Pharmaceutical Compounding

Legal Requirements and Good Compounding Practices

Tom Hazlet

Autumn 2008

Pharmaceutical Compounding: Learning Objectives

- Describe the historical precedents and incidents that led to the development of FDA scrutiny of pharmacists' compounding
- Differentiate between "Compounding" and "Manufacturing"
- List and interpret the FDA compliance policy guide on pharmacy compounding
- List and interpret the major provisions of the RCW and WAC as they apply to compounding and manufacturing

What's the fuss with compounding

- Way back when …
  - FDA recognizes that the traditional role of compounding is *not* manufacturing FDCA - 21 USC 353a. Pharmacy compounding
  - Manufacturer obligations under FDCA
    - Safe, effective →NDA, BLA
  - Is pharmacist compounding an end-run on manufacturing requirements?

21 USCS § 353a

§ 353a. Pharmacy compounding

(a) In general. Sections 501(a)(2)(B), 502(f)(1), and 505 [21 USCS §§ 351(a)(2)(B), 352(f)(1), and 355] shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding--

(1) is by--

(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or

(B) a licensed physician,

on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

(2) (A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between--

(i) the licensed pharmacist or licensed physician; and

(ii) (I) such individual patient for whom the prescription order will be provided; or

(II) the physician or other licensed practitioner who will write such prescription order.

Fuss [2]

- Schering & albuterol – 1980's-'90s
  - Drugs "requiring" administration by a pump, etc., get paid for by HCFA (CMS)
  - Home respiratory services
  - Schering complained to HCFA that it was reimbursing for an unapproved new drug
  - HCFA→FDA→ [compounding|manufacturing]?
- Other "disasters" – IV solutions, ophthalmics
- Broader issue of safety / efficacy of compounded drugs
- FDA Compliance Policy Guide [aka "9 points of light"]
- Food & Drug Modernization Act (FDAMA) of 1997

Fuss [3]

- Supreme Court case and FDAMA
  - Abolished advisory committee – Thompson v. Western States Medical Center
  - Reissued Compliance Policy Guide
- KC chemotherapy
- California, South Carolina injections
- Nicotine lollipops
- FDA analysis of compounding
- Bio-identical hormones

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

April 9, 2002

Larry Melton
Owner
Ashland Drug
Highway 5
P.O. Box 126
Ashland, MS 38603

Dear Mr. Melton:

This letter concerns **Nicotine Lollipops,** which are currently marketed by your firm as shown on your Internet sites www.nicotinelollipops.com and www.storesonline.com. According to information on these sites, your product consists of Nicotine combined with a natural sweetener, and flavorings in a sugar-free base, and is available in ½ mg., 1 mg., 2 mg., or 4 mg. dosages. Based on this product's description on your Internet sites, the **Nicotine Lollipops are** intended as an aid for smoking cessation or to reduce nicotine addiction.

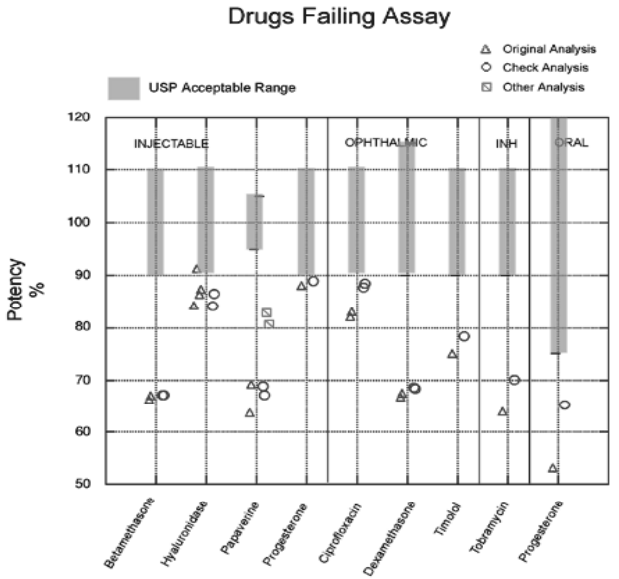
FDA Compounding Survey

- Compounding drugs are a significant share of market.
  - Rx's for compounded products is ~250 million/yr (Estimated 1-8% of total prescriptions)
- Some compounders are high volume operations
  - An estimated 658 of ~72,000 pharmacies fill over 13 million compounded Rx's/year (<1% of pharmacies control 5% of compounding market)

www.fda.gov/cder/pharmcomp/communityPharmacy/default.htm

Results

- 10 / 29 Samples failed
  - 9 failed Assay (1 CU) all were subpotent
  - 1 failed LAL
- Failure by dosage form:
  5/13 (38%)injectables
  3/9 (33%) ophthalmics
  1/1 (100%) inhalation
  1/4 (25%) oral



jurisdiction

- Does FDA have any jurisdiction over pharmacist compounding?
- Who else?

- What FDA would enforce
- FDA “preferences”

Compliance Policy Guide 460.200

- FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.
- Otherwise, potential regulatory action

CPG 460.200

1. Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions.
2. Compounding drugs that were withdrawn or removed from the market for safety reasons. [Appendix A]
3. Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR 312.

CPG 460.200

4. Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.
5. Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements.
6. Using commercial scale manufacturing or testing equipment for compounding drug products.

CPG 460.200

7. Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale.
8. Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products.
9. Failing to operate in conformance with applicable state law regulating the practice of pharmacy.

WA Compounding Defined: **RCW 18.64.011 (18)**

Compounding shall be the act of combining two or more ingredients in the preparation of a prescription.

Federal Manufacturing Defined
21CFR207.3(a)(8)

- manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process

- repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug

WA Manufacturing Defined:
RCW 18.64.011 (20), WAC 246-895-101

- production, preparation, propagation, compounding or processing of a drug or other substance or device or
- packaging or repackaging of such substance or device
- labeling or relabeling of the commercial container

- does **not** include the activities of a practitioner who, as an incident to his or her administration or dispensing such substance or device in the course of his or her professional practice, prepares, compounds, packages or labels such substance or device.

WAC 246-878
Good Compounding Practices

020 Compounded Drug Products

- allows compounding of a commercially available product if prescriber authorizes in writing or verbally and patient agrees
- Official compendial ingredients
- batch preparation in anticipation of future prescriptions
- not for resale, no advertising of specific products

Note: presumption of prescriber→ pharmacist→ patient relationship

WAC 246-878
Good Compounding Practices

- 030 Personnel
  - pharmacist responsibilities
  - Level A pharmacy assistants = “technicians”
  - Clean clothing and appropriate protective apparel when needed
  - authorized personnel only in the area
  - “open lesion” rule

WAC 246-863-095
Pharmacist's professional responsibilities.

Recall …

(1) A pharmacist shall not delegate …

(d) Extemporaneous compounding of the prescription provided that bulk compounding from a formula and IV admixture products prepared in accordance with chapter 246-871 WAC may be performed by a level A pharmacy assistant when supervised by a pharmacist.

WAC 246-878
Good Compounding Practices

- 040 Facilities
  - Quality, clean, separate area for sterile compounding
  - proper storage of drugs and materials
  - adequate lighting and ventilation; potable water; washing facilities
  - clean and sanitary; free of infestation from insects, rodents and other vermin

WAC 246-878
Good Compounding Practices

- 070 Special Precautions
  - dedicated equipment or special procedures for drugs with greater potential for contamination
- 080 Equipment
  - clean, sanitary, appropriately stored, inspected, etc.
  - routine inspection and calibration of automated, mechanical and electronic equipment

WAC 246-878
Good Compounding Practices

- 090 Control of components and drug product containers and closures
  - handled properly to prevent contamination
  - inert containers (non-reactive, additive, absorptive)
  - written procedures for sterilization and removal of pyrogenic materials followed for sterile products

WAC 246-878
Good Compounding Practices

- 100 Drug Compounding Controls
  - written procedures (compounding logs and master formulas)
  - checking and rechecking weights and measures
  - QA: capsule weight variation, adequacy of mixing, clarity, pH, procedures for sterilization and process validation

WAC 246-878
Good Compounding Practices

- 110 Labeling control of excess products
  - excess product must be labeled with complete list of ingredients; preparation date; assigned beyond-use date based upon professional judgment, testing, or published data;
  - properly stored and accounted for in compounding records

WAC 246-878
Good Compounding Practices

- 120 Records and reports
  - records retained for the same length of time as prescription records (2 years+)
  - readily available for inspection and copying
  - may be retained as either original records or as true copies

USP/NF

<795> Pharmaceutical Compounding – Nonsterile Preparations

- Environment: Facilities, Equipment
- Stability
  - packaging
  - sterility → <797>
  - stability
    - non-aqueous liquid & solid formulations – 6 months, or 25% of the remaining ingredient dating
    - aqueous – 14 days, stored at "cold" temperature (5-8°C)
- Ingredient Selection
- Compounding process, records, documents, QC, verification
- Patient Counseling

USP/NF – 2

<797> Pharmaceutical Compounding – Sterile Preparations

- Requirements essentially match manufacturing
- Heavy emphasis on verification of compounding accuracy & sterility, patient monitoring, quality assurance
- Dating

Veterinary Compounding

- Special concern – will someone eat the critter?
  - A "valid veterinarian-client-patient relationship"
- Compliance policy guide

http://www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg608-400compounding.pdf

Disclosure Obligations

- WAC 246-878-020
  - When a compounded product is to be substituted for a commercially available product, both the patient and also the prescriber must authorize the use of the compounded product.
- … what else?

Questions

Points of Emphasis

- Differentiate manufacturing and compounding
- Agency jurisdiction
- Adequate understanding of technology; adequate facilities
- Importance of prescriber – compounder – patient triad