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CLIENT ALERT

FDA Signals Restrictive Regulatory Approach in Draft Guidance on Animal Drug Compounding

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On May 18, 2015, the U.S. Food and Drug Administration ("FDA") withdrew its 2003 *Compliance Policy Guide – Section 608.400, Compounding of Drugs for Use in Animals* and signaled new plans to constrain animal drug compounding in its *Draft Guidance for Industry (GFI) #230, Compounding Animal Drugs from Bulk Drug Substances* ("Draft Guidance").[1] The Draft Guidance suggests that a dramatic shift in the FDA's enforcement approach may be underway and provides insight into the FDA's enforcement priorities and its interpretation of the applicable regulatory regime. Stakeholders have until August 17, 2015, to submit comments that could influence the final guidance and policies adopted by the agency.

The Draft Guidance states that, like human drug compounding, the FDA aims to ensure that state-regulated traditional compounding of animal drugs is permitted only in response to prescriptions for individually identified patients. This conflicts with laws in several states that currently authorize the practice of "office use" compounding, in which animal drugs are compounded in advance of receiving patient-specific prescriptions. In addition, the FDA encourages sterile animal drug compounders to register as "outsourcing facilities"—a category of federally regulated entities that was established through enactment of the Drug Quality and Security Act of 2013 ("DQSA") and has been utilized for human drug compounding facilities.

However, unlike its approach to the enforcement of human drug compounding activities, the FDA's proposed enforcement approach for animal drug compounding relies almost exclusively on its statutory authority over animal drug *manufacturing*. In the Draft Guidance, the FDA does not point to any statute or regulation that expressly permits the agency to regulate animal drug *compounding*. By its terms, the DQSA does not apply animal drug compounding (which the FDA acknowledges), and, during the term that it passed the DQSA, Congress considered but declined to pursue legislation that would

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[1] 80 Fed. Reg. 28624 (May 19, 2015). The Draft Guidance is available online at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM446862.

have subjected animal drug compounding to regulatory oversight in a manner similar to human drugs. (Congress made this decision despite a 2011 court case limiting the FDA's authorities over animal drug compounding.) All of this may raise questions about the FDA's plans.

In this Client Alert, we outline the parameters of the Draft Guidance and identify some of the legal hurdles that the FDA may have to overcome in seeking to translate the Draft Guidance into official agency policy.

The FDA's Draft Guidance

In the Draft Guidance, the FDA expresses its view that compounding from bulk substances is a practice that is permissible only as an option of last resort. In effect, the agency proposes that pharmacies and veterinarians adhere to the following decision-making hierarchy for treatment options:

- Option 1: Animal patients should be treated with any available FDA-approved or indexed[2] animal drugs.

- Option 2: In the absence of an approved animal drug, an approved human drug may be used for "extralabel use" under Sections 512(a)(4) and (5) of the Federal Food, Drug, and Cosmetic Act ("FDCA").

- Option 3: Where there is no available drug to treat a particular animal patient's unique condition, a drug may be compounded from animal or human drugs that contain the needed active ingredient(s).

- Option 4: In "limited circumstances," where there is no available animal or human drug that may treat a particular animal's unique condition (either directly or through compounding with the drug), it may be appropriate to compound a drug from bulk drug substances.

With regard to this last option, while the FDA views the compounding of animal drugs from bulk substances to be unlawful, it proposes to refrain from taking enforcement action against pharmacies, veterinarians, and registered outsourcing facilities that engage in the practice, as long as the compounding activities comply with the conditions outlined below.

State-Licensed Pharmacies

The Draft Guidance provides that state-licensed pharmacies are permitted to compound animal drugs from bulk drug substances, provided that the following conditions are met:

[2] An "indexed" animal drug is a drug listed on the FDA's Index of Legally Marketed Unapproved New Animal Drugs for Minor Species ("Index"). Although technically unapproved, a drug listed on the Index may be legally marketed for a specific use in certain minor species.

- The drug is compounded by or under the direct supervision of a licensed pharmacist, in accordance with Chapters 795 and 797 of the *United States Pharmacopeia and National Formulary.*

- The drug is dispensed after the receipt of a valid prescription from a veterinarian for an individually identified animal patient that comes directly from the prescribing veterinarian or from the patient's owner or caretaker to the compounding pharmacy.

    - With regard to "anticipatory compounding," a drug may be compounded in advance of receipt of a prescription in a quantity that does not exceed the amount of drug product that the state-licensed pharmacy compounded pursuant to *patient-specific prescriptions* based on a history of receipt of such patient-specific prescriptions for that drug product over any consecutive 14-day period within the previous six months.

    - Under the above definition, anticipatory compounding that is not tied to specific patients (i.e., "office use" compounding) may not be permitted.

- The drug is not intended for use in food-producing animals, and the prescription contains the following statement: "This patient is not a food-producing animal."

- If the drug contains a bulk drug substance that is a component of any marketed FDA-approved animal or human drugs—

    - there must be a change between the compounded drug and the comparable FDA-approved drug that produces a *clinical difference* for that individually identified animal patient, and

    - the prescription or documentation accompanying the prescription must contain a statement confirming that the change produces a clinical difference.

- If there is an FDA-approved animal or human drug with the same active ingredient(s), there must be documentation of the pharmacy's determination that the compounded drug cannot be made from the FDA-approved drug(s). In other words, the FDA would prefer reconstitution of approved drugs in other forms, as opposed to starting from the active ingredients.

- The pharmacy must receive prescription documentation that identifies the species of animal for which the drug is prescribed and states the following: "There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner under section 512(a)(4) or (5) and 21 CFR Part 530 to appropriately treat the disease, symptom, or condition for which this drug is being prescribed."

- The bulk drug substance used to compound the drug must be manufactured by an establishment that is registered under Section 510 of the FDCA and be accompanied by a valid certificate of analysis.

- The drug must not be sold or transferred by an entity other than the entity that compounded the drug.

- Within 15 days of becoming aware of any product defect or serious adverse event associated with the drug compounded from bulk drug substances, the pharmacy must report it to the FDA.

- The label of any compounded drug must indicate the species and name of the intended animal patient and the name of the owner or caretaker.

Veterinarians

Licensed veterinarians that compound animal drugs are subject to conditions similar to those imposed upon pharmacies, with the following modifications:

- The drug is compounded and dispensed by a veterinarian to treat an individually identified *animal patient under his or her care*.

- There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner to appropriately treat the disease, symptom, or condition for which the drug is prescribed.

- The drug is not sold or transferred by the veterinarian compounding the drug. For purposes of this condition, a sale or transfer does not include administration of the compounded drug to a patient or the dispensing of the compounded drug to the owner or caretaker of an animal under his or her care.

The conditions that apply to veterinarians do not mention “office use” compounding.

Outsourcing Facilities

Finally, under the Draft Guidance, FDA-registered outsourcing facilities (non-traditional compounders) may compound animal drugs from bulk drug substances, provided that the following conditions are met:

- The drugs are compounded only from bulk drug substances appearing on an appendix that will be published along with the finalized Draft Guidance. The FDA has issued a *Federal Register* notice soliciting nominations for such bulk drug substances.[3] The agency plans to review and periodically update the nominated bulk drug substances on a rolling basis.

[3] 80 Fed. Reg. 28622 (May 19, 2015).

- The drug is compounded by, or under the direct supervision of, a licensed pharmacist.

- The drug is compounded in accordance with current good manufacturing practice ("cGMP") requirements.

- The bulk drug substance used to compound the drug must be manufactured by an establishment that is registered under Section 510 of the FDCA and be accompanied by a valid certificate of analysis.

- The drug must not be sold or transferred by an entity other than the outsourcing facility that compounded the drug.

- Within 15 days of becoming aware of any product defect or serious adverse event associated with the drug compounded from bulk drug substances, the outsourcing facility must report it to the FDA.

- All drugs compounded for animals by an outsourcing facility are included in the report required by Section 503B of the FDCA to be submitted to the FDA each June and December identifying the drugs made by the outsourcing facility during the previous six-month period and providing:

    - the active ingredient(s) along with their source(s);

    - the national drug code ("NDC") number of the source ingredient(s);

    - the strength of the active ingredient(s) per unit;

    - the dosage form and route of administration;

    - the package description;

    - the number of individual units produced; and

    - the NDC number of the final product, if assigned, along with an identification of which reported drugs were intended for animal use.

- The veterinarian's prescription or order must state that the drug is intended to treat the species and condition(s) for which the substance is listed in the finalized appendix.

- The drug label must comply with certain requirements and must include language such as "not for resale," "compounded by [name of outsourcing facility]," and "adverse events associated with this compounded drug should be reported to FDA on Form FDA 1932a."

- Drugs *may* be compounded by registered outsourcing facilities for office use.[4]

The Significance of the Draft Guidance for Animal Drug Compounders and Manufacturers

The FDA has long maintained that, while it generally defers to state authorities regarding the day-to-day regulation of animal drug compounding, it retains enforcement discretion over activities that resemble drug manufacturing. This policy remained unchanged in the wake of the DQSA, which overhauled the regulatory treatment of human drug compounding but did not address animal drugs or veterinary medicine. However, through the Draft Guidance, the FDA has signaled its intent to take a more aggressive enforcement posture and subject animal drug compounding to far greater regulatory scrutiny. Veterinarians and smaller pharmacies may view the proposed conditions and associated documentation requirements as especially burdensome. Additionally, the FDA is indicating that it will use its enforcement powers to significantly restrict "office use" compounding, which will only be permitted on an anticipatory basis for specific patients with a history of prescriptions. This could be a very significant change because, although the FDA essentially discouraged this practice in its 2003 Compliance Policy Guide, over the last several years, the practice has been fairly common and the agency had appeared to accept the practice, provided that the volume of office use compounding was not exorbitant.

While the Draft Guidance will likely invite pushback from compounders and veterinarians who compound their own drugs, it will likely be embraced by pharmaceutical manufacturers, which often face significant competition from compounded drugs that are not subject to the same market entry costs as FDA-approved animal drugs. The limits that the Draft Guidance, if finalized, will place on compounders will likely reduce the threat of competition on certain animal drugs, which, in turn, could encourage new investments in drug development.

Unanswered Questions Regarding the FDA's Authority to Regulate Animal Drug Compounding

While the Draft Guidance announces the FDA's proposed enforcement approach, it does not address the question of the FDA's statutory authority to regulate animal drug compounding. The agency previously argued that the compounding of animal drugs from bulk drug substances is impermissible, but this interpretation was rejected by the only federal court that has directly addressed the scope of the FDA's authority over this practice. *See United States v. Franck's Lab, Inc.*, 816 F. Supp. 2d 1209 (M.D. Fl. 2011) (holding that the FDCA did not authorize the FDA to enjoin a state-licensed pharmacy from compounding animal drugs from bulk substances pursuant to a valid veterinary prescription). Leading up to the passage of the DQSA, Congress originally proposed to establish a regulatory framework for animal drug compounding that would be similar to the framework for human drug compounding.[5] However, the language addressing animal drug compounding was left out of the DQSA. All of this will undoubtedly lead

[4] Draft Guidance, Appendix A.
[5] S.959, Pharmaceutical Quality, Security, and Accountability Act (introduced May 15, 2013).

some to question whether Congress has granted authority to the FDA to regulate animal drug compounding as it proposes to do in the Draft Guidance.

Finally, it is unclear whether the FDA will move forward with trying to enforce the principles of the Draft Guidance before it is finalized. In certain instances, the FDA has taken enforcement action even before the publication of final guidance. The agency may choose to do the same here.

All interested stakeholders should take the opportunity to present their views to the FDA by offering comments on the Draft Guidance and proposing bulk drug substances for inclusion in the accompanying appendix that would define what bulk compounds outsourcing facilities can use to compound animal drugs. In the meantime, pharmacies and veterinarians that engage in animal drug compounding should carefully review relevant FDA pronouncements and be prepared to modify their current practices, policies, and procedures, if necessary. Also, if inspected by the FDA, pharmacies and veterinarians should be prepared to address the issues raised by the Draft Guidance.

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