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White Paper

Compounding of Animal Drugs: The New Regulations and What they Mean for Veterinarians in the Laboratory and Practice

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Minor species represent a particular challenge to the safe and effective delivery of drugs. Although drugs approved by the Food and Drug Administration (human or animal, generic or pioneer) may be used extra-label in these animals, the marked diversity in size, physiology, and pathology which characterizes them frequently leads to the need for alternative approaches.

One answer is the use of indexed drugs. While not approved by the FDA, they nonetheless undergo an extensive alternate review that provides some assurances. However, these drugs cannot be used extra-label. Because of these limitations, practitioners providing care to minor species often reach for compounded animal drugs. Yet, while on the one hand, the compounding of a formulation targeting minor species may improve the accuracy, safety or convenience of drug delivery, more so than drugs approved or indexed by the Food and Drug Administration (FDA), compounded animal drugs are likely to increase the risk of adversity, including therapeutic failure.

The FDA's approach to regulation of compounded animal drugs reflects an intent to assure safe public and animal health. However, the rules which guide the FDA's regulatory approach to compounding of animal drugs are complex and ever changing.

This document will attempt to provide clarity to the current approach of FDA regulation from the practitioners' perspective. This includes a focus on the recent release of Guidance for Industry (GFI) # 256, Compounding of Animal Drugs from Bulk Substances, and how this Guidance will impact the veterinary practitioner of minor species. Let's start with terminology.

FDA-approved drugs

An FDA-approved drug (https://www.fda.gov/drugs/development-approval-process-drugs) is one the FDA has determined that the data demonstrate the drug is safe, effective, properly manufactured to ensure drug quality, is adequately labeled, and that the benefits of the drug outweigh its risks when used according to its approved labeling. In addition to pre-market review, FDA-approved animal drugs are subject to requirements once they are on the market, including that sponsors must submit reports of adverse events.

- Example: Zorbium® (Elanco) is an FDA-approved buprenorphine transdermal solution indicated for the control of post-operative pain associated with surgical procedures in cats.

Generic drugs are included in this definition. (https://www.fda.gov/drugs/frequently-asked-questions-popular-topics/generic-drugs-questions-answers; https://www.fda.gov/drugs/frequently-asked-questions-popular-topics/generic-drugs-questions-answers). Generic drugs are also fully approved by the FDA. The medication in a generic drug is the same as an already marketed brand-name (approved, reference) drug in regard to the dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. It undergoes an abbreviated approval process requiring a bioequivalence study to the approved drug. Clinical safety and efficacy studies are not required because the exposure to the generic drug is the same as the already marketed drug.

FDA-Indexed drugs

FDA-indexed drugs (https://www.fda.gov/animal-veterinary/minor-useminor-species/drug-indexing) are unapproved new animal drugs for which safety and effectiveness has been FDA reviewed and affirmed/accepted for use in a minor species. Often, the diseases that occur in these animals are too rare or too varied. Therefore, adequate, and well-controlled studies necessary to support full drug approval are not practical. The FDA allows indexing for drugs intended for minor species or uncommon diseases in major species through the Minor Use and Minor Species (MUMS) Animal Health Act of 2004. The review of indexed drugs is through an alternate pathway with the FDA. Substantial evidence of data demonstrating the efficacy primarily through pharmacokinetic studies and safety of the drug in specific species must be provided and if sufficient, indexed drugs are legally allowed to be marketed. However, they cannot be used extra-label. This means their use is limited to the species and indications for which they are indexed. Manufacturers of indexed drugs must also report adverse events to the FDA.

- Example: Ethiqa XR® (www.ethiqaxr.com, Fidelis Animal Health, Inc.) is an FDA-indexed extended-release buprenorphine injectable suspension indicated for post-procedural pain in mice, rats, ferrets, and non-human primates.

Minor species

A minor species is anything other than a major species. Horses, dogs, cats, cattle, pigs, turkeys, and chickens are examples of major species. Mice, rats, and ferrets are examples of minor species.

Extra-label use

Extra-label use of a drug occurs when the drug is prescribed or administered in clinical practice for a use not described in the approved labeling. The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 legalized the common practice of extra-label drug use (ELDU) in animals under certain conditions. This law allows veterinarians to use any drug fully approved for use in any other species unless there are specific prohibitions of that use. Because the drug must be approved, this means that indexed drugs are not protected by AMDUCA. However, the use of a compounded drug is considered an example of extra-label drug use.

Compounded drugs

Compounded drugs (https://www.fda.gov/animal-veterinary/unapproved-animal-drugs/animal-drug-compounding) have been prepared by the mixing, assembling, packaging, or labeling of a drug in response to a practitioner's prescription based on an individual patient's or group of patients' needs. Simplistically, compounding includes any manipulation of an approved or indexed drug beyond that stated in its accompanying package insert. The product resulting from compounding is considered an unapproved new animal drug. This causes them to be much different from FDA-approved drugs (which includes generic drugs) or FDA-indexed drugs in terms of assurance of quality, safety, or efficacy. Compounded animal drugs can range from simple dilutions of an approved product to complex formulations compounded from approved products or bulk drug substances. Compounded drugs are not subject to ongoing pharmacovigilance.

Examples of compounding include:

- Diluting the approved BUP HCl solution or suspension to allow for easier and more accurate administration to smaller animals. This would be allowed as long as the currently marketed, approved (human or animal) or indexed products would not meet the needs of the patient.

- Compounding a buprenorphine gel intended for oral transmucosal use. Whether or not this product would be allowed depends on the source of the active pharmaceutical ingredient (API), in this case buprenorphine. If from an approved product, compounding would be allowed if the needs of the patient cannot be met by an approved or indexed product. If compounded from a bulk drug substance, the requirements are more stringent.

Bulk Drug Substance

A bulk drug substance (BDS) is any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. The FDA perceives that compounding from bulk substances increases the risk of adversity compared to using a currently marketed, approved, indexed, or conditionally approved drug.

503A (Pharmacies) vs 503B Outsourcing facilities:

Most animal drug compounding is implemented by state licensed pharmacists. The 503A distinction reflects section 503A of the Food, Drug and Cosmetic Act (FDCA) that addresses human pharmacy laws. Although state boards of pharmacy will differ on the expectations of quality assurance determination for compounding of drugs by 503A pharmacies, in general, these assurances are limited and do not include, for example, adherence to current Good Manufacturing Practices (cGMP). This contrasts with drugs compounded by 503B Outsourcing Facilities.

The 503B Outsourcing Facilities were legalized with passage of the Drug Quality and Security Act (DQSA) of 2013, which amended the FDCA with section 503B. These facilities were allowed because of the need to compound large volumes of quality sterile injectable products for human patients. Requirements for these facilities include oversight by a licensed pharmacist, following cGMP, registration with and inspection by the FDA, reporting of adverse events and specific labeling requirements. They must comply with standards set by the United States Pharmacopeia in Chapters <795> and <797>. They are only allowed to compound drugs from a bulk substance if it is on a list maintained by the FDA.

Notably, the FDA's Center for Veterinary Medicine (CVM) has determined that DQSA does not apply to the compounding of animal drugs. However, some states currently allow acquisition of compounded animal drugs from 503B Outsourcing Facilities.

Going Deeper…Indexed versus Compounded Animal Drugs

FDA-Indexed Drugs

Unlike compounded drugs that are compounded in a 503A pharmacy, indexed drugs follow cGMP and must be pharmaceutical grade, which provides assurance of the product's reproducibility, integrity, quality, and consistency. The manufacturing facilities for FDA-indexed drugs are regularly inspected by the FDA for adherence to cGMP standards. Companies must also comply with strict pharmacovigilance processes, where adverse events are reported to the FDA and the drug's labeling is updated as deemed necessary to provide the veterinarian with the most up-to-date safety information to protect the animal as well as the administrator.

The current list of FDA-indexed drugs can be found here: https://www.fda.gov/animal-veterinary/minor-useminor-species/index-legally-marketed-unapproved-new-animal-drugs-minor-species.

Compounded Drugs

The FDA-CVM is responsible for regulating those portions of the FDCA that apply to animal drugs, such as AMDUCA. The FDA-CVM is responsible for regulating who compounds animal drugs and the compounded animal drug itself, which is considered a new (ready to use), unapproved animal drug subject to FDA regulation. The FDA assumes that both the public and animal health are potentially put at risk if compounded drugs are administered to animals since, unliked approved or indexed drugs, they do not go through a pre-market process that includes FDA review of information related to safety, effectiveness, and manufacturing. There is good reason for concern.

The following are examples of what might go wrong when using a compounded drug compared to an approved or indexed drug.

- **Pharmaceutical-related issues** such as quality of the source of the ingredient, adequate stability data to support the shelf-life of the product, chemical interactions, inappropriate pH, inconsistencies between different batches that could impact the quality or potency, and microbial contamination**.**
- **Mathematical errors** that can result in either an exaggerated response or therapeutic failure.
- **Pharmacokinetic concerns** which lead to altered absorption and thus bioavailability. This is particularly problematic with novel drug delivery systems that have not been supported by scientific studies. Examples include slow-release formulations, transdermal gels, compounding in oil suspensions or products that contain multiple APIs. Another issue with bioavailability is having too much drug exposure to the animal, which would require a dose decrease to avoid a toxic adverse response. However, perhaps more problematic--because it is harder to detect--is therapeutic failure resulting from failed drug delivery because bioavailability is reduced. Dose increases would likely be needed in a case of lowered bioavailability. Importantly, even if a scientific study documented the bioavailability of a compounded drug, that data would only be relevant for that specific formulation and recipe.

When is compounding acceptable?

Compounded drugs should not be used unless the needs of the patient cannot be met with a currently marketed FDA-approved (animal or human, pioneer or generic), FDA-conditionally approved, or FDA-indexed drug.

Among the controversies that have impacted the compounding of animal drugs is the source of the API. The FDA interprets AMDUCA to permit compounding of animal drug from a finished FDA-approved or indexed drug and not a BDS as the source of the API.

However, the FDA also recognizes that there are circumstances in which no FDA-approved or indexed drug can be used to treat a specific animal or animal condition. In such limited circumstances, the FDA understands that an animal drug compounded

from bulk may be medically appropriate and will not regulate the product as a new unapproved drug, meaning it will allow the use of that drug under those conditions.

The FDA publishes GFI's to explain how it plans to implement the laws that it regulates. The GFI are not legally binding, but have been available for public review, comment, and input. Simplistically, they represent FDA's current thinking and expectations on the entitled topics. The recently issued GFI #256 Compounding Animal Drugs from Bulk Drug Substances (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-256-compounding-animal-drugs-bulk-drug-substances offers a view into how the FDA anticipates regulating animal drugs compounded from bulk. The GFI are NOT legalizing compounding from BDS but rather are providing circumstances in which the FDA will follow regulatory discretion (allow or tolerate) animal drugs compounded from BDS.

FDA Guidance for Industry #256

The circumstances under which the FDA will follow regulatory discretion for an animal drug compounded from a BDS for non-food producing animals depend upon whether or not the compounded animal drug is intended for an individual patient, or for office stock (that is, intended for the in-clinic use or dispensing for multiple animals). In each case, the standard requirement is that the needs of the patient cannot be appropriately met with a currently marketed approved animal or indexed drug. It is largely up to the compounder to make sure these requirements are met.

Note that State laws regarding animal compounding are regulated by state pharmacy and veterinary licensing boards. The FDA will rely on state boards of pharmacy to implement the regulations. Regulations vary among individual states. Increasingly, states require that compounding follows USP General Chapters. State laws vary on whether compounded drugs can be prescribed, administered, and/or dispensed in the office.

What if you only need to treat a specific patient ("Patient-Specific Use") for non-food-producing animals? In this case, compounding is allowed only when all the following are met:

1. The drug is NOT a copy of a marketed FDA approved or indexed drug. A copy is one that contains the same active ingredient or active moiety and is given by the same route of administration as the marketed FDA-approved, conditionally approved, or indexed drug.
    a. If the drug is a copy, the use of the compounded drug must result in a clinical difference in the identified patient compared to the approved or indexed drug, as determined by the treating veterinarian.
    b. The medical justification must be provided on the prescription and the compounder must keep a record of the clinical difference justification.
    c. Examples would be the approved product contains an allergen or toxic ingredient, or has too high or low a concentration, or cannot be administered safely to the patient.

What if you want to have a quantity of the compounded drug on hand ("Office Stock") to treat a patient in-house or dispense to the patient upon discharge?

In this situation, the FDA will only allow specific animal drug formulations to be compounded from a BDS in nonfood-producing animals if it is on the List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals (https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-stock-drugs-use-nonfood-producing-animals). To be on the list, the formulation must be nominated for consideration. The FDA will review the information provided in the nomination packet and if a need for the specific formulation compounded from the BDS is found, the specific formulation will be listed. The formulation is specific in route, concentration, and species. If the application packet is reviewed and a need is not found for the nominated formulation, the formulation cannot be compounded from a BDS. Drugs that have been reviewed and are not available for use as a BDS are listed on the Bulk Drug Substances Reviewed and Not Listed (https://www.fda.gov/animal-veterinary/animal-drug-compounding/bulk-drug-substances-reviewed-and-not-listed).

For example, the use of bulk buprenorphine HCl for compounding a variety of formulations in minor species has been nominated. After review, the FDA did not list these formulations because currently marketed and approved products (e.g., Zorbium®, Simbadol® and human solutions) can be used to meet their needs. Further, the extended-release buprenorphine (Ethiqa XR®), indexed for rats, mice, ferrets, and non-human primates, means that compounding of office stock from bulk buprenorphine will not be allowed for these species with two exceptions: in the case of captive non-human primates and captive marine animals, a higher concentration buprenorphine injectable solution has been listed because it will allow for easier dosing. Veterinarians and pharmacsts must always check the allowable list of BDS, or drugs not listed, to ensure compliance. In situations when sponsors receive label extensions for other species the FDA lists get updated.

Other requirements for regulatory discretion stipulated in GFI #256

- Compounding occurs by or under the direct supervision of a veterinarian or a pharmacist in a State-licensed pharmacy or Federal facility.
- The standards set by USP must be met and all state and Federal requirements must be met: USP-NF monograph and compliance with other FD&C Act requirements for drug components.
- The drug cannot be distributed by a 3rd party.
- Adverse events must be reported to the FDA within 15 business days.
- The labeling of the compounded drug includes all the required labeling outlined in GFI #256.

What else should I know?

One of the key implications of GFI #256 for practitioners that use buprenorphine in general practice or the laboratory setting for office stock or patient-specific use is that

they must use FDA-indexed buprenorphine in the indexed species unless they have a medical rationale. It is likely the FDA will enforce this since the compounded product is a “copy” of a marketed FDA-approved or indexed drug.

GFI #256 applies to 503A Pharmacies only. Section 503B applies to human drugs and does not apply to animal drugs, and, therefore, does not create an exemption that allows outsourcing facilities to sell animal drugs as office stock**.**

This means that the current GFI #256 does not apply to compounding by 503B Outsourcing Facilities. However, some states currently allow acquisition of compounded animal drugs from 503B Outsourcing Facilities. The FDA is developing additional guidance, “GFI #256B - Compounding Animal Drugs from Bulk Drug Substances: Compounding in Federally-Registered Facilities that are Subject to CGMP” which, when finalized, will explain FDA’s current thinking and regulatory approach for the compounding of animal drugs from bulk substances (see https://www.fda.gov/animal-veterinary/guidance-industry/guidances-under-development-2024).

The GFI indicates that the FDA will rely on State licensing boards to provide routine oversight, but the FDA can also inspect.

What does this all mean for buprenorphine use in your practice?

The currently marketed buprenorphine products that are approved for use in the United States which should be used to treat animals are:

1. Ethiqa XR® injectable extended-release suspension (1.3 mg/ml), unapproved, but FDA-indexed for use in mice, rats, ferrets, and non-human primates for the control of post-procedural pain (cannot be used extra-label).
2. Zorbium® transdermal buprenorphine solution (10 mg/ml), approved for use in cats for treatment of post-operative pain. The anticipated duration of analgesia for the approved use is 4 days.
3. Simbadol® injectable buprenorphine solution (1.8 mg/ml), approved for use in cats for treatment of post-operative pain. The anticipated duration of analgesia for the approved use is 24 hours.
4. Buprenorphine injectable solution (0.3 mg/ml) approved for use in humans as a generic product.
5. Buprenorphine injectable extended-release solution (multiple concentrations ranging from 50 to 356 mg/ml), approved for us in humans (Sublocade®, Brixadi®)

For an individual patient, if the medical needs of the patient cannot be met with any of the above products being used on-label (including Ethiqa XR®) or extra-label (any of the above except for Ethiqa XR®), the following compounding should be used subject to regulatory discretion:

1) Compounding any type of preparation from any of the above approved or indexed products

2) Compounding from a bulk buprenorphine substance if the route of administration is not injectable or topical.
3) Compounding from a bulk buprenorphine substance if the route of administration is injectable or topical, as long as a medically justifiable reason is provided to the compounder.

For office stock (after confirming the state regulations in regard to the administration or dispensing of compounded office stock):

1) Compounding any type of preparation from any of the above approved or indexed products
2) Compounding from bulk buprenorphine only if the product is a 5 to 10 mg/ml injectable polymeric matrix solution for captive non-human primates or captive marine mammals. This is based on the current List of Bulk Drug Substances for Compounding Office Stock drugs for Use in Nonfood-Producing Animals.

Regardless, the regulations set by the board of pharmacy in the state of veterinary licensure must be followed as well as the Drug Enforcement Agency rules and regulations.

Pulling it all together: What does all this mean for me?

1. Compounded drugs present a greater risk of adversity compared to FDA-approved or FDA-indexed drugs. Their use should not be considered equivalent in terms of safety or efficacy compared to FDA-approved or FDA-indexed drugs.
2. Drugs compounded from a bulk drug substance are stringently regulated.
    - If a copy of an FDA approved or indexed drug for a patient-specific use, a medical rationale of the clinical difference from the approved or indexed drug must be documented.
    - If used for office stock, the specific formulation can be compounded only if on a List of ingredients provided by the FDA.
3. Veterinarians should always use a currently marketed FDA-approved (human or animal) or FDA-indexed drug unless the needs of the patient cannot be met.

Important Safety Information

For Captive Rodents, Ferrets, Laboratory Rabbits, and Non-Human Primates:

Only administer Ethiqa XR® by subcutaneous injection. Ethiqa XR is not intended for intravenous, intra-arterial, intrathecal, intramuscular, or intra-peritoneal injection. Do not use in animals with pre-existing respiratory compromise.
Death has been reported when non-steroidal anti-inflammatory drugs (NSAIDs such as meloxicam and carprofen) and Ethiqa XR have been administered concomitantly in mice.

Do not house rats on wood chip-type bedding after administration of Ethiqa XR. **Pica involving wood chip type bedding can be lethal.**

Ethiqa XR may cause sedation, decreased blood pressure, decreased heart rate, decreased gastrointestinal mobility, and respiratory depression. Use caution with concomitant administration of Ethiqa XR with drugs that cause respiratory depression. Animals should be monitored for signs of decreased cardiovascular and respiratory function when receiving Ethiqa XR.

The safety of Ethiqa XR has not been evaluated in pregnant, lactating, neonatal, or immune-compromised animals.

For Humans:

Not for use in humans. Keep out of reach of children and pets.

Ethiqa XR contains buprenorphine, a Schedule III controlled substance with an abuse potential similar to other Schedule III opioids, which may lead to overdose and death.

Ethiqa XR should be handled appropriately to minimize the risk of misuse, abuse, addiction, and criminal diversion, including restriction of access, the use of accounting procedures, and proper disposal methods as appropriate to the laboratory setting and as required by law.

Ethiqa XR should only be handled and administered by a veterinarian, veterinarian technician, or laboratory staff trained in the handling of potent opioids. Wear protective clothing when administering Ethiqa XR to avoid direct contact with human skin, eyes, oral, or other mucus membranes which could result in absorption of buprenorphine and adverse reactions.

For more information, consult the Prescribing Information including the Boxed Warning.

BOXED WARNING

Abuse Potential

ETHIQA XR contains buprenorphine, an opioid that exposes humans to risks of misuse, abuse, and addiction, which can lead to overdose and death. Use of buprenorphine may lead to physical dependence. The risk of abuse by humans should be considered when storing, administering, and disposing of ETHIQA XR. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drugs or alcohol) or mental illness (e.g., depression).

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with accidental exposure to or with misuse or abuse of ETHIQA XR. Monitor for respiratory depression if human exposure to buprenorphine occurs. Misuse or abuse of buprenorphine by swallowing, snorting, or injecting poses a significant risk of overdose and death.

Accidental Exposure

Because of the potential for adverse reactions associated with accidental exposure, ETHIQA XR should only be administered by veterinarians, veterinary technicians, or laboratory staff who are trained in the handling of potent opioids. Accidental exposure to ETHIQA XR, especially in children, can result in a fatal overdose of buprenorphine.

Risks From Concurrent Misuse or Abuse with Benzodiazepines or Other CNS Depressants

Concurrent misuse or abuse of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

See HUMAN SAFETY WARNINGS for detailed information.

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