REGULATORY STATUS OF COMPOUNDED TREATMENTS, BY COUNTRY

Note: This is our understanding of regulatory status of non-FDA-approved compounded treatments such as calcium chloride sterilization in the U.S. and various countries, based on input from two regulatory consultants, one regarding the U.S. and European Union and one international, and input from two U.S.-based attorneys specializing in animal law. It is meant to give a general idea of regulatory requirements, as a starting point for your own research and information-gathering. Before using Calchlorin (calcium chloride/alcohol sterilization), do not rely on this information; consult veterinary authorities, thought leaders, and, if needed, an attorney specializing in animal law in your country and/or state.

Countries without a strong veterinary regulatory structure:
"Greatest good" principle

Veterinary drug regulation capacities vary widely. In 2003, even for medicines for humans, the WHO estimated that fewer than 20% of WHO Member States were thought to have a well-developed drug regulation system, and those that did were mostly industrialized countries. Of the remaining Member States, about 50% implemented drug regulation at varying levels of development and operational capacity. The other 30% either had no drug regulatory authority (DRA) in place, or had only a very limited capacity that barely functioned. *Well-developed* veterinary regulatory agencies are even less widespread. Countries that do not have a strong veterinary regulatory pathway may include Nigeria, Trinidad and Tobago, Bangladesh, Fiji, Ghana, Iraq, Kenya, Nepal, Tanzania, and Sierra Leone.

In general, in countries without a strong veterinary regulatory structure, a veterinarian should make a decision whether or not to use a treatment based on the **greatest good** for the animal and the community, after acquiring as much information as possible about benefits and risks.

For example, a veterinarian may decide that although 1 out of 200 dogs in a surgical spay program will be lost to anesthesia complications and 5 out of 100 will develop an infection at the incision site requiring treatment, the benefits to the dogs' overall lifespan and to the community in general make the treatment worth doing; or that although 1-2 cases of Vaccine Associated Sarcoma (VAS) may occur per 10,000 rabies and feline leukemia vaccinations, the benefits to the animal and community or guardian outweigh the risk. Similarly, benefits and risks must be weighed when choosing to use a new treatment.

In addition to weighing risks and benefits, veterinarians and should also consider social perceptions, the opinion of colleagues, and their ability to monitor animals and provide follow-up care. In all cases, veterinarians should seek the backing and support of local thought leaders before conducting a procedure that is unfamiliar to the community, even if improved outcomes over current procedure are expected.

Countries with a strong veterinary regulatory structure, including the U.S.:
"It depends"

In general, in countries with a strong regulatory structure, veterinarian use of a non-regulator-approved, compounded treatment such as calcium chloride may be permissible if conditions such as the following are true:

- there is no regulatory body-approved veterinary drug for the same indication[1]
- the veterinarian can provide justification and precedence for its use in the peer-reviewed literature

[1] Interpretation of this provision may vary. Does the regulator consider the indication to be "sterilization," in which case Zeuterin™/ Esterilsol™ can be used if available, or "nonsurgical neuter" (a sterilant also designed to reduce hormones and change behavior), in which case no regulator-approved alternative exists?

- the injection solution is sterile-filled by a reputable compounding pharmacy[2]
- there is a valid veterinarian-client-patient relationship[3]
- the veterinarian keeps records of patient outcome

In considering use of calcium chloride, veterinarians in countries with strong regulatory structures should also consider any additional regulations of their local jurisdiction (e.g. state or province) and the expectations of their veterinary board, along with the greatest good for the animal and the community. As in any country, veterinarians should seek collaboration with, and the support of, local thought leaders.

Jurisdictions with a strong veterinary regulatory structure include the European Union, Canada, China, South Africa, Australia, and Japan.

Special situation: Mexico, Bolivia, Panama, Colombia, and Brazil

- Mexico, Bolivia, Panama, Colombia: Esterilsol™ (distribution temporarily on hold as of 2013-2014)
- Brazil: Infertile®

In these countries, an injectable male dog sterilant is already approved for use in dogs. If behavior change is not needed and the approved sterilant is available for purchase, the approved, standardized product should be used. This eliminates the need for a compounded and non-standardized alternative. However, if behavior change similar to that of surgical castration is needed, Esterilsol™ is not an option, since Esterilsol is marked as being more hormone-preserving and causing no significant behavior change.

As of November 2014, international distribution of Esterilsol™ is temporarily on hold while regulatory agencies review paperwork from a new manufacturer, but the makers of Esterilsol™ are hoping for a return to market. Until that return to market, calcium chloride is the only nonsurgical option for either indication (sterilization or sterilization plus neuter) in those countries. In Brazil, Infertile® is on the market for sterilization, but no regulator-approved commercial product exists for sterilization plus neuter.

Special situation: The United States

The United States generally falls under the "strong regulatory structure" category above. However, Zeuterin™ zinc gluconate injection (formerly known as Neutersol) returned to the United States market as an FDA-approved dog sterilant in February 2014, after use in Mexico and Central America under the name Esterilsol™. However, Zeuterin™ became unavailable in early 2016 and the website information has been taken down.

Although the FDA is generally loath to interfere with an individual veterinarian's practice of veterinary medicine unless drug residue in food animals is involved or it receives complaints of bad outcomes, United States veterinary law generally provides for compounding only when there is no commercially-available drug available for the indication. This is partially to protect companies which have spent many years developing products, and partly to ensure the greatest standardization, safety, and oversight of drugs reaching the public. When Zeuterin™ was approved by the FDA for puppies 3-10 months of age, there was no longer a need for a compounded product for young dogs if only sterilization was needed. Now that Zeuterin™ has been taken off the market, the need for a compounded sterilant has returned. Additionally, even if Zeuterin™ comes back on the market sometime in the future, it only provided a partial testosterone reduction, and was not expected to produce significant behavior change. It produced chemical sterilization, not chemical castration/neuter. So if castration-type behavior change is needed, there would still be no commercially-available nonsurgical product on the market that could be used instead of Calchlorin.

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[2] Some U.S. compounding pharmacies have been in the news lately for lax oversight; veterinarians should take care to use a compounding pharmacy known by colleagues to be reliable. In countries without reliable compounding pharmacies and/or with widespread corruption, sterile filling by a trusted university laboratory colleague may be preferable.

[3] The implications of this for use on ferals and street animals are unclear, and may vary from jurisdiction to jurisdiction.

The regulatory status in cats is simpler. There is no FDA-approved nonsurgical sterilant with an indication for use in cats, with or without hormonal and behavior impact; so in cats, calcium chloride remains the only nonsurgical option.

High-volume use of calcium chloride is new in the United States, only beginning in 2014. A number of spay/neuter programs are now using it. Because the regulatory rules are ambiguous and subject to varying interpretations, and also because the letter of the law and the current near-universal practice patterns of compounding are far apart, further pioneers in the use of calcium chloride should not only be sure that they can meet the types of conditions listed above under "Countries with a strong veterinary regulatory structure," but also inform their state veterinary board before widespread use, seek support of key veterinary board thought leaders, be sure they are prepared to defend their actions in front of a state veterinary board should objections be raised, have the full support of their community to reduce the chance of objections being raised, or all of the above. In sum, the second-adopter users of calcium chloride should lay a groundwork of support with their state veterinary board before use and be sure enough of their mission to be prepared to defend it to the state veterinary board and in the public eye.

About compounding in the U.S.

Great ambiguity exists around compounding in the U.S., with nearly all small-animal veterinarians ordering drugs compounded from bulk substances in situations that are technically contrary to FDA regulations, and even the AVMA recognizing the reality that compounding from bulk substances is medically necessary in certain situations (see general policy and bulk substances policy, https://www.avma.org/KB/Policies/Pages/Compounding.aspx and https://www.avma.org/KB/Policies/Pages/Compounding-from-Unapproved-Bulk-Substances-in-Non-Food-Animals.aspx , as well the AVMA's activism on this front and letters sent by the AVMA to the FDA).

Because the FDA is primarily concerned about safety and residue in food animals, the primary risk to veterinarians is likely to be questions around "standard of practice" and use of a new, not-yet-standard procedure in the case of a complaint to the state veterinary board, not risk of action by the FDA against an individual veterinarian (unless extreme harm is being created) for compounding from bulk subtances that is widely recognized to be a near-universal practice, under a situation which the AVMA considers medically necessary (no approved drug is available for the indication, sterilization with neuter). To follow best practices and be most protected, a veterinarian should order from a PCAB-certified pharmacy known to be reputable and considered to by of high quality by colleagues and thought leaders.

Can veterinarians self-compound calcium chloride in alcohol to avoid some of the ambiguities surrounding compounding pharmacies? According to U.S. law, self-compounding is legal for veterinarians, but only in states in which state law has specifically granted permission. Only 3 of the 39 states reviewed appear have specifically granted this permission to veterinarians to compound under specific sets of circumstances: Colorado, Georgia and Texas. In any case, in all states in the U.S., veterinarians would do best, for the protection of both themselves and the animals, to use a highly-regarded, PCAB-approved sterile-filling-capable compounding pharmacy.

Information about the U.S. regulatory structure can be found at the FDA website: http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074656.htm and by searching "veterinary compounding regulation." Information about the AVMA's policy on compounding can be found on the AVMA website, (https://www.avma.org/KB/Policies/Pages/Compounding-from-Unapproved-Bulk-Substances-in-Non-Food-Animals.aspx . State-by-state listing of veterinary boards and authorities can be found at the AVMA's website, https://www.avma.org/advocacy/stateandlocal/resources/pages/state-legislative-resources.aspx .

Non-U.S.: Unsure of your country's status?

Information about your country's regulatory status may be sought by doing an online search of your country name and "veterinary drug regulations compounding;" by consulting colleagues; by seeking the guidance of a paid regulatory expert; from documents such as "The Role of Official Bodies in the International Regulation of Veterinary Biologicals" and "Background and objectives of the VICH considerations regarding wider international harmonisation" produced by the World Organisation for Animal Health and its collaborating center on veterinary medical products in Fougeres, France (http://www.oie.int/our-scientific-expertise/veterinary-products/); and possibly from the International Journal of Compounding Pharmacists. The Alliance for Contraception in Cats & Dogs may be able to put practitioners in contact with an appropriate regulatory consultant familiar with international veterinary law and regulations in your country.

For more information:

- For the U.S., the AVMA maintains a state-by-state listing of veterinary authorities, online https://www.avma.org/advocacy/stateandlocal/resources/pages/state-legislative-resources.aspx .
- California-based veterinarians who are members of the CVMA can make use of its legal services resource, http://www.cvma.net/4DCGI/cms/review.html?Action=CMS_Document&DocID=70136&MenuKey=5 .
- For U.S.-based use, legal opinions and guidance can be obtained from attorneys specialized in animal and shelter medicine law. Two resources: Bonnie Lutz at Klinedinst and Dan Baxter at Wilke Fleury .
- Further resources and links available at ParsemusFoundation.org and Calchlorin.org .

For informational purposes only; animal population management stakeholders should read all information available, including all published studies, in order to make an informed decision about whether use is consistent with the greatest good, and permitted by regulation, in their context.

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