Compounding: What’s on the Horizon

Disclosure

Ronna Hauser declares no conflicts of interest or financial interest in any product or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.
Discuss the current position of the FDA on compounding and the ramifications for your compounding practice.

Explain how office use compounding and the memorandum of understanding are being addressed by the FDA and state boards of pharmacy and potential practice effects for compounding pharmacies.

Identify the legal/regulatory basis for FDA's ability to inspect pharmacies.

Explain how hazardous drugs are defined by USP <800> and require engineering controls and facility design.

Learning Objectives

• NCPA Compounding Committee guides our positions (focused on 503A)
• NCPA Active participant in FDA Listening Sessions, PCAC Bulk Drug Substance Nominations, DQSA stakeholder coalition
• NCPA Top Issues of Concern
  • Office use compounding
  • MOU
  • Inspections
  • USP Monograph Issue
  • Essential Copies
  • Creation of bulk positive list
  • PCAC Processes and Makeup

NCPA Protecting Your Right to Compound
NCPA Compounding Committee

Members

• Chair Kristen Riddle
• Board Liaison Jeff Carson
• Members
  • Donnie Calhoun
  • A.J. Day
  • Cheri Garvin
  • Michael Kim
  • Rich Moon
  • Kelly Selby
• Student Kimberly Paulson

NCPA Compounding Committee

Focus

• Implementation and initiatives associated with the Drug Quality and Security Act (DQSA)
• Work to stop state adoption of USP <800> and need to educate members on the business impact of the Chapter
  • Letter signed by 7 national pharmacy orgs sent to all state boards asking for 5 year enforcement delay
• Continue efforts with Compounding Best Practice Principles Forum in regards to quality compounding and billing practices
• Third party compounding provider networks
DQSA Where are We Now?

- 2016 FDA Activities
- 4/15/16: FDA Releases Draft Guidance Prohibiting 503A Office Use
- 6/9/16: FDA Releases Interim Policy on 503A Bulk Substances
- 7/7/16: FDA Releases Draft Guidance on Essential Copies
- 8/1/16: FDA Releases Notice Changing Inspection Procedure
- 8/3/16: FDA Releases Draft Guidance on Insanitary Conditions

- FDA’s guidance documents do not establish legally enforceable responsibilities but describe the Agency’s current thinking on a topic.

DQSA Coalition

Broad Group of Prescribers, Pharmacists and Patients (ex. Alliance for Natural Health, APhA, IACP, NASPA, NCPA, NHIA, PCCA, Fagron, Dermatology Association, Naturopathic Physicians)

DQSA Stakeholder Coalition Activities
- Office Use
- MOU
- Inspections
- Potential Legislation
- Appropriations
- Hearings
- PCAC
- Citizens Petition
- Listening Session Response
DQSA Where are We Now?

- Office Use OUTSTANDING
  - strong lobbying effort
- 503A Bulk Positive List FINAL GUIDANCE
  - USP Monograph Issue
- Essential Copies OUTSTANDING
  - Is compound an essential copy and if so was it compounded regularly or in inordinate amounts
- Inspections 8/1/16 PROCESS CHANGE
  - Prelim assessment to determine if 503A
  - No cGMP observations if 503A
- Insanitary Conditions OUTSTANDING
- MOU OUTSTANDING
- Vet Guidance OUTSTANDING

Outstanding 503A issues:
- Withdrawn/Removed List: FDA intends to update this list periodically, and expects compounders to comply with the list as it currently exists and with any final updates.
- Bulk Drug Substances List: FDA does not intend to take action against those healthcare providers compounding with certain bulk substances (503A List 1). FDA does not consider USP monographs for dietary supplements to be "applicable" monographs.

Outstanding 503A issues:

- "Demonstrable Difficulties" for Compounding: This provision is not enforceable until FDA promulgates an implementing regulation.
  - MDIs and Dry Powder Inhalers
- Memorandum of Understanding Between FDA and the States: FDA does not intend to enforce the 5% limit on interstate distribution until after FDA has finalized an MOU and made it available to the states for their consideration and signature.

**FDA Pharmacy Compounding Advisory Committee (PCAC)**

- FDA Pharmacy Compounding Advisory Committee
- 13 Total Members **Currently** 11 Voting 2 Non-voting
- Temporary Members may be voting members

**Chairperson**
- Jurgen Venitz, MD, PhD
  Associate Professor, Virginia Commonwealth University School of Pharmacy, Department of Pharmaceutics

**Ned S. Braunstein, MD (Industry Rep)**
Senior Vice President and Head of Regulatory Affairs Regeneron Pharmaceuticals, Inc.

**Michael A. Carome, MD, FACP (Consumer Rep)**
Director, Health Research Group, Public Citizen
PCAC Members

- **Gigi S. Davidson, BSPh, DICVP**
  Director, Clinical Pharmacy Services, North Carolina State University College of Veterinary Medicine

- **John J. DiGiovanna, MD**
  Senior Research Physician, DNA Repair Section, Dermatology Branch, Center for Cancer Research, National Cancer Institute

- **Padma Gulur, MD**
  Professor, University of California, Irvine Department of Anesthesiology and Perioperative Care

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PCAC Members

- **Stephen W. Hoag, PhD**
  Professor, University of Maryland, Baltimore Department of Pharmaceutical Science

- **William A. Humphrey, BSPharm, MBA, MS**
  Director, Pharmacy Operations, St. Jude Children’s Research Hospital

- **Elizabeth Jungman, JD**
  Director, Public Health Programs, The Pew Charitable Trusts

- **William Mixon, RPh, MS, FIACP (Industry Rep)**
  Former Owner, The Compounding Pharmacy
PCAC Members

- **Katherine Pham, PharmD, BCPS**
  Neonatal Intensive Care Unit Pharmacy Specialist, Children’s National Medical Center
- **Allen J. Vaida, BSc, PharmD, FASHP**
  Executive Vice President, Institute for Safe Medication Practices
- **Donna Wall, PharmD**
  Clinical Pharmacist, Indiana University Hospital

NCPA PCAC Concerns

NCPA Voicing Concerns with PCAC Processes and Makeup
- Inadequate PCAC member selection and renewal processes
- Conflicts of Interest
- FDA’s insistence that any bulk drug substance not voted onto the positive list can easily be obtained via the investigational new drug (IND) process
- Unequal time allotted for nominators to defend substances
- FDA’s indication that it does not consider USP monographs for dietary supplements to be “applicable” USP or NF monographs
- A confusing nominating and review process that leaves many unanswered questions
PCAC Votes

• 5 meetings to date
• 503A Positive List
  • Votes on Bulk Substances
    • YES(11) vs. NO(20)

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Compounding Best Practice Principles Forum

• Live meeting and series of calls
  • NASPA, NCPA, IACP, APH-A, PersonalMed, ACHC/PCAB, NABP, ACA
• Development of draft Guidelines for Quality Compounded Preparations
• Payer “buy-in”
• Dissemination of Guidelines to relevant stakeholders
Compounding:
What’s on the Horizon

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Rachael Pontikes declares no conflicts of interest or financial interest in any product or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.
What is a compounding pharmacy to do in these times of uncertainty?

- Understand all state rules that apply to compounding
- Understand—as best you can—FDA thinking on compounding

What is FDA thinking when it comes to compounding? How do I know?

- Drug Quality And Security Act—Section 503A
- Regulations
- Guidance/Draft Guidance
- FDA Notices
Final Guidance for 503A Pharmacies

- Pharmacy Compounding of human drug products under Section 503A
- Final Interim Policy on 503A Bulk Substances

Draft Guidances For 503A Pharmacies

- Draft Guidance Prohibiting 503A Office Use
- Draft Guidance on Essential Copies
- Draft Guidance on Insanitary Conditions
- Draft Memorandum of Understanding
FDA Notice of Change in Inspection Procedures

- Initial determination of Section 503A compliance
- Note: FDA procedure for determining insanitary conditions

Where the Rubber Hits the Road—FDA Inspections

- What happens during an inspection?
  - Records
  - Processes
  - State Board Involvement
- Current Trends
  - Insanitary Conditions
  - Compounding practices
- Best Practices For Inspections
Thank You!

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Compounding: What’s on the Horizon
USP <800>
Disclosure

John Voliva declares no conflicts of interest or financial interest in any product or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

What is USP Chapter <800>?

• General Chapter published by USP regarding the handling of hazardous drugs in healthcare settings
• Theoretically, would apply to all settings where hazardous drugs are present – pharmacies, hospitals, doctor’s offices, veterinary clinics, etc.
• Published February 1, 2016
• Chapter becomes official (read: enforceable) on July 1, 2018
• Primary adoption & enforcement responsibility will fall to the States
What is a Hazardous Drug?

- <800> directly references the “NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings”
- List is available here: http://bit.ly/2duqsO7
- Split into three different groups:
  - Antineoplastic Drugs
  - Non-antineoplastic drugs which meet one or more NIOSH criteria for a hazardous drug
  - Non-antineoplastic drugs which primarily have adverse reproductive effects
- List is update approx. every two years – last update, September 2016

Examples of NIOSH Hazardous Drugs

- Anastrozole
- Apomorphine
- Azathioprine
- Carbamazepine
- Chlorambucil
- Chloramphenicol
- Clonazepam
- Colchicine
- Diethylstilbestrol
- Estradiol (all forms)
- “Estrogen / Progesterone Combinations”
- Fluconazole
- Fluorouracil
- Gonadotropin, Chorionic (hCG)
- Hydroxyurea
- Mecloretamine
### Examples of NIOSH Hazardous Drugs

- Medroxyprogesterone
- Megestrol
- Methotrexate
- Methyltestosterone
- Misoprostol
- Mitomycin
- Mitotane
- Oxytocin
- Phenoxybenzamine
- Phenytoin
- Progesterone
- Propylthiouracil
- Spironolactone
- Tacrolimus
- Tamoxifen
- Testosterone
- Topiramate
- Tretinoin
- Valproate / Valproic Sodium
- Warfarin

### Facility & Engineering Controls

**Definitions**
- C-PEC: Containment Primary Engineering Control
  - Powder Containment Hood, Biologic Safety Cabinet, Negative Pressure Glove Box
- C-SEC: Containment Secondary Engineering Control – the negative pressure room

**Hazardous Drugs must be compounded in a C-PEC which is located in a C-SEC (the “hood” must be located in a negative pressure room)**

**The C-SEC MUST:**
- Be externally vented
- Be physically separate from other prep area
- Have appropriate air changes per hour (ACPH)
- Have a negative pressure between 0.01 and 0.03 relative to all adjacent areas
**Non-Sterile Compounding**

- USP <795> applies and:
- C-PEC must be externally vented (preferred) OR have redundant-HEPA filters in series
- The C-SEC nor the C-PEC are required to be ISO classified
- The C-SEC must achieve 12 ACPH
- “… surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the nonsterile compounding area must be smooth, impervious, free from cracks and crevices, and non-shedding.
- Bulk drug products must be stored under negative pressure

**Sterile Compounding**

- USP <797> applies and:
- C-PEC must be externally vented & must meet ISO 5 classification
- C-SEC must meet ISO 7 classification - preference is given for an ISO Class 7 buffer room with an ISO Class 7 ante-room
- Unclassified containment segregated compounding area is allowed, however, BUDs are restricted to no more than 12 hours
- C-SEC must achieve 30 ACPH
  - Compounding in a segregated compounding area – 12 ACPH
Additional Information

• USP FAQ on <800>: [http://bit.ly/1PCi6yY](http://bit.ly/1PCi6yY)
• Pharmacy org. letter to Board of Pharmacy
  • Requested five year delay in enforcement to July 1, 2021
  • NCPA, IACP, APhA, ASCP, CPNP, NASPA, NACDS
• Continued educational opportunities
• Important for pharmacists to get involved with State Boards regarding the implications of this Chapter on patient access
• Some States will write their own regulations - California