COMPOUNDING AND VETERINARY MEDICAL DEVICES

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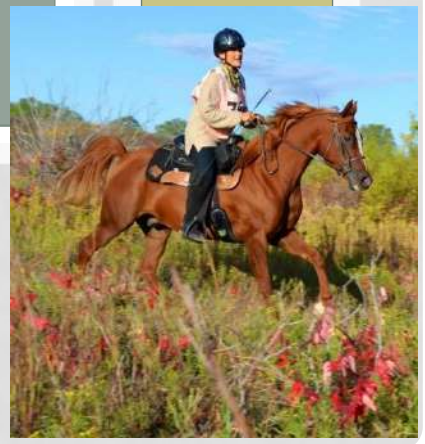


WHAT IS COMPOUNDING?

- **TRADITIONAL INDUSTRY DEFINITION**
- "A ***pharmaceutical practice*** in which drugs are ***manipulated*** in ***dosage, form and flavor*** to accommodate a ***specific patient's individual*** needs".

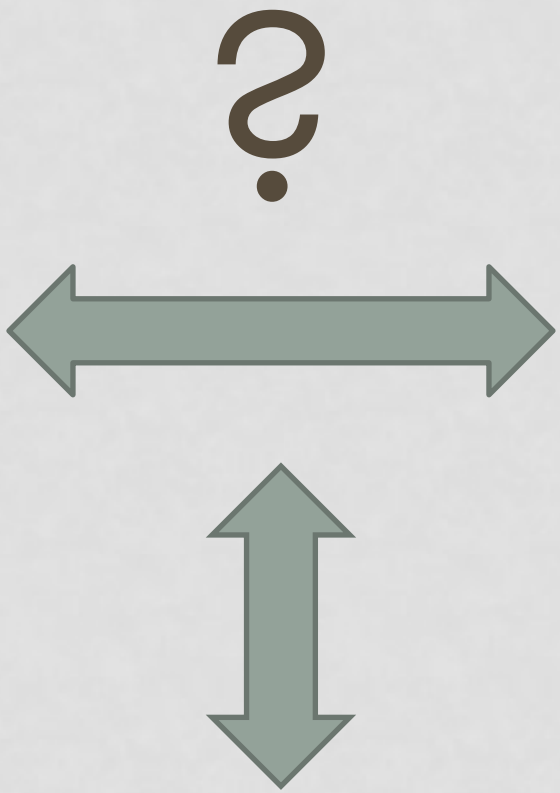
  Edie Lau, "Confounding Compounding", VIN News (11/23/2009).

- "Compounding is a process by which a pharmacist **combines, mixes, or alters ingredients** to create a medication **tailored to the needs of an individual human or animal patient**. *Francks*, citing *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 360-61 (2002)

COMPLICATED REGULATORY SCHEME

- Pre-1938: All pharmacology was "compounded"
- 1938: FDCA Enactment; creation of FDA
  - Applicable to human drugs only; flow over to Animal
- 1994: AMDUCA
  - Applying FDCA to animal drugs
  - Allowing the use of approved human and animal drugs extra label in certain circumstances.
- 1994 – 2011: CPGs (FDA Compliance Policy Guides)
- 2009: FL Death 21 polo ponies
- 2011: Case Law: *Franck's* [Compounding from Bulk]
- 2013: Compounding Quality Act
  - Human drugs only
  - Flow over to animal drugs
- 2015: Veterinary Medical Devices
- 2015: Increased compounding litigation-EPM

CONTINUED INDUSTRY CONFUSION



FRANCKS BIODYL 2009
DEATH OF 29 POLO PONIES

FRANCK'S COURT CASE

- United States of America v. Franck's Lab, Inc. et al, No. 5:2010cv00147 - Document 68 (M.D. Fla. 2011)
- 80 page decision
  - Arising out of – BUT NOT RELATED TO – 2009 Polo Pony Deaths FL
  - Primarily focused on authority of FDA to sanction Franck's over compounding with bulk active ingredients
  - Decision chastised FDA for legislative holes in the enabling statute
    - Prohibition against compounding from bulk ingredients
    - Lack of statutory authority defining right to sanction
    - Fact that per State Statute compounding from bulk permitted

KEY FRANCK STIPULATIONS

- The FDA has taken the bright-line position that **any compounding of animal medications from bulk substances** violates its enabling statute, the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301, et seq. ("FDCA"), even when conducted by a state-licensed pharmacist for an individual animal patient pursuant to a valid veterinary prescription. **Pg. 7**
- **"Though the FDA had ample opportunity to dispute these assertions, it chose not to do so" Pg. 8 and throughout brief**
- Section 530.13, entitled "**Extralabel use from compounding of approved new animal and approved human drugs," provides that "[t]his part applies to compounding of a product from approved animal or human drugs by a veterinarian or a pharmacist on the order of a veterinarian within the practice of veterinary medicine. Nothing in this part shall be construed as permitting compounding from bulk drugs." 21 C.F.R. § 530.13(a) (emphasis added).**
- **Despite this language, the regulations do not purport to regulate the practice of compounding, and instead refer parties to FDA's non-binding guidance documents on the subject. See id. § 530.13(c) ("Guidance on the subject of compounding may be found in guidance documents issued by FDA"). Pg. 19**

FRANCKS' STIPULATIONS

- Although the FDA's complaint and declarations contain allegations that Franck's has engaged in conduct indicative of a "manufacturer" of drugs, such as compounding commercially available drugs or compounding drugs in advance of a valid prescription, **it has provided no factual support for such claims and ultimately does not rely on them to maintain this action. P. 39**
- **The FDA expressly disclaims reliance upon any other legal source, including AMDUCA**, (see Doc. 54 at 7 ("AMDUCA does not encompass compounding from bulk drugs")); **p. 40**
- 69 The "plain statement rule" requires that Congress speak in clear terms when displacing traditional state regulation of a particular practice. Gregory v. Ashcroft, 501 U.S. 452, 460-61 (1991). 70 **The "rule of lenity" requires that when a statute carries criminal penalties, any ambiguities must be interpreted in the defendant's favor to avoid "prohibit[ing] more conduct or punish[ing] more severely than Congress intended."** United States v. Wright, 607 F.3d 708, 717 (11th Cir. 2010)(Pryor, J., concurring). **P 48**

FRANCK'S STIPULATIONS

- Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs"); Med. Ctr., 536 F.3d at 398 p. 57
- This requires data from large populations of animals and the application of powerful statistical techniques. No solitary medical professional can carry out this program of knowledge acquisition for even one drug, let alone for the bevy of drugs a veterinarian may choose to compound."). P. 57
- **Therefore, to the extent Congress has addressed the issue, it has decided to focus governmental resources upon the commercial distributors of drugs rather than upon the trained pharmacists and physicians who must reconstitute drugs for patient use on a smaller scale. One sound argument for this choice is evident: A drug improperly compounded on a large scale will harm more patients than the same compounding mistake made on a smaller scale.")(emphasis added). P. 60**

FRANCKS' DICTA

- The legislative history of the FDCA also supports the view that manufacturers, not compounding pharmacists, were the intended target of the FDCA's new drug approval scheme. **P. 61**
- **To the extent that a pharmacist's bulk compounding activity moves beyond the bounds of traditional compounding and begins to approximate the "manufacturing**" of unapproved drugs, **there seems little question that this activity is squarely within the crosshairs of the FDCA.** Cf. W. States, 535 U.S. at 361 ("The Federal Food, Drug, and Cosmetic Act of 1938 . . . regulates drug manufacturing, marketing, and distribution")(emphasis added). **P. 62-63**
- The Florida statutory scheme recognizes a critical difference between traditional pharmacy compounding and manufacturing: the existence of a pharmacist-prescriber-patient relationship that controls the preparation of the compounded drug product.83 Traditionally compounded drugs are not for resale, but rather are responsive to the patient's immediate needs as diagnosed by the patient's licensed healthcare professional, i.e., a veterinarian. **P. 65**

FRANCKS DICTA

- **Though it certainly has the statutory authority to do so, the FDA has chosen not to draw the line between manufacturing and traditional compounding with formal regulations. Nor has it sought to distinguish traditional pharmacy compounding from pharmacists who are manufacturing under the guise of compounding. P 66**
- **Here, the FDA's authority to regulate pharmacy compounding as a disguise for manufacturing is not at issue. P. 69**
- **As a result, though § 321(v)'s "new animal drug" definition affords the FDA license to enforce against pharmacists who manufacture in the guise of compounding, Congress did not, by any remaining contextual ambiguity, give the FDA the authority to enjoin traditional pharmacy compounding of animal drugs, a practice never before regulated by a federal agency and never mentioned in the FDCA. See ABA I, 430 F.3d at 469. The FDA is certainly statutorily authorized to draw clear distinctions between manufacturing and compounding generally. See W. States, 535 U.S. at 372-73. p. 70**

FRANCK'S DICTA

- Even if Congress had implicitly delegated authority to the FDA to regulate traditional pharmacy compounding of animal medications, **the FDA has never promulgated regulations to this effect through notice-and-comment rule-making**. Rather, as discussed supra, the **agency has instead utilized non-binding Compliance Policy Guides**, such as the 1996 and 2003 Guides, **to assert its authority**. **P. 72**
- Just as it has failed to explain its prohibition of bulk compounding of animal drugs via a "relatively formal administrative procedure," Mead, 533 U.S. at 230, the FDA has chosen not to dispute Franck's showing in this case that the practice is an essential component of veterinary medicine. **P. 75**
- **96 Had the FDA done what it said it would do or, even better, gone through formal rulemaking, it might have been able to develop criteria for determining whether a large, interstate compounding pharmacy such as Franck's is engaging in impermissible manufacturing or permissible, traditional compounding. See W. States, 535 U.S. at 372-73 (suggesting such criteria); supra n. 45, 83. Though it is not my place to say so, FDA could still choose to follow this alternative course. See supra n.52 (FDA seeking comments in related area). Or, as it did in the case of tobacco, see Family Smoking Prevention and Tobacco Control Act of 2009, Pub. L. 111-31 (HR 1256) (2009), it could ask Congress for the explicit authority to regulate this practice. p. 79**

FINAL HOLDING

- **FINAL HOLDING:**
- The Court holds that, in enacting the FDCA in 1938, Congress did not intend to give the FDA ***per se*** authority to enjoin the long-standing, widespread, state-regulated practice of pharmacists filling a veterinarian's prescription for a non food-producing animal **by compounding from bulk substances.** p. 80

2012 HUMAN MENINGITIS OUTBREAK

- New England Compounding Pharmacy
- Epidural Steroid Spinal Injections (compounded)
- Contaminated containers
- 64 deaths from fungal meningitis
- Legislative response by Senator Upton (MA) and Senator Roberts (KS)

ENACTMENT OF 2012 COMPOUNDING QUALITY ACT

- Mass manufacture of compounded drugs
  - For more than "a single patient or group of patients"
- Requires registration & FDA oversight
  - Registered "outsourcing" facilities
  - Quality of bulk ingredients
  - Record of "batch" mx
  - Facilities subject to FDA inspection and record keeping
  - More minimal than FDA approved manufacturers
- APPLIES TO HUMAN Rx ONLY
- Flow over to animal by analogy only
  - https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm375804.htm

FDA / GENERIC / COMPOUNDED

- Why does it matter?

FDA-APPROVED, GENERICS & COMPOUNDED DRUG TESTING COMPARISON

MEETS FDA TESTING STANDARDS FOR:	FDA APPROVED	GENERIC	COMPOUNDED
Active Ingredients	X	X	N/A
Labeling	X	X	N/A
Dosage Strength	X	X	N/A
Administration Route	X	X	N/A
Chemistry	X	X	N/A
Manufacturing Procedures	X	X	N/A
Quality Control	X	X	N/A
Stability Studies	X	X	N/A
Facility Inspection	X	X	N/A
Pkg/Testing Sites	X	X	N/A
Adverse Event Reporting	X	X	N/A

BIG 5 CONCERNS: "P A S S S" FACTORS

- **COMPOUNDED PRODUCTS ARE NOT TESTED OR REGULATED FOR:**
- **1. POTENCY**
  - Even if product contains stated amount of "active substance", no guarantee it's as potent as the FDA approved product.
  - Shelf life is markedly shorter; administration methods impact effectiveness.
  - Patient's specific metabolic system impacts effective of the drug
- **2. ADVERSE REACTIONS: NO REPORTING REQUIREMENTS**
  - Lack of identifiable negative consequences unless dramatic circumstances generate publicity
- **3. SAFETY**
  - Absorption rates may differ or have irritating effects on different animals
  - pH of the product or inactive ingredients could increase or decrease bio-availability of product (i.e. under or over dosing)
  - What's safe in some may be toxic to others
- **4. STERILITY**
  - No guarantee that ingredients, means and methods are sterile
  - Lacking FDA GMP oversight, many compounded delivery mechanisms are contaminated with mold, fungus, etc.
- **5. SHELF LIFE**
  - Significantly lower shelf life leading to total lack of efficacy in just a few days or less

CURRENT RULES

- Federal level
- State level
- Agency (AAEP AVMA State VMAs)

FEDERAL RULES: AMDUCA

- **Federal: Animal Medicinal Drug Use Clarification Act**

- **AMDUCA Excerpts**
- **Rule 1: Section 530.11 Limitations**
  - **Section (d): Prohibits extra label use resulting in any API (active pharmaceutical ingredient) residue above established safe level, safe concentration or tolerance**
- **Rule 2: Section 530.12 Labeling**
  - **Off Label use requires: Name, address of prescribing veterinarian; or compounding pharmacy; established name of drug and ALL active ingredients; directions for use including specific animal treated, dosage, frequency and route of administration and duration of therapy; warning statements; and specific withdrawal times for food producing animals if applicable.**
  - **WHAT STEPS DID YOU TAKE TO ENSURE COMPLIANCE?**

AMDUCA DETAILS (CONTD)

- **AMDUCA Section 530.13 Extra label use from Approved New Animal and Human Drugs**
  - **NOT PERMITTED if there is an FDA approved drug that when used per label in available dose and form treats the animal's diagnosed condition.**
  - **NOT PERMITTED if the drug is compounded by other than a licensed pharmacist or veterinarian**
  - **NOT PERMITTED if compounding is outside the parameters of the professional practice**
  - **NOT PERMITTED if the compounding operations cannot ensure safety and effectiveness of the product**
  - **NOT PERMITTED if done under the guise of "mass compounding" – large scale manufacture is "suspect**
  - **NOT PERMITTED if prohibited by State Law**
  - **WHAT STEPS HAVE YOU TAKEN TO ENSURE COMPLIANCE**

FDA TREATMENT OF AMDUCA

- Online Research:
  - Multiple examples of FDA Sanctioning Actions for unauthorized compounding
- FDA Warning Letter: GastroMax
- Outlines FDA treatment of adulterated drugs
- Against manufacturers **AND DISTRIBUTORS**
- **QUERY: If you are being deposed in a litigation and you are shown the AMDUCA regulations and AN FDA warning letter related to the product you recommended, how <u>will you reply?</u>**

FDA/CVM PERMITTED USES AVMA WEBSITE EFF. 2/1/2018

- Valid VCPR Relationship
- General Conditions for Extra Label Drug Use
- Special Factors Food Producing Animals
- Compounding Uses
- Prohibited drugs for animal extra-label use

FDA/CVM POLICY ON EXTRA LABEL DRUG USE

- Starts with **FDA approved** human or animal drug
- Modification Extra Label ONLY IF:
  - There is **no animal drug approved** for the **intended use**; or
  - There is an animal drug approved for the intended use, but the **approved drug does not contain the active ingredient you need** to use; or
  - There is an animal drug approved for the intended use, but the **approved drug is not in the required dosage form** (for example, you need **a liquid** dosage form, but the approved drug is only available as a **tablet** dosage form); or
  - There is an animal drug approved for the intended use, but the **approved drug is not in the required concentration** (for example, you need 5 mg, but the approved drug is only available at 50 mg); or
  - You have found, in the ***context of a valid veterinarian-client-patient*** relationship, that **the approved drug is clinically ineffective** when used as labeled.

- **"THOROUGH RECORD KEEPING IS VITAL"**
  - **https://www.fda.gov/AnimalVeterinary/ResourcesforYou/ucm380135.htm#General_Conditions_for_Extra-Label_Drug_Use**

FDA / CVM POLICY ON COMPOUNDING

- **Compounding**
- "Under the FD&C Act, **an animal drug that is compounded using an unapproved drug or bulk drugs as the starting material is adulterated.** An animal drug that is compounded using an approved human or animal drug as the starting material is not adulterated, and using such a drug is considered a legal extra-label use as long as all other conditions required by law are met. You can find these requirements in:
- Sections 512(a)(4) and (5) of the FD&C Act [Sections 360b(a)(4) and (5) of Title 21 of the United States Code (New Animal Drugs, 2017)] and;
- Section 530.13 of Title 21 of the Code of Federal Regulations (Extra-label use from compounding of approved new animal and approved human drugs, 2017).

AAEP/AVMA POSITION ON USE OF COMPOUNDED PRODUCTS

- **Permissible when:**
  - Lack of FDA approved drug
  - Temporary shortage of FDA approved drugs
  - Dosage /Administration Issues
  - Animal Allergies
  - Justified Extra label / Off Label Needs (see AMDUCA handout Ex. 1)
- **NOT permissible for:**
  - **Price savings only**

AAEP / AVMA GUIDELINES (CONT'D)

- **COMPOUNDING TYPICALLY PERMISSIBLE WHEN:**
  a. A valid **vet/client/patient relationship** exists (VCPR Rule)
  b. Use is limited to unique need in **a specific patient** or group of patients
  c. No other method or type of drug delivery is practical, **AND**
  d. **No equivalent FDA approved product is on the market.**

- **COMPOUNDING TYPICALLY NOT PERMISSIBLE WHEN:**
  a. Exceeds VCPR rule (i.e., mass manufacture, advertising and distribution except in limited circumstances)
  b. Mass advertised for large population of end users without justification (i.e. lack of other products to treat condition in that species)
  d. Compounded product mimics **equivalent FDA approved product available on market**

COMPLICATED STATE REGULATIONS

- **Summaries of individual states' laws and regulations**
- AL | AK | AZ | AR | CA | CO | CT | DE | DC | FL | GA | HI | ID | IL | IN | IA | KS | KY | LA | ME | MD | MA | MI | MN | MS | MO | MT | NE | NV | NH | NJ | NM | NY | NC | ND | OH | OK | OR | PA | RI | SC | SD | TN | TX | UT | VT | VA | WA | WV | WI | WY
- **Kansas**
  - No specific verbage on compounding, BUT SEE Conduct Disciplines
- **Missouri**
  - A pharmacist shall not offer compounded drug products to practitioners for **subsequent resale or administration**, except in the course of professional practice for a **prescriber to administer** to an individual patient by prescription.
- https://www.avma.org/Advocacy/StateAndLocal/Pages/compoundinglaws.aspx

STATE REGULATIONS: GENERAL SUMMARIES

- **State laws and regulations that allow veterinary offices to administer compounded products and dispense the products to clients but may be subject to conditions or limitations in some cases:**
  - California, Colorado, Florida, Maine, Maryland, Massachusetts, Michigan, Minnesota, Nebraska, Ohio, Tennessee, Texas, Virginia (13)
- **State laws and regulations that allow veterinary offices to administer compounded products but do not specifically address or the law is not clear regarding dispensing products compounded by a pharmacy:**
  - Idaho, Illinois, Mississippi, Montana, Nevada, New Hampshire, New Jersey, Oregon, South Carolina (9)

STATE REGULATIONS- COMPOUNDING

- **State laws and regulations that allow veterinary offices to administer compounded products but specifically prohibit them from dispensing or reselling products compounded by a pharmacy:**
  - Alabama, Alaska, Arizona, Arkansas, Connecticut, Georgia, Iowa, Kentucky, Louisiana, **Missouri,** North Carolina, North Dakota, Oklahoma, Rhode Island, Utah, Vermont, Washington, West Virginia, Wyoming (19)
- **States that prohibit compounding for office use:**
  - Delaware, New Mexico, New York (3)
- **States where we did not find laws and regulations addressing compounding:**
  - Hawaii, Indiana, **Kansas**, Pennsylvania, South Dakota, Wisconsin (6)

ASSOCIATION REGULATIONS

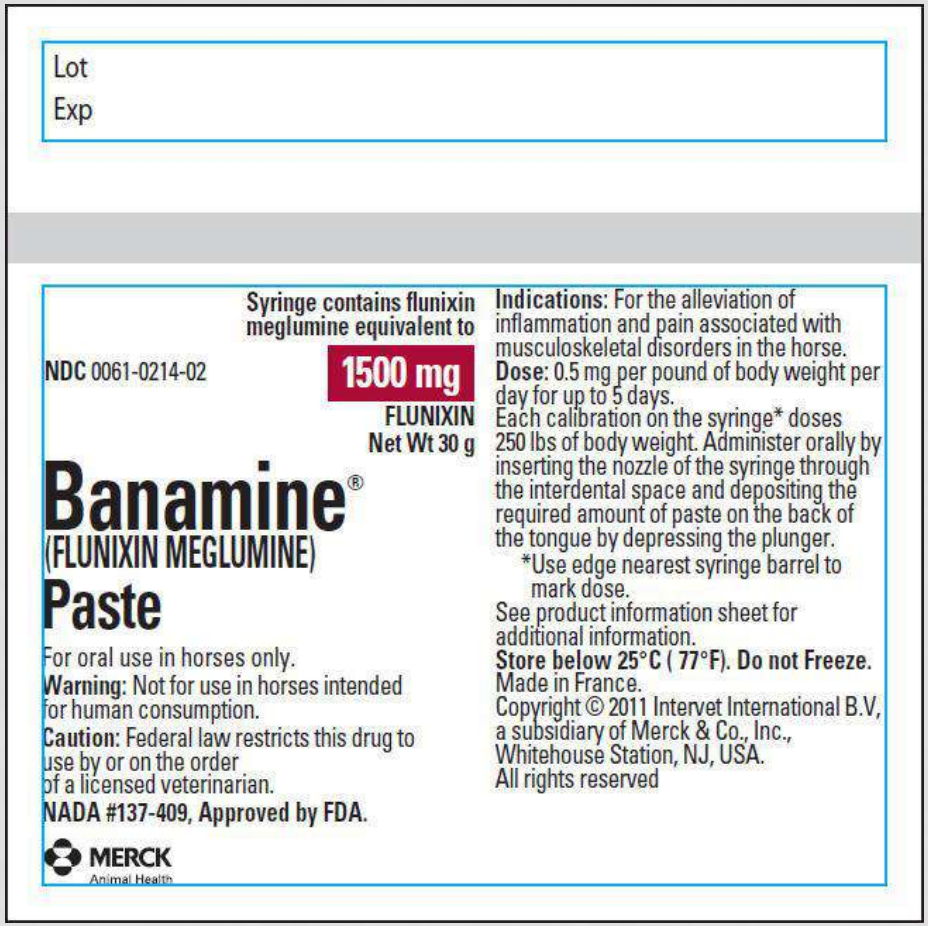
- **AVMA:**
  - **Policy:**
    - https://www.avma.org/KB/Policies/Pages/Compounding.aspx
  - **AVMA Link to State Veterinary/Pharmaceutical Board Regulations**
  - https://www.avma.org/KB/Resources/Reference/Pages/Compounding-What-are-the-rules.aspx
- **AAEP**
  - **Policy**
  - http://www.aaep.org/custdocs/drug_compounding_guidelines.pdf?osCsid=rhpp15r2rajnh82g5er5gviu33

IS IT A COMPOUNDED PRODUCT?

- Does the label reflect an NADA Number?
- Does the label identify "FDA approved"
- Is the product being used as indicated on the label?
- If "no" to any of

The above, its compounded

SAMPLE NADA LABEL



Lot
Exp

Syringe contains flunixin meglumine equivalent to

NDC 0061-0214-02

1500 mg

FLUNIXIN
Net Wt 30 g

Banamine®
(FLUNIXIN MEGLUMINE)
Paste

For oral use in horses only.
Warning: Not for use in horses intended for human consumption.
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA #137-409, Approved by FDA.

MERCK
Animal Health

Indications: For the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse.
Dose: 0.5 mg per pound of body weight per day for up to 5 days.
Each calibration on the syringe* doses 250 lbs of body weight. Administer orally by inserting the nozzle of the syringe through the interdental space and depositing the required amount of paste on the back of the tongue by depressing the plunger.
*Use edge nearest syringe barrel to mark dose.
See product information sheet for additional information.
Store below 25°C (77°F). Do not Freeze.
Made in France.

COMMERCIAL BANAMINE LABEL

- Flunixin (Banamine) Powder 500mg / Teaspoon, 15g Jar
- Email to a Friend
- **$100.00**
- Buy 2 for **$85.00** each and ***save 15%***
- Buy 4 for **$75.00** each and ***save 25%***
- Qty: Add to Cart
- **OR** Add to Saved Items
- Add to Compare
- **Description**
- Flunixin (Banamine) is a potent non-narcotic, non-steroidal analgesic agent with anti-inflammatory and fever-reducing activity. Flunixin (Banamine) is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in horses. Each teaspoon of Flunixin powder contains 500mg of Flunixin Meglumine. The 30g jar is contains the same amount of Flunixin Meglumine as 20 Banamine syringes. Flunixin powder is apple-flavored and expires 180 days after it is compounded.
- **RX - Prescription Required**
- Source: http://www.thrivingvets.com

RESOURCES

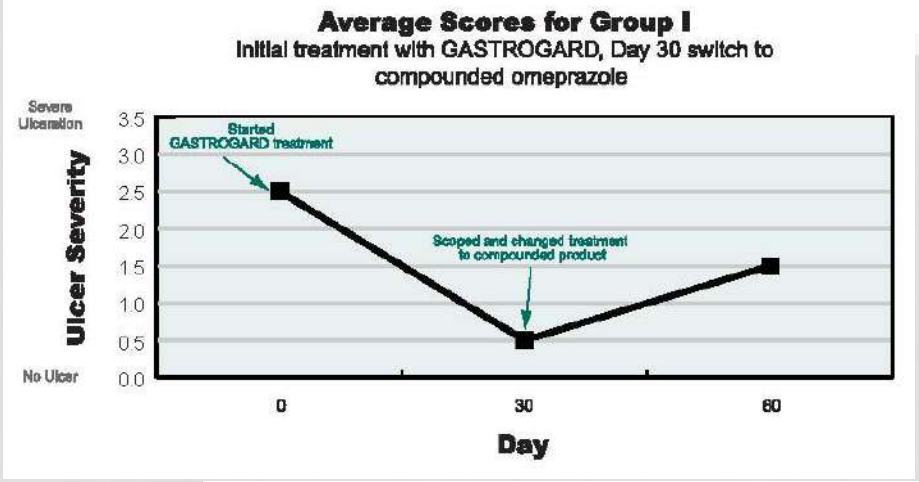
- You can research FDA, Generic and Compounded status at the following web sites:

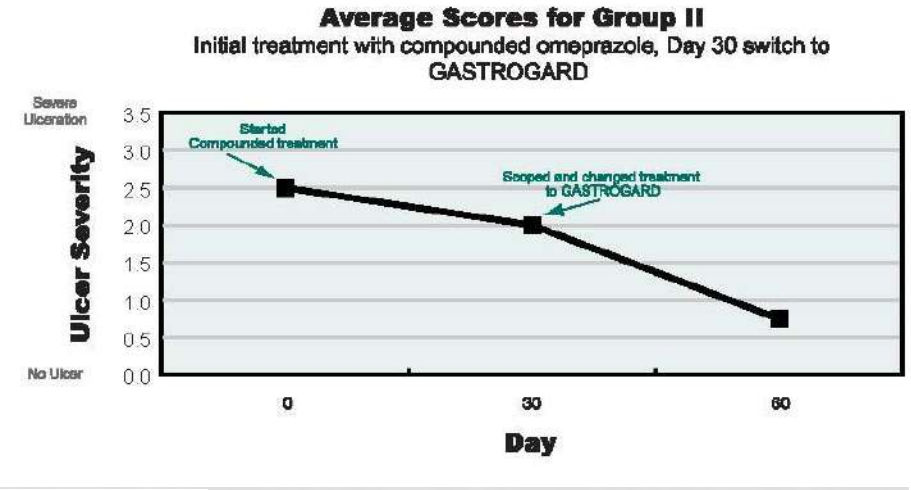
- http://www.Equinedrugfacts.com
- http://www.accessdata.fda.gov/scripts/animaldrugsatfda/index.cfm

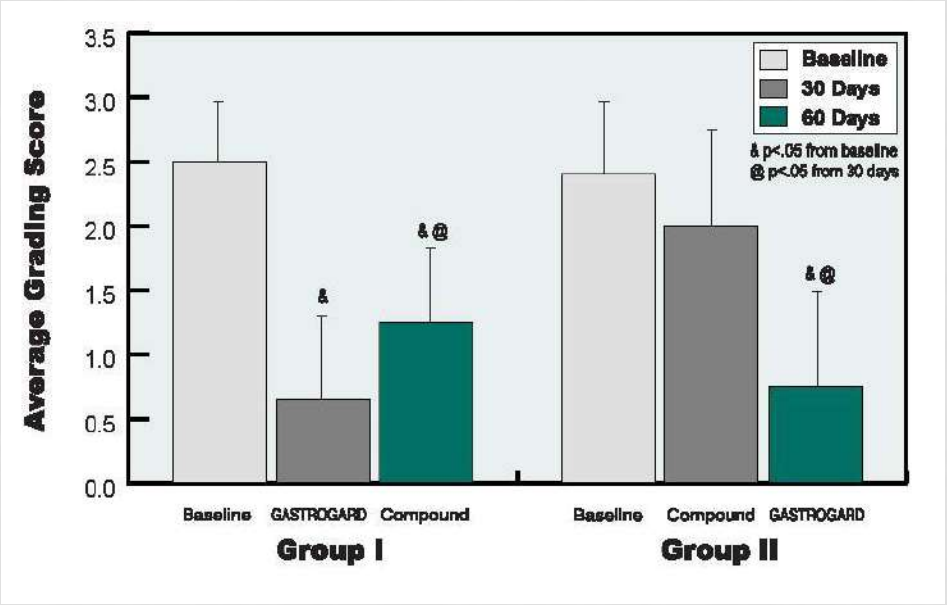
WHY IS NADA REQUIRED?

- Issues of scale versus potential of harm
- Or: veterinary misrepresentation re: "informed consent" to client

OMEPRAZOLE VS GASTROGARD™ COMPOUNDED VS FDA APPROVED PERFORMANCE



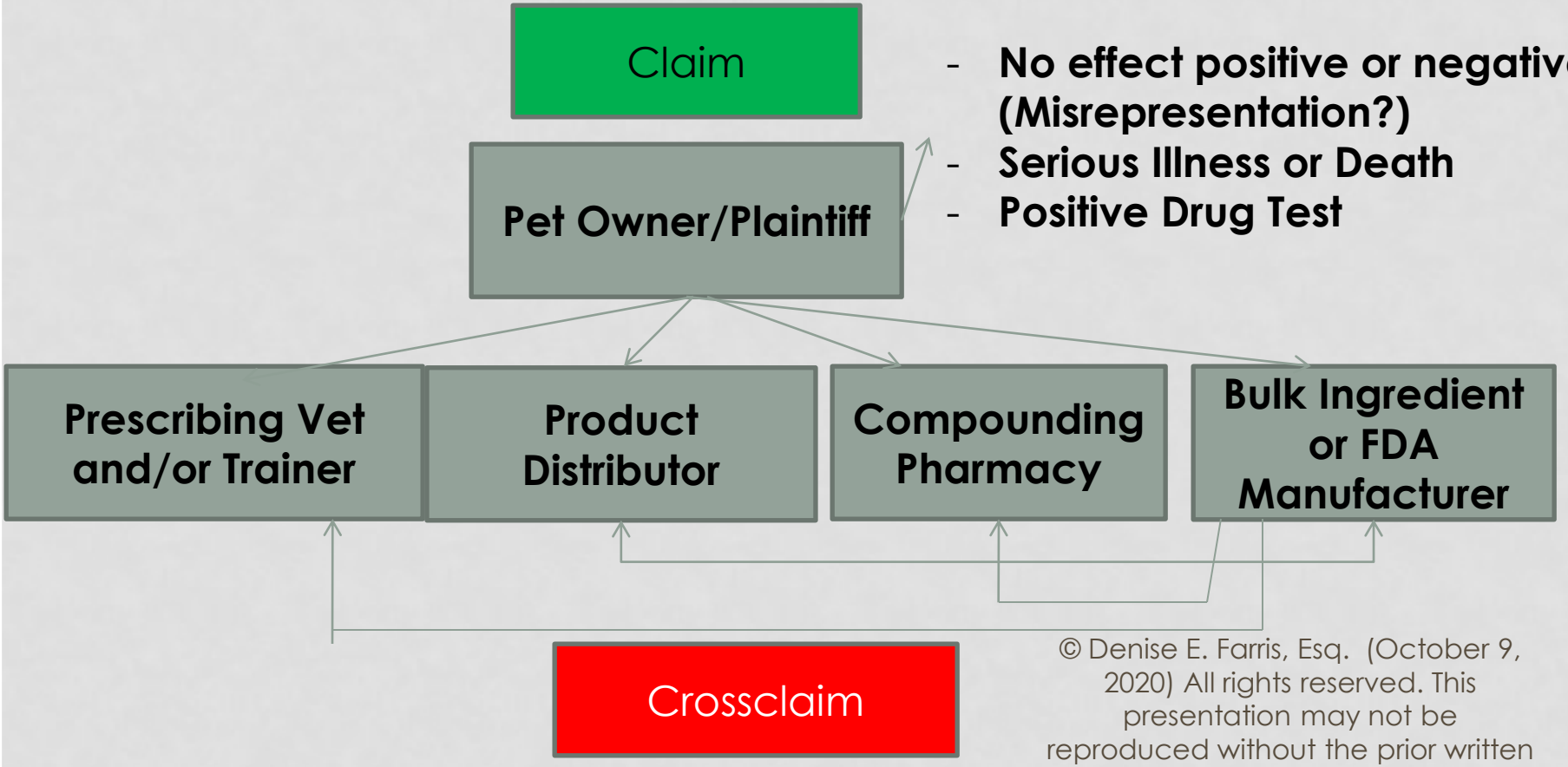




Reprint courtesy of Dr. Scott Stanley UCC-Davis and Merial, Ltd.

WHY SHOULD YOU CARE?

- **Litigation Parties**



Probably Not Covered by Prof. Liability Insurance ! !

"UNAUTHORIZED TREATMENT" VS INFORMED CONSENT

- Veterinarians, to the best of their ability, should **inform** the client or authorized agent, in a manner that would be **understood by a reasonable person**, of the **diagnostic and treatment options, risk assessment, and prognosis**, and should provide the client or authorized agent with an **estimate of the charges** for veterinary services to be rendered.
- The client or authorized agent should indicate that the **information is understood** and **client consents** to the recommended treatment or procedure.
- **Documentation** of verbal or written informed consent and the client's understanding is recommended.

AVMA Guidelines May 15, 2007
https://www.avma.org/News/JAVMANews/Pages/070515e.aspx

Have you informed the client re: compounded vs FDA Approved?

STATE EXAMPLES-KS SECTION 47-830 DISCIPLINARY ACTIONS

47-830. Grounds for revocation or suspension of license or other restrictions.

…

(d) false or misleading advertising; …

(q) fraud, deception, negligence or incompetence in the practice of veterinary medicine;

(r) the use, prescription, administration, dispensation or sale of any veterinary prescription drug or the prescription of an extra-label use of any over-the-counter drug in the absence of a valid veterinary-client-patient relationship;

(s) … or failing to provide the owner or owner's agent with a summary of the medical record within a reasonable period of time and upon proper request by the owner or owner's agent, or failing to comply with any other law relating to medical records; or

BEWARE THE LANHAM & CONSUMER PROTECTION ACTS!

- **Lanham Act**
  - **Primary federal trademark law**
  - **Creates a private cause of action**
  - **For violations of:**
    - **Trademark infringement**
    - **Trademark dilution**
    - **<u>False Advertising (i.e. representations re: efficacy)</u>**

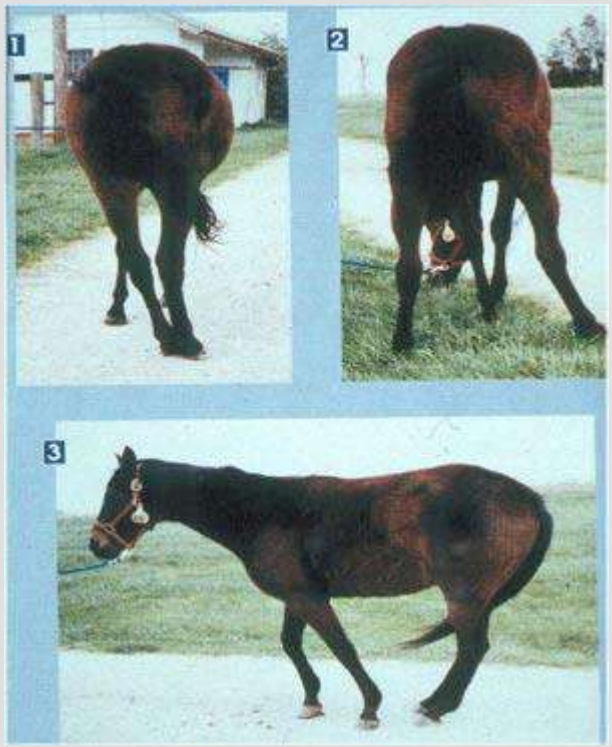
- **Consumer Protection Acts**
  - **<u>Misrepresentations</u> made in the sale of products to consumers**

LANHAM ACT LANGUAGE

- **Typically an Action Between Competitors**
- Any person who, on **or in connection with any goods or services**, or any container for goods, uses in commerce any word, term, name, symbol, or device, or any combination thereof, or any false designation of origin, false or misleading description of fact, or **false or misleading representation of fact, which—**
- is likely to cause confusion, or to cause mistake, or to deceive as to the affiliation, connection, or association of such person with another person, or as to the origin, sponsorship, or approval of his or her goods, services, or commercial activities by another person, or
- **in commercial advertising or promotion, misrepresents the nature, characteristics, qualities,** or geographic origin of his or her or another person's goods, services, or commercial activities,
- **shall be liable in a civil action by any person who believes that he or she is or is likely to be damaged by such act.**
- 41 U.S.C. § 1125(a)(1).

THE LITIGATION DIDN'T END WITH FRANCK'S…

- Wickliffe Compounded EPM medication
- March 2014:
  - Notice by University of KY diagnostic laboratory of equine deaths related to EPM compound.
  - Wickliffe fails to investigate, pull product
- May 2014
  - Additional illnesses / deaths resulting from Wickliffe compounded EPM product



EPM PASTE PER FDA TESTING

BAPI	REC LEVELS	LABEL STATED	ACTUAL DOSE GIVEN	DIFF
Toltrazuril*	416 mg/ml	227 mg/ml	184 mg/ml	-44%
Pyrimethamine	17 mg/ml	340 mg/ml	283 mg/ml	+600%

*Toltrazuril not approved by FDA for use in horses
*Ponazuril FDA approved for use in horses; used in Marquis ™

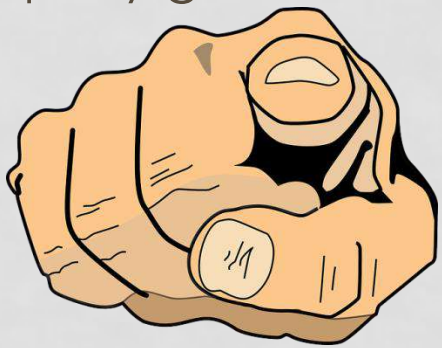
RESULTING LAWSUITS:

1. ***Galen Ho LLC, vs Wickliffe Pharmacy*** (June 2014 Ocala, FL)
2. ***JMJ Stable vs Wickliffe Pharmacy*** (June 2014 Ocala, FL)

Status: Confidential settlements between the parties
FDA penalties and fines assessed against Wickliffe

EPM CURRENT LITIGATION

- ***LuAnn Burton & Max Domaschko vs Wickliffe Pharmacy, Benchmark Farm LLC, Sheldon Ulrich,* (Lexington KY 2015)**
- ***Wickliffe Pharmacy vs Dr. Cory Williams and Jamie Corbett* (Crossclaim, Lexington, KY 2015)**
  - Alleging Dr. Williams failed to issue adequate instructions for giving the medication
  - Alleging farm manager Jamie Corbett improperly gave the medication
  - Confidential Settlement 2017



FDA APPROACH: DRAFT COMPLIANCE POLICY GUIDE AUG. 2015 (ADVISORY ONLY)

- **The compounding of an animal drug from Bulk Substances results in a "New Animal Drug"**
- **"New Animal Drugs" must comply with FDCA's approval/indexing requirements**
- **New animal drugs must comply *with* current good manufacturing practices (cGMP)**
  - FD&C Act, Section 501(a)(2)(B) and 21 CFR parts 210-211)
- **New animal drugs must have adequate directions for use**
  - FD&C Act Section 502(f)(1)
- **Animal drugs NOT approved or indexed are deemed "unsafe"**
  - (FD&C Act Section 512(a)(1)) and adulterated (FD&C Act Section 501(a)(5))

FDA EXCEPTIONS COMPOUNDING

- **FOR State Licensed Pharmacy**
- **Bulk Compounding Only Permitted Where**
  - Compounding under direct supervision of licensed pharmacist
  - Drug dispensed per VCPR parameters
  - Not intended for food producing animals
  - **No FDA approved product on market unless compounded product justified by "clinical difference" opinion letter by vet**
  - **Product can't be made from FDA approved base**
  - **Veterinarian statement placed on label:**
    - **Identification of species for which compound is prescribed; AND**
    - **The statement: "There are no FDA-approved animal or human drugs that can be used as labeled or in an extra label manner under Section 512(a)(4) or (5) and 21 CFR part 530 to appropriately treat the disease, symptoms or condition for which this drug is being prescribed."**
  - **15 day adverse reaction reporting requirement**

2016 FDA PROPOSED SANCTIONS

- **Over the past few decades, an increasingly global and national marketplace has expanded the number of complex multi-party transactions involving FDA-regulated products. Modern technologies such as the Internet have made direct sales from global and national manufacturers and distributors to a wider range of middlemen both more feasible and more common. Given the changes in technology and the greater variety of transactions, FDA is clarifying its enforcement policy with respect to certain types of conduct under section 301(a) or (d) of the FD&C Act, under a causing theory.**
  - Compliance Policy Guide Section 101.100 FDA Considerations for Recommending Charges Under 21 U.S.C. §331(a) or (d) for Causing the Introduction of Violative Products into Interstate Commerce Guidance for FDA Staff (October 2016) (Ex. 7)
  - http://www.fda.gov/downloads/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/UCM525418.pdf

JUST WHEN YOU UNDERSTAND…

- **We throw in Veterinary Medical Devices**
- Issues:
  - **Veterinary Medical Devices**
    - Not typically regulated by FDA
    - Does not require New Drug Approval Process
  - **Versus New Animal Drug**
    - Regulated by FDA
    - Mass manufacture requires New Drug Approval Process compliance

VMD: SUMMARIZED

- A device which will act upon the structure and function of the body
- Of man or animal
- **BUT**:
  - **Does not achieve intended purpose through chemical reaction, and**
  - **Is not metabolized to achieve intended purpose**
    - *Medical Devices: A White Paper on Medical Devices in Equine Medicine. (Biological and Therapeutic Agents Committee of the AAEP July 10, 2011)*

VETERINARY MEDICAL DEVICES

- Compounding influence most visible in
  - Joint injections not FDA approved for therapeutic treatment
  - New innovations showing promise but not yet FDA approved

AAEP GUIDELINES 2011

- Under FDCA, veterinary device cannot be:
  - Misbranded
  - Mislabeled
  - Adulterated
- A veterinary device is misbranded or mislabeled when:
  - **Labelling is false or misleading**
  - **The device is used or promoted or makes claims which are not consistent with the labeling**
    - *Medical Devices: A White Paper on Medical Devices in Equine Medicine. (Biological and Therapeutic Agents Committee of the AAEP July 10, 2011)*

NO AMDUCA DISCRETION!

- AMDUCA Discretion on Compounding:
  - Does not extend to "veterinary medical devices"
  - I.E. **there is no "discretionary purview" in AMDUCA related to "extra label use of medical devices" in veterinary medicine**
    - *Medical Devices: A White Paper on Medical Devices in Equine Medicine. (Biological and Therapeutic Agents Committee of the AAEP July 10, 2011)*

AAEP RULES ON MEDICAL DEVICES (CONT'D.)

- **It is AAEP's position that if there are FDA-approved products available and formulated in the appropriate dosage for the disease indication of the patient, those products should be used in preference to a medical device as a pharmaceutical.**
- **It is unethical for a veterinarian to promote or represent a medical device as equivalent to an approved pharmaceutical product.**
- **It is illegal for a manufacturer to promote or represent a medical device as a pharmaceutical.**
  - *Medical Devices: A White Paper on Medical Devices in Equine Medicine. (Biological and Therapeutic Agents Committee of the AAEP July 10, 2011)*

STEPS TO AVOID MALPRACTICE

- Keep current and updated patient treatment charts
- Only use Compounded / Off Label Products IF:
  - No FDA approved product exists to treat that condition in that species, or
  - There is a temporary product shortage of FDA approved drug, or
  - A particular animal cannot take that drug for some medical reason
- Record why you are using the compounded product, and WHAT you are using
- Be sure the product is properly labeled
- Document "informed consent" discussion with client
- Be sure your Professional Liability carrier will cover compounding exposures
- Remain educated and advocate for your positions
- Understand ever changing regulations, guides and rules on compounding

Q/A?