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Human and Veterinary Pharmacy Compounding: Industry, Regulatory and Consumer Perspectives

Robert J. Timko, R.Ph., Ph.D., RhoTau Pharma Services LLC, and Philip E. M. Crooker, J.D., Shire Development LLC

Abstract

Purpose: To present the current status of human and veterinary compounding.

Methods: Review and discuss the regulatory concerns and status of human and veterinary compounding from an industry, consumer and health authority perspectives.

Results: At one time, nearly all prescriptions were compounded preparations. There is currently an ongoing demand for compounded prescription medications because manufacturers cannot fulfill all needs. Compounding pharmacies are a long-standing yet less-frequently discussed element in the complex matrix of prescription drug manufacturing, distribution and patient use. The drug shortage situation for many necessary drug products is a complicating factor that has led to the numerous quality issues which currently plague large scale compounding pharmacies. The Food, Drug and Cosmetic Act does not distinguish compounding from manufacturing or other processing of drugs for use in humans and animals. The United States Congress has recently passed the Drug Quality and Security Act which is applicable to human drugs. This legislation establishes a clear boundary between traditional compounding pharmacy and compounding manufacturers. It clarifies a national uniform set of rules for compounding manufacturers while preserving the States' primary role in traditional pharmacy regulation. It also clarifies the Food and Drug Administration's (FDA's) authority over the compounding of human drugs while requiring the Agency to engage and coordinate with States to ensure the safety of compounded drugs. For veterinary drugs, compounding can only occur under certain limited situations as specified by the Food, Drug and Cosmetic Act, the Extra Label Drug Use regulations and the Animal Medicinal Drug Use Clarification Act (AMDUCA) and judicial interpretation of these instruments through individual case law. Under AMDUCA and its implementing regulations published in the Code of Federal Regulations, Title 21, Part 530 (21 CFR 530), any extralabel use of an approved new or animal or human drug must be by or on the lawful order of a veterinarian with the context of the veterinarian-client-patient relationship. Extralabel use must also comply with other provisions of 21 CFR 530. These regulations further stipulate that nothing in the regulations should be construed as permitting compounding of animal drugs from bulk drug substances. The recently issued Draft Guidance for Industry, 'Compounding Animal Drugs form Bulk Drug Substances,' replaces the FDA Compliance policy Guide Section 608.400 entitled 'Compounding of Drugs for use in Animals.' This draft guidance outlines specific limited conditions when compounding of animal drugs form bulk drug substances may be an appropriate treatment option.

Conclusions: The individual States and FDA authority covers compounding for both human and veterinary drugs. The States are the primary regulator of community drug stores, large chains, and specialty pharmacies. Pharmacies making and distributing drugs in a way that is outside the bounds of traditional pharmacy compounding are of great concern to the FDA

Introduction

Pharmacy compounding is a vital service that helps many people and animals, and serves an important public health need for patients who cannot be treated with a U.S. Food and Drug Administration (FDA)-approved medication.

Pharmacy compounding is the art and science of preparing personalized medications for patients. Compounded medications may be made by combining or altering individual ingredients which are mixed together in the exact strength and dosage form required by the patient. Commercially available dosage forms may sometimes be modified to better fit the dosing needs of an individual. These operations are performed by a licensed pharmacist in response to a prescription written by a licensed physician or veterinarian based on the medical needs of an individual patient.

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling.

History of Pharmacy of Compounding

Compounding of medicines can be traced back to ancient times with compounding pharmacies existing for thousands of years in some form. The Middle East purportedly had the first pharmacy in Baghdad in the first century AD; alchemy and compounding were used.

Compounding pharmacies have been in America since the early 1800s and eventually gave way to the modern pharmaceutical industry. Pharmacy owners of the past like Merck and Dohme from Merck Sharp and Dohme; Eli Lilly; Warner; Lambert; Smith of Smith Kline; and French Labs went on to be manufacturers making many of the commercial medications we have today.

With the advent of mass drug manufacturing in the 1950s and 1960s, compounding rapidly declined. The pharmacist's role as a preparer of medications has evolved to primarily that of a dispenser of manufactured dosage forms. However, this one-size-fits-all nature of many mass-produced medications meant that some patients' needs were not being met.

Human and Veterinary Compounding Current Environment

There is an ongoing demand for compounded prescription medications because manufacturers cannot fulfill the needs of all individual human or animal patients. The drug shortage situation for many necessary drug products is a complicating factor that has led to the numerous quality issues that currently plague large scale compounding pharmacies. In particular, the generic injectable preparations are a major source of concern. Also, with the concept of personalized medicines gaining popularity, many physicians are seeing the benefit of custom compounded preparations and adding them to their daily prescription protocols.

The modern compounded prescription is typically defined as being for a single, individual patient only. The most common modern day preparations are for:

- ❑ Patients requiring limited dosage strengths.
- ❑ Patients requiring a different formulation, such as turning a tablet into a liquid or topical ointment or cream.
- ❑ Patients requiring an allergen-free medication.
- ❑ Patients who absorb or excrete medications abnormally.
- ❑ Patients who need drugs that have been discontinued by pharmaceutical manufacturers.
- ❑ Individuals who may require flavored additives in preparations.

Examples of Recent Compounding Issues

- ❑ The Fall 2012 outbreak of fungal meningitis has been linked to an injectable steroid medication prepared by a firm in Framingham, Massachusetts. Hundreds of people across the country were infected with serious injuries and deaths were also reported.

- ❑ In April 2013, the FDA announced that as a result of a priority inspection program, federal regulators found numerous unsafe practices at 31 compounding pharmacies located in 18 states. Observations concerning sterility practices, inappropriate conditions for sterile processing, and other practices that create risk of contamination were noted. All but one pharmacy that was inspected received an inspection observation report (FDA Form 483) that lists objectionable conditions observed at the facilities. The one firm that did not receive a FDA Form 483 was not preparing sterile drugs. Some of the problems found included unidentified black particles floating in vials of sterile medicine; rust and mold in cleanrooms where sterile injectable medications were manufactured; employees wearing nonsterile lab coats and handling sterile preparations with bare hands.

- ❑ In June 2015 as a result of an FDA inspection, the National Institute of Health (NIH) suspended its compounding pharmacy operation due a range of issues including facilities, training and non-compliance to standard operating procedures that resulted in injectable products with fungal contamination.

- ❑ Recent FDA inspections for the compounding of veterinary drugs by compounding pharmacies have resulted in a number of Warning Letters citing significant violations of the regulations governing the compounding of veterinary drugs. The most common violations cited were:
  - o The use of bulk drug substance to compound veterinary drugs;
  - o Compounding veterinary drugs from bulk drug substances which have been withdrawn or removed from the market for human use for safety reasons;
  - o Compounding of drugs where FDA approved animal drug products as labeled will appropriately treat the diagnosed condition;
  - o Compounding of veterinary drug products outside the context of a valid VCPR;
  - o Compounded drug products were not labeled with adequate directions for use as specified by the veterinarian.

States Regulatory Status

The States are the primary regulator of pharmacies, including community drug stores, large chains, and specialty pharmacies. The practice of pharmacy, including the licensing of individual pharmacist and pharmacies, is regulated by a State Board of Pharmacy which has the primary responsibility for day-to-day oversight. In general, State rules and regulations address pharmacy standards and requirements, including items such as required licenses for each facility and for the credentialed pharmacists and other employees who work there.
In general, State regulations grant the pharmacists and pharmacies, upon the receipt of a prescription written by an authorized physician or veterinarian, the explicit authority to compound or mix pharmaceutical ingredients into a patient-ready preparation. Some States address this responsibility in broad terms simply stating that it is a pharmacist's responsibility. Other States have more detailed compounding requirements. For many States, under current rules and regulations, there is no differentiation between licensed pharmacists and pharmacies that simply dispense commercially manufactured pharmaceutical preparations made by large-scale pharmaceutical companies and those that prepare specially compounded preparations based on personalized prescriptions. Since 2011, at least 16 States have enacted laws affecting the practices of compounding pharmacies.

U.S. Food and Drug Administration

Until recently, compounding pharmacies have not been required to register with the FDA. Therefore, they did not need to tell the FDA what drugs they were making or how, even though their operations may have appeared more consistent with large-scale drug manufacturers than with traditional pharmacies.

Compounded medications are not FDA approved. This means that the FDA has not verified their quality, safety, and effectiveness. Poor compounding practices can result in contamination or in medications that don't possess the required strength, quality, and purity.

Pharmacies making and distributing drugs in a way that is outside the bounds of traditional pharmacy compounding are of great concern to the FDA. Compounding pharmacies are a long-standing yet less-frequently discussed element in the complex matrix of prescription drug manufacturing, distribution, and patient use. Generally, the FDA will continue to defer to State Authorities regarding less-significant issues related to pharmacy compounding of drugs. However, the FDA expects that, in such cases where more serious quality or safety situations occur, cooperative efforts will result in coordinated investigations, referrals, and follow-up actions by the States.

Relevant Websites

American Association of Bovine Practitioners – www.aabp.org
American Association of Equine Practitioners – www.aaep.org
American Association of Feline Practitioners – www.catvets.com
American Veterinary Medical Association – www.avma.org
Animal Drugs @ FDA – www.accessdata.fda.gov/scripts/animaldrugsatfda
FDA Center for Veterinary Medicine – www.fda.gov/AnimalVeterinary/default.htm
National Association of Boards of Pharmacy – www.nabp.net
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations – www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm
Pharmacy Compounding Accreditation Board – www.pcab.info
United States Pharmacopeia National Formulary (USP-NF) - www.usp.org

United States Pharmacopeial Convention – Pharmacy Compounding

Drugs subject to USP standards include both animal and human drugs. USP-NF standards also have a role in U.S. federal law; a drug or drug ingredient with a name recognized in the USP-NF is deemed adulterated if it does not satisfy compendia standards for strength, quality or purity. General chapters numbered below <1000> are required while those numbered above <1000> are informational and are not intended to be required by regulatory agencies.

There are currently five compounding General Chapters in the USP–NF.

- ❑ **Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations** provides guidance on applying good compounding practices in the preparation of nonsterile compounded formulations for dispensing and/or administration to humans or animals. It includes simple, moderate, and complex categories of compounding; definitions of terms (e.g., beyond-use date, hazardous drug, stability); and criteria for compounding of drug preparations (e.g., suitable compounding environment, use of appropriate equipment).
- ❑ **Chapter <797> Pharmaceutical Compounding—Sterile Preparations** provides procedures and requirements for compounding sterile preparations.
- ❑ **Chapter <1160> Pharmaceutical Calculations in Prescription Compounding** provides guidance and assistance to pharmacists in performing the necessary calculations when preparing or compounding any pharmaceutical drug.
- ❑ **Chapter <1163> Quality Assurance in Pharmaceutical Compounding** describes a quality assurance program as a system of steps and actions that must be taken to ensure the maintenance of proper standards in compounded preparations.
- ❑ **Chapter <1176> Prescription Balances and Volumetric Apparatus** provides information about acceptable balances and volumetric apparatus (e.g., burets, pipets, cylinders, conical graduates, medicine droppers) used to weigh or measure medicinal and other substances required in prescriptions or in pharmaceutical compounding.

An additional General Chapter that should be considered when preparing compounded prescriptions is **Chapter <1191> Stability Considerations in Dispensing Practice**. General Chapter topics in development that also have implications for Compounding Pharmacists include Hazardous Drugs – Handling in Healthcare Settings and Compounding for Investigational Studies.

Human Drug Compounding

The United States Congress recently passed the Drug Quality and Security Act (DQSA) (2013). This Act created Section 503B in the Food Drug and Cosmetic Act which establishes a clear boundary between traditional compounding and compounding manufacturers. It clarifies a national, uniform set of rules for compounding manufacturers while preserving the States' primary role in traditional pharmacy regulation. It defines FDA's authority over the compounding of human drugs while requiring the Agency to engage and coordinate with States to ensure the safety of compounded drugs. This legislation also bans compounding pharmacies from making a copy of an approved and marketed drug product.

Compounding pharmacies that practice outside the scope of traditional pharmacy practice must register as an outsourcing facility that is subject to FDA oversight in much the same way as traditional pharmaceutical manufacturers.

The law defines an "outsourcing facility" as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of section 503B. An outsourcing facility is not required to be a licensed pharmacy and may or may not obtain patient specific prescriptions. Patients and providers have the ability to purchase preparations from outsourcing facilities that comply with FDA quality standards.

Outsourcing facilities:

- ❑ Must comply with CGMP requirements;
- ❑ Will be inspected by FDA according to a risk-based schedule; and
- ❑ Must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound.

An outsourcing facility can qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from current good manufacturing practice (CGMP) requirements.

Patient Considerations

Historically, legally authorized prescribers, wrote a prescription for a patient with special needs, and the pharmacist prepared a suitable dosage form to meet the individual patient's requirements. In today's environment, this may no longer be an accurate description of pharmacy compounding. In some cases, it has evolved into a more complex large-scale, manufacturing-type operation.

Patients must still rely on the expertise of the individual pharmacist who prepares the compounded medicament for its quality, safety, and effectiveness. It is the pharmacist's responsibility to ensure that all State and federal requirements are met in preparing and dispensing a legally compounded prescription for a specific patient.

The ingredients added to a drug formulation are intended to provide an optimal chemical and physical environment to ensure the stability of the drug and aid in its packaging and handling. The safety and efficacy of a compounded drug product may be adversely impacted by the addition of other inactive ingredients which may alter the chemical potency or physical and chemical stability of the drug substance.

Many drugs intended for humans are frequently compounded for a veterinary species (e.g. dog, cat, horse, etc.). In these instances, there is the need for the veterinarian to take into consideration the differences in anatomy and physiology which can impact drug pharmacokinetics and ultimately its efficacy and safety.

The following are some tips for patients when receiving compounded prescriptions.

- ❑ Ask your physician or veterinarian if an FDA-approved drug is available and appropriate for the condition being treated.
- ❑ Check with the pharmacist to see if he or she is familiar with compounding the preparation in your prescription, and whether he or she has the training, equipment, and processes in place to compound that preparation.
- ❑ Get information from your physician, veterinarian or pharmacist about proper use and storage of the compounded preparation.
- ❑ If you receive a compounded drug, ask the pharmacist if your physician or veterinarian asked for it to be compounded.
- ❑ If as a patient, you experience any problems or adverse events, contact your physician, veterinarian or pharmacist immediately.
- ❑ Report any adverse events experienced while using the preparation to FDA's MedWatch program (Human Drugs) or to the Center for Veterinary Medicine (CVM) via its Adverse Event Reporting System (Animal Drugs).

Veterinary Drug Compounding

Palatability, ease of administration, and dispensing consideration are factors when formulating drugs for animals. Veterinary Compounding is legal when both Federal and State rules are followed. The State Boards of Pharmacy oversee pharmacy practices within the states, while the state veterinary medical boards oversee the practice of veterinary medicine, including prescribing.

FDA permits veterinary compounding under the requirements of the Federal Food, Drug & Cosmetic Act (FFDCA), the Extra Label Drug Use (ELDU) regulations and the Animal Medicinal Drug Use Clarification Act (AMDUCA) from FDA-approved animal or human drug products when a veterinarian believes there is no approved animal or human drug product available in the relevant dosage form and concentration to appropriately treat the diagnosed condition. Compounding from human drugs for use in food animals is not allowed if an approved animal drug can be utilized. The recently enacted DQSA does not apply to veterinary drug compounding.

Although FDA considers it a violation of the FD&C Act, it acknowledges the need for compounding from bulk active or raw ingredients within certain areas of veterinary practice. The recently issued Draft Guidance on Animal Drug Compounding from Bulk Drug Substances outlines circumstances when animal drugs compounded from bulk drug substances may be an appropriate treatment option.

In cases where no approved drug or combination of approved drugs can adequately address a specific patient's need, veterinarians and pharmacists must carefully assess whether the use of an unapproved substance in a compounded veterinary prescription is consistent with state and federal law and FDA policy.

Before prescribing a compound preparation, the following requirements should be met:

- ❑ A valid Veterinarian-Client-Patient Relationship (VCPR),
- ❑ The health of the animal is threatened or suffering or death may result from failure to treat,
- ❑ There is no FDA-approved, commercially available animal or human drug that, in its available dosage form and concentration, will appropriately treat the patient,
- ❑ The product is made from an FDA-approved commercially available animal or human drug,
- ❑ The product is compounded by a licensed veterinarian or a licensed pharmacist on the order of a veterinarian within the practice of veterinary medicine,
- ❑ The compounded product is safe and effective,
- ❑ For animals produced for human consumption, a withdrawal time for the compounded product has been established and observed by the veterinarian.

Compounding in Food-Producing Animals

Using a compounded drug in food animals is reserved for when there is absolutely no other choice for treating that animal's medical condition and when safe use of that animal for human food purposes can be predicted following discontinuation of the drug.

All federal requirements for use of drugs in food producing animals apply, including that the veterinarian must establish a substantially extended withdrawal interval for the compounded preparation supported by appropriate scientific information.

Safety and Effectiveness of Compounded Medicaments

Compounded drugs have not been evaluated by the FDA approval process for safety, efficacy, stability, potency and consistency of manufacturing.

The use of compounded preparations should be limited to the unique needs in specific patients for which a physiological response to therapy or systemic drug concentrations can be monitored, or those for which no other method or route of drug delivery is practical.

Do not assume compounded drugs contain the stated amount of drug substance or the desired drug substance, or are safe and efficacious for the intended use unless adequate documentation is available.

Only licensed pharmacists acting on orders of licensed veterinarians can compound veterinary drugs.

Physicians and Veterinarians can help to ensure therapeutic success:

- ❑ Prescribe from a reputable and trustworthy compounding pharmacy.
- ❑ Consider whether the pharmacy is compliant with the United States Pharmacopeia Convention (USP) standards.
- ❑ Consider whether the pharmacy is certified by an independent body, for example, the Pharmacy Compounding Accreditation Board, and/or the National Association of Boards of Pharmacy's Vet-VIPPS, as appropriate.
- ❑ Most State Boards of Pharmacy require that an out-of-state pharmacy register with their State prior to filling prescriptions to be mailed into their State.
- ❑ For a Compounding Pharmacy, verify that it is in compliance with the FD&C Act Section 503B for Human Drug Compounding Facilities.
- ❑ Ask the Compounding Pharmacist for evidence that the compounded drug is safe and effective. For example, request information to support the stability and assigned beyond use (expiration) date.

The Future for Compounding Pharmacy

Traditional compounding pharmacies will continue to be regulated by State Boards of Pharmacy. Compounding pharmacies that practice outside the scope of traditional pharmacy practice need to register as an outsourcing facility that would be subject to FDA oversight in much the same way as traditional pharmaceutical manufacturers.

For veterinary products, current FDA regulations clearly describe specific circumstances under which the FDA will either permit compounding for use in animals or may exercise its enforcement discretion.

There is clearly a need to build quality into compounded drug products. Inclusion of a Control Strategy involving risk assessment and mitigation for the personnel, facilities, documentation and various operations involved in compounding preparations can help minimize/eliminate a number of the recent issues that that have plagued compounding. Development of quality management systems for compounding pharmacies is key to assuring that the prescribed compounded medicament meets all current good preparation (manufacturing) standards while delivering the drug at the prescribed dose in a suitable and safe manner to the human or animal patient.

Conclusions

Compounding of medications is an important part of the practice of the pharmacy profession. Because compounded medications do not have FDA approval, a Pharmacist has the responsibility to ensure that compounded medications are of suitable quality, safety and efficacy.

Compounding pharmacies, in addition to complying to State regulations, must now ensure that they comply with the recently implemented federal legislation and FDA requirements. The FDA expects that, in such cases where serious quality or safety situations occur, cooperative efforts between the States and the Agency will result in coordinated investigations, referrals, and follow-up actions. When the scope and nature of a pharmacy's activities raise concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the FD&C Act, the FDA will consider enforcement action.

In essence, compounding Pharmacists need to build quality into their compounded products. Inclusion of the concepts of Quality-by-Design in to compounding of preparations can help ensure their safety, stability, and efficacy.

Development of quality systems for compounding pharmacies can aid in optimizing the preparation performance and assuring the overall quality of the compounded preparation. It is about building quality into the preparation process by understanding the potential pitfalls and taking the necessary actions such that the prescribed compounded medicament is suitable and safe for the human or animal patient.

Food and Drug Administration Guidance Documents on Pharmacy Compounding

Guidance for Industry: Interim Product Reporting for Human Drug Compounding Outsourcing Facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act. U.S. Department of Health & Human Services. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. December 2013.
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377050.pdf.

Draft Guidance for Industry, Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Office of Regulatory Affairs (ORA), June 2014
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400470.pdf

Guidance for Industry: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), July 2014
www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm377052.pdf

Draft Guidance for Industry: Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, U.S. Department of Health and Human Services , Food and Drug Administration , Center for Drug Evaluation and Research (CDER), July 2014
www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm403496.pdf

Guidance for Industry: Registration of Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), November 2014
www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm377051.pdf

Draft Guidance for Industry: For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act, U.S. Department of Health and Human Services , Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February 2015
www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434171.pdf

Draft Guidance for Industry: Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Office of Compliance/OUDLC, February 2015
www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434174.pdf

Draft Guidance for Industry Compounding Animal Drugs from Bulk Drug Substances, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine (CVM), May 2015
www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM446862.pdf

Animals Drugs, Feeds and Related Products, Part 530 Extralabel Drug Use in Animals, Subchapter E–Title 21—Food and Drugs, Chapter I—Food and Drug Administration, Department of Health and Human Services
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=530

Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products between the State of [insert State] and the U.S. Food and Drug Administration
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounPhar/UCM434233.pdf

Guidance for FDA Staff and Industry Compliance Policy Guides Manual
Sec. 608.400 - Compounding of Drugs for Use in Animals (Withdrawn May 2015)
www.fda.gov/OHRMS/DOCKETS/98fr/03d-0290-gdl0001.pdf

Guidance for Industry: Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) , February 2015
www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434188.pdf

***Draft Guidance for Industry:* Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application,** U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER)
And Center for Biologics Evaluation and Research (CBER) , February 2015
www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434176.pdf