmintic boluses (fenbendazole, oxfendazole)
  - Trace element boluses (copper, cobalt, selenium)
- pH-triggered release systems release API only after passing into the abomasum (pH 2–3)

Monogastrics (Pigs, Canines, Felines, Horses)

Monogastrics have faster gastric emptying, higher gastric acidity, and more predictable absorption compared to ruminants.



Common formulation strategies include:

- Taste-masked oral suspensions are common due to dosing volume and palatability needs.
- Multiparticulate pellets or granules are used for horses to mix with feed.
- Chewable tablets and soft chews are developed especially for canines and felines.
  - Examples:
    - Flavored NSAID chewables
    - Antiparasitic soft chews
- Standard tablets and capsules can be used for a variety of different species, especially with high weight variability due to breed.
- Sprinkle capsules can also be mixed with food.

Long-Acting Injectables and Implants

Long-acting formulations are widely used in veterinary medicine to reduce handling stress and improve compliance. These technologies must comply with GMP for veterinary APIs and finished products and species-specific safety guidelines. Manufacturing considerations include sterility assurance, uniformity of API distribution, polymer molecular weight control, and release rate validation.

Some examples include:

1. **Oil-based depots**
   - Slow the release of lipophilic APIs
   - Common for antiparasitics
2. **Biodegradable polymer microspheres**
   - PLGA-based systems
   - Used for sustained hormone delivery
3. ***In situ* forming depots**
   - Injectable liquids that solidify after administration

Controlled Release Technologies for Livestock

Livestock formulations often require:

- Intraruminal boluses for ruminants
- Extended release injectables for antiparasitics
- Medicated premixes for feed (regulated under CVM GFI 13, 23, 73)

VICH GL8 and GL73 provide stability testing guidance for medicated premixes and veterinary dosage forms, ensuring consistent release profiles and product quality.

Intraruminal Boluses

Used for:

- Anthelmintics
- Trace minerals
- Growth promoters

Design considerations:

- Density > 2.5 g/cm^3 to remain in rumen
- Controlled erosion or diffusion
- Months-long release profiles

Extended Release Injectables

Examples include:

- Antiparasitic oil-based depot for cattle
- Long acting antimicrobials

Release mechanisms include:

- Solvent diffusion
- Polymer degradation
- Oil phase partitioning

Medicated Feed Premixes

Examples include:

- Antibacterial and antibiotic premixes
- Anticoccidials
- Antiparasitics
- Specialized uses, such as reducing emissions and suppressing heat in beef cattle

Manufacturing considerations include:

- Homogeneity of mixing
- Stability under pelleting temperatures
- Dust control and worker safety

Table 3: Species-Specific Formulation Strategies

Species	Physiological Challenge	Formulation Strategy	Example
Cattle (Ruminants)	Rumen degradation	Rumen bypass coating	Protected amino acids
Cattle/Sheep	Long retention in rumen	Density-controlled bolus	Anthelmintic boluses
Pigs	Bitter taste sensitivity	Taste-masked suspensions	Macrolide antibiotics
Canines	Compliance	Flavored chewables	NSAID chewables
Felines	Neophobia	Fish-based flavors, microencapsulation	Flavored antibiotics
Horses	Large dose volume	Granules/pellets	PPI granules
Cattle	Long acting therapy	Oil-based depots	Antiparasitics
Livestock	Sustained nutrient delivery	Controlled release bolus	Trace element boluses

MANAGING EXCIPIENT SELECTION RESTRICTIONS FOR ANIMAL HEALTH PRODUCTS

Excipient selection for veterinary drug products is governed by a combination of statutory requirements, CVM guidance, compendial standards, and species-specific safety considerations. Unlike human pharmaceuticals for which the FDA's Inactive Ingredient Database (IID) provides a reference for previously accepted excipients, veterinary products do not have an equivalent centralized list. As a result, excipient acceptability is determined through case-by-case evaluation during the New Animal Drug Application (NADA) or Abbreviated NADA (ANADA) review process. This framework places significant emphasis on species safety, residue depletion, and public health protection for food-producing animals.



FD&C Act Requirements

Under the Federal Food, Drug, and Cosmetic Act (FD&C), all components of a veterinary drug product—including excipients—must be demonstrated to be safe for the target animal species and, when applicable, safe for human consumers of edible tissues. This requirement applies to all dosage forms, including injectables, oral solids, oral liquids, topicals, and medicated feeds.

21 CFR Requirements

Although 21 CFR Parts 210 and 211 do not list specific excipients, they require:

- Identity testing of each component
- Verification of quality and purity
- Documentation of specifications and acceptance criteria
- Demonstration that each excipient is suitable for its intended use

These requirements effectively restrict excipients to those with established safety profiles and well-controlled manufacturing quality.

CVM Guidance for Industry (GFI)

Center for Veterinary Medicine (CVM) evaluates excipients through the NADA/ANADA process using multiple guidance documents, including those addressing:

- Component control
- Stability testing
- Residue depletion
- Medicated feed manufacturing
- Species-specific safety and efficacy

Because excipients can influence absorption, metabolism, and tissue persistence, CVM may require additional data even for excipients widely used in human medicines. There are restrictions on excipients for veterinary products, specific to species and by formulation (see Tables 4 and 5).



Table 4. Excipient Restrictions by Species

Species	Key Physiological or Safety Constraints	Excipient Restrictions and Considerations	Examples
Canines	Sensitive to certain sweeteners; risk of pancreatitis; taste-driven compliance	Avoid xylitol, propylene glycol, and sulfites; limit high fat flavor systems; evaluate preservatives for GI tolerance	Xylitol-free chewables; glycerin-based soft chews
Felines	Limited glucuronidation; strong aversion to bitter tastes; narrow flavor preferences	Avoid benzoic acid derivatives; avoid strong bittering agents; use feline-safe flavors. Do not use propylene glycol or acetaminophen (and associated binders/excipients)	Fish-based flavors; yeast extracts; microencapsulated APIs
Horses	Large dose volumes; feed-based administration; risk of colic with irritants	Avoid irritant solvents; ensure excipients do not alter feed palatability; avoid high-osmolarity liquids	Pellets/granules with minimal binders; low-irritant suspensions
Cattle (Ruminants)	Rumen degradation; long retention time; microbial metabolism	Avoid excipients rapidly degraded by rumen microbes; use rumen bypass coatings; avoid residues in edible tissues	Enteric coatings; high-density bolus matrices
Swine (Monogastric)	Bitter taste sensitivity; feed-based dosing	Taste masking required; avoid excipients that alter feed stability; ensure heat stability for pelleting	Flavor-masked suspensions; heat-stable binders
Poultry	Rapid GI transit; water-based dosing; flock-level exposure	Avoid insoluble excipients; avoid waterline biofilm promoters; ensure no harmful residues in eggs/meat	Water-soluble carriers; low-viscosity suspensions
Aquaculture Species	Environmental exposure; water solubility; gill sensitivity	Avoid persistent or bioaccumulative excipients; avoid irritants; environmental assessment required	Water-stable pellets; low-leach binders
Food-Producing Animals (General)	Human food safety; residue depletion; withdrawal times	Excipients must not accumulate in edible tissues; must not form harmful metabolites; require residue studies	Solvents with rapid clearance; low-residue polymers

Table 5. Excipient Restrictions by Dosage Form

Dosage Form	Key Regulatory or Technical Constraints	Excipient Restrictions and Considerations	Examples
Injectables (Parenterals)	Sterility; endotoxin limits; tissue residue concerns	Avoid irritant solvents (e.g., high DMSO); limit benzyl alcohol; ensure excipients do not persist in tissues	Oil-based depots; polysorbate-controlled emulsions
Oral Tablets/ Chewables	Palatability; species-specific safety; dose uniformity	Avoid toxic sweeteners (xylitol in canines); avoid feline-unsafe preservatives; ensure flavor safety	Soft chews with glycerin/gelatin; flavored tablets
Oral Suspensions	Stability; taste masking; GI tolerability	Avoid high-osmolarity vehicles; avoid irritant solvents; ensure excipients do not degrade in rumen	Aqueous suspensions with cellulose derivatives
Oral Powders/ Granules	Feed compatibility; mixing uniformity	Avoid excipients that alter feed texture or palatability; ensure heat stability for pelleting	Heat-stable binders; flow agents
Intraruminal Boluses	Density; controlled release; rumen stability	Avoid rapidly degradable polymers; avoid excipients that ferment; ensure no harmful residues	High-density mineral matrices; controlled-erosion polymers
Medicated Feed Premixes	Feed manufacturing constraints; residue safety	Only certain carriers allowed; excipients must withstand pelleting; must not accumulate in edible tissues	Calcium carbonate carriers; lignosulfonate binders
Topical/Dermal Products	Skin absorption; species grooming behavior; environmental exposure	Avoid solvents causing dermal irritation; avoid excipients toxic if ingested during grooming; avoid persistent environmental chemicals	Alcohol-free spot-ons; silicone-based carriers
Transdermal Gels	Skin permeability; systemic absorption	Avoid enhancers causing irritation; ensure excipients are safe if licked; avoid volatile solvents in felines	PLO gels; carbomer-based gels

Novel Excipients in Veterinary Products

A novel excipient is one not previously used in an approved veterinary drug product. CVM may require:

- Target animal safety studies
- Multi-species toxicology (if intended for multiple species)
- Residue depletion studies for food animals
- Environmental assessments

Because of these requirements, novel excipients are used sparingly in veterinary products unless they provide a clear functional advantage (e.g., controlled release matrices, palatability enhancers). Early engagement with CVM is recommended when proposing excipients without established veterinary precedence.

DERMAL AND TRANSDERMAL VETERINARY PRODUCTS

Dermal and transdermal products are common in veterinary medicine, and their manufacture involves specific considerations. They include spot-on ectoparasiticides, pour-on livestock antiparasitics, transdermal gels, dermal sprays and rinses, and medicated shampoos.

- They use unique excipients (penetration enhancers, solvents, polymers) not common in oral or injectable products.
- They pose species-specific risks, especially in animals that exhibit grooming behavior and dermal sensitivity.
- They often require environmental assessments due to runoff, shedding, or water contamination.
- They represent a large segment (e.g., flea/tick preventives, antiparasitics, hormone therapies).

Excipient Considerations for Dermal Veterinary Products

Species Grooming Behavior

- Felines ingest a significant portion of dermally applied products through grooming.
- Excipients must be safe both dermally and orally.

Skin Barrier Differences

- Felines have thinner skin and are more sensitive to solvents.
- Cattle and horses have thicker skin, allowing use of more robust penetration enhancers.

Environmental Impact

- Pour-on livestock products can contaminate soil and water.
- CVM may require environmental assessments for excipients with persistence or bioaccumulation potential.

Human Exposure

- Many dermal veterinary products pose risks to humans through accidental contact.
- Excipients must minimize dermal irritation and volatility.

Common Dermal Excipient Restrictions

- Avoid high-volatility solvents in felines.
- Avoid strong penetration enhancers that cause irritation.
- Avoid persistent silicones or oils in food animals unless residue studies support their use.
- Avoid fragrances that may cause allergic reactions in animals or humans.

MANUFACTURING PROCESS VALIDATION OF AN INJECTABLE SUSPENSION FOR TESTING IN RODENTS

Executive Summary

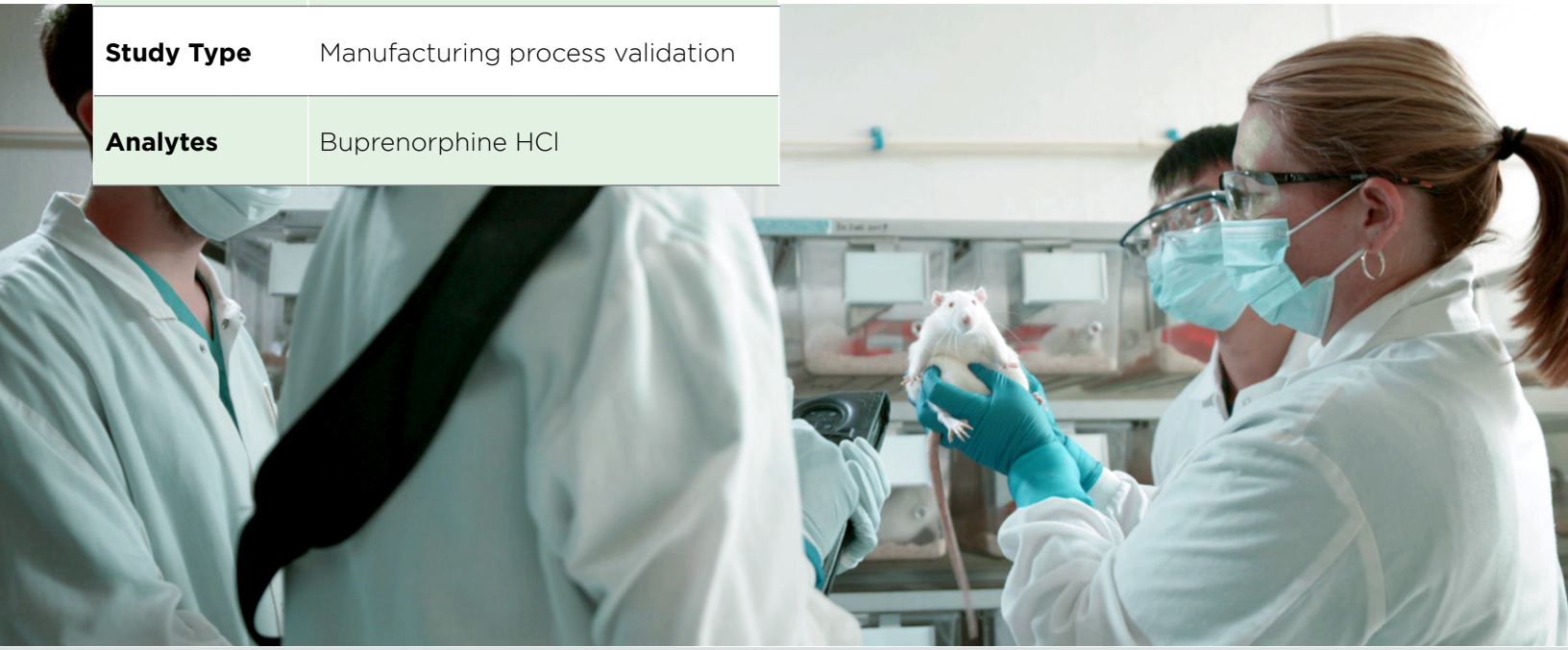
A robust manufacturing process for complex animal health products overcomes formulation, scale-up, and consistency challenges while maintaining compliance with GMP and regulatory expectations. The process validation program described demonstrates how a scientifically driven approach, combined with continuous improvement and rigorous investigation, can transform manufacturing challenges into a validated, commercially sustainable process.

The product underwent an extensive process validation campaign designed to confirm that the manufacturing process could consistently produce high-quality product at commercial scale. The validation program utilized the same equipment, processes, and controls intended for routine commercial manufacturing and included four successful validation batches. Throughout the program, process parameters were refined, formulation expertise was leveraged, and investigational findings were translated into meaningful process improvements.

The final validation campaign demonstrated consistent batch homogeneity, reliable fill performance, acceptable product quality attributes, and reproducible manufacturing outcomes. As a result, the process was determined to be capable of consistently producing products that meet predetermined quality specifications and are suitable for commercial production.

Study Details

Drug Class	Narcotic analgesic
Study Type	Manufacturing process validation
Analytes	Buprenorphine HCl



The Challenges

Achieving Suspension Homogeneity

As with many extended-release injectable suspensions, maintaining uniform distribution of the active ingredient throughout the manufacturing process presented a significant challenge. Early validation batches revealed variability in assay results, indicating opportunities to improve bulk mixing and material dispersion.

The team conducted detailed investigations, engaged an independent formulation expert, and implemented targeted process enhancements, including:

- Changed ingredient addition sequence
- Increased and optimized mixing times
- Adjusted mixing speeds
- Rotated vessel during mixing
- Enhanced post-screening mixing controls

These improvements significantly increased process consistency and product homogeneity.



Managing Formulation and Raw Material Variability

During development, the use of a higher-purity cholesterol grade unexpectedly altered the viscosity profile of the suspension, creating processing difficulties and preventing effective mixing. Rather than forcing the process forward, the team paused the campaign, investigated root causes, and redesigned the approach using material better aligned with the formulation's performance requirements.

This demonstrates the importance of understanding not only chemical specifications but also the physical characteristics of raw materials when developing complex injectable products.

Investigating Analytical and Process Outliers

Several isolated events occurred during validation, including assay outliers, chromatography anomalies, stability testing discrepancies, and content uniformity calculations. Each event triggered formal investigations, scientific assessments, and corrective actions. Importantly, these investigations demonstrated that the observed anomalies were either analytical artifacts, isolated laboratory events, or calculation-related issues rather than evidence of process failure.

Our commitment to thorough root-cause analysis and data-driven decision-making ensured confidence in the overall validation outcome.

The Outcome

Four validation batches were successfully manufactured and met specifications for critical quality attributes, including assay, content uniformity, fill performance, viscosity, and microbiological quality.

Key accomplishments included:

- Successful manufacture of four commercial-scale validation batches
- Consistent in-process mixing and filling performance
- Demonstrated batch-to-batch reproducibility
- Resolution of formulation and manufacturing challenges through process optimization
- Successful qualification of the manufacturing process for routine commercial production
- Validation performed in accordance with GMP principles and FDA process validation guidance

The validation conclusion confirmed that the manufacturing process is capable of reproducibly delivering high-quality products and is suitable for its intended commercial use.

Why It Matters

This case study highlights the value a skilled CDMO can bring, beyond simply executing batch manufacturing. Through scientific expertise, cross-functional collaboration, rigorous investigation, and disciplined process development, the team successfully transformed a complex extended-release injectable suspension into a validated commercial process.

For animal health innovators, this translates to:

- Reduced manufacturing risk
- Greater confidence in commercial supply reliability
- Improved product consistency and quality
- Strong regulatory supportability
- Faster progression from development to commercialization

The validation program demonstrates how a systematic, science-based approach to process development and validation can overcome complex formulation challenges and enable successful commercialization of innovative animal health products.



HOW ALTASCIENCES CAN HELP

With nearly a decade of experience in veterinary drug product manufacturing, Altasciences combines human pharmaceutical expertise with veterinary and nonclinical capabilities to provide comprehensive support for animal health sponsors.

We leverage integration with our four nonclinical facilities, drawing from their expertise in animal husbandry, behavior, and species-specific physiology. This knowledge, backed by daily hands-on experience, gives our manufacturing team a thorough understanding of the unique considerations involved in developing and manufacturing veterinary drug products.

Our fully qualified, FDA-inspected manufacturing facility houses an analytical lab, R&D formulations lab, multiple manufacturing suites, and a cGMP warehouse, all on one campus. Segregated Grade C cleanrooms also support potent compound handling, from API and potent API formulation through commercial-scale manufacturing.

Respect and care are central to our approach, reflected in our C.A.R.E. animal welfare program: Compassion, Alternatives, Reduction, and Enrichment. This commitment extends beyond the research environment to the development and manufacture of high-quality veterinary medicines. By combining our understanding of animal physiology and welfare with pharmaceutical expertise in GMP, Quality by Design (QbD), and established manufacturing technologies across a broad range of dosage forms, we offer a unique perspective on veterinary drug product development. Altasciences brings together animal health knowledge, pharmaceutical experience, and commercial manufacturing capabilities to help sponsors bridge the gap between understanding the animal and manufacturing the medicine, supporting veterinary products through commercialization.

Our contract development and manufacturing solutions include:

- Formulation development and manufacturing of your drug substance, from early stages through commercialization
- Cost-effective, flexible optimization experience from small prototype batches to commercial scale
- In-house research and development and analytical testing to drive formulation success
- Receipt, storage, manufacturing, release, and distribution capabilities
- Environmental monitoring system
- Continuous monitoring of temperature, humidity, and pressure with real-time notification
- Package design capabilities
- Primary and secondary packaging
- Bottle and blister packaging

Explore our development and manufacturing solutions

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ABOUT ALTASCIENCES

Altasciences is a drug development organization dedicated to safely accelerating early-phase development for biotech, biopharmaceutical, and pharmaceutical companies. By combining the scale and expertise of a leading CRO/CDMO with the flexibility and personalized approach of a mid-size partner, Altasciences delivers unified solutions across nonclinical, clinical, bioanalytical, formulation, and manufacturing services. Through intentional integration and true collaboration, the company removes barriers from lead candidate selection to clinical proof-of-concept—helping sponsors save time, reduce complexity, and make confident, data-driven decisions that enable earlier returns on investment. Guided by over 30 years of experience, Altasciences helps clients reach critical milestones faster.