Compounding Medication: Are You Liable?

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Supporter

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Target Audience: Pharmacists and Pharmacy Technicians

• ACPE#: 0202-9999-16-020-L03-P
  0202-9999-16-020-L03-T
• Activity Type: Knowledge-based

Learning Objectives

• At the completion of this knowledge-based activity, participants will be able to:
  1. Describe the historical development of compounding law and regulation including FDAMA and 503A, and the Drug Quality and Security Act (DQSA) and its current implementation of 503B Outsourcing Facilities.
  2. Describe the current role of USP 795 and 797 in non-sterile and sterile compounding.
  3. Discuss current coverage, reimbursement and audit issues.
With regard to Section 503A, after the DQSA:

a. Prescription drugs can be filled without prescriptions for named patients
b. Prescriptions can be unsolicited
c. Purchase orders are acceptable in place of prescriptions
d. State boards of pharmacy no longer have any jurisdiction.

After the DQSA, 503B Outsourcing Facilities:

a. Can prepare non-sterile compounds as long as they prepare at least one sterile product
b. Must follow USP 797
c. Are inspected by the board(s) of pharmacy in the state(s) in which they are located
d. Cannot fill individual prescriptions for named patients

Under USP 795, for nonaqueous formulations, the beyond use date (BUD) is:

a. Not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier
b. Not later than 30 days
c. Not later than 14 days when stored at controlled cold temperatures
d. Not later than 60 days

Under USP 797, when nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g. oral), are incorporated or a nonsterile device is employed before terminal sterilization, this is considered:

a. Low risk
b. Medium risk
c. High risk

The following federal legal protections are afforded to compounding pharmacies with regard to third party audits:

a. The DQSA expressly includes protections for compounding pharmacies against egregious private third party payor audits.
b. The DQSA expressly includes protections for compounding pharmacies against egregious government-sponsored third party payor audits.
c. Congress is currently looking into passing new legislation to protect compounding pharmacies against egregious private third party payor audits.
d. There are no federal legal protections afforded to compounding pharmacies against any third party payor audits.

Compounded drugs is an entitled benefit according to Medicare.

a. True
b. False
Future trends strongly indicate expansions of compounded drugs as a covered benefit by government and private payors.

a. True  
b. False

Presenter Information: Lee Rosebush

- Background
  - PharmD from Purdue University
  - JD from Case Western in Cleveland
  - MBA and MS in Finance from Indiana University – Kelley School of Business
  - Chair of Baker Hostetler’s Pharmacy and Reimbursement Team
  - Previously, worked in both the retail and hospital settings as a RPh in both Indiana and Ohio (still hold both licenses today)

A Quick Compounding History Lesson

- Historically virtually all prescriptions were compounded
- Many were still compounded at time of passage of 1938 Food Drug & Cosmetic Act
- Manufactured drugs were phased into the market over many years
- FDA started showing concerns about pharmacy compounding in the early 1990s
- FDA issues Compliance Policy Guide (CPG) 7132.16 (later renumbered as 460.200) in 1992
  - The CPG acted as a “guidance” for pharmacy compounding and compounders
- Essentially, the CPG stated that FDA could exercise enforcement discretion and initiate enforcement actions when pharmacies acted as manufacturers

A Quick History Lesson

- Food and Drug Administration Modernization Act (FDAMA) of 1997
  - Created section 503A of the Federal Food, Drug, and Cosmetic Act (FFDCA)
  - Acknowledged FDA’s right to regulate pharmacy compounding
  - Created an exemption for compounded products that are compounded by pharmacies meeting specific standards
  - Put in place marketing prohibitions for compounding pharmacies

A Quick History Lesson

- FDAMA challenged in court
  - Thompson v. Western States
  - Appeal from Ninth Circuit reached U.S. Supreme Court (2002)
  - Compounding pharmacies challenged FDAMA as an undue burden on speech (First Amendment)
  - Specifically, that the marketing prohibitions went too far
  - Pharmacy compounders won in the District Court, Ninth Circuit, and U.S. Supreme Court
    - All 3 courts held that the marketing prohibitions were an undue burden
    - BUT…the U.S. Supreme Court did not rule on the invalidity of the entire statute (never appealed)
    - Ninth Circuit held that the statute was invalid
    - Decision led to a new CPG from FDA in 2002 with the advertising provisions removed
A Quick History Lesson

• FDAMA challenged in court
  • Medical Center Pharmacy v. Mukasey
  • Reached Fifth Circuit in 2008
  • Held that certain compounded products are exempt from certain requirements under the FFDCA by acknowledging FDAMA
  • But, the compounded products are “new drugs”
  • This decision led to a split between the 9th Circuit and 5th Circuit
  • FDAMA invalid in the 9th Circuit while valid (without the marketing prohibitions in the 5th Circuit)
  • Consequently, compounders in California (9th Circuit) faced different federal standards than those in Louisiana (5th Circuit)

Where Are We Now?

• The DQSA

In Addition to DQSA

• FDA Guidance Documents
  • Compounding of Animal Drugs from Bulk Drug Substances
  • Draft Guidance issued May 2015
  • Entities Considering Whether to Register as Outsourcing Facilities under Section 503B
  • Draft Guidance issued May 2015
  • Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the FFDCA
  • Draft Guidance issued February 2015
  • Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities
  • Draft Guidance issued February 2015

The DQSA

• Officially signed into law by President Obama on November 27, 2013
• Legislation consisting of two Titles
  • Title I - Compounding Quality Act
  • Title II - Drug Supply Chain Security
• Address several areas of concern for pharmacy compounders

In Addition to DQSA

• Mixing, Diluting, or Repackaging Biological Products Outside the Scope of and Approved Biologics License Application
  • Draft Guidance issued February 2015
• Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products
  • Draft MOU issued February 2015
• Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act
  • Guidance issued July 2014
• Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act FD&C Act
  • Draft Guidance issued July 2014
In Addition to DQSA

- Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
  - Draft Guidance issued December 2013
- Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
- Fees for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug, and Cosmetic Act
- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm
  - Includes FAQs, outsourcing facility registration information, warning letters, and other information

Benefits of Registering as an Outsourcing Facility

- Products Compounded by Registered Outsourcing Facilities are exempt from:
  - Drug approval requirements (ANDA, NDA)
  - Portions of Sections 502 (misbranded) and 505 (new drug) of the FFDCA do not apply to a drug “properly” compounded at an Outsourcing Facility
  - Certain labeling requirements (adequate directions for use)
  - What has commonly become known as the track and trace requirements
- Registration is completely VOLUNTARY
  - If a facility registers, the facility’s information is made public on FDA’s website
  - The information includes the date of last inspection and whether the facility has received a Warning Letter

DQSA Section 503B—Outsourcing Facilities

- Outsourcing Facilities
  - Section 503B(d)(4) defines an outsourcing facility as a facility at one geographic location or address that—(i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section.

The DQSA: Drug Reporting

- Upon initially registering, as well as in both June and December of each year, each outsourcing facility must submit a report:
  - Identifying the drugs compounded during the prior 6-month period
  - For each compounded drug, the report must state the
    - Active ingredient strength and source
    - Dosage form and route of administration
    - Package description
    - Number of individual units produced
    - NDC of active ingredient source and final product (if applicable)
  - Reports are confidential, exempt from inspection, and submitted electronically

FDA GUIDANCE DOCUMENTS
**FDA Draft Guidance: Whether to Register as an Outsourcing Facility Under 503B (Feb. 2015)**

- The facility must meet the following conditions:
  - Compliance with registration and reporting requirements of 503B(b), including twice annual reports and adverse event reporting.
  - If compounding from bulk drug substances, those substances must meet certain requirements.
  - No compounding of drugs on "withdrawn or removed" from the market list.
  - No copying of one or more approved drugs.
  - If drug is subject to REMS, facility must use control comparable to those applicable to REMS.

**FDA Draft Guidance: Whether to Register as an Outsourcing Facility Under 503B (Feb. 2015)**

- Compounded drugs will not be sold or transferred by an entity other than the outsourcing facility (can’t use wholesalers).
- Payment of applicable establishment and re-inspection fees.
- Include required labeling as set out by 503B(a)(10).
- Compound all drugs (sterile and non-sterile) in accordance with section 503B, including those compounded pursuant to an individualized prescription.
- Comply with current good manufacturing practices ("cGMP").

**Interim Guidance: cGMPs for Outsourcing Facilities**

- The guidance is "only applicable to drug compounded in accordance with section 503B."
- FDA plans to eventually promulgate regulations specific to cGMPs for Outsourcing Facilities.

**Compounded Labeling Requirements: Outsourcing Facilities**

- Outsourcing Facility Labeling Requirements
  - Outsourcing Facilities MUST include the following on the label:
    - "This is a compounded drug" or a similar statement that "prominently identifies" the drug as a compounded drug
    - Name, address, and phone number of outsourcing facility

- Drug information
  - Lot or batch number
  - Established name, dosage form and strength
  - Quantity or volume
  - Date of compounding
  - Expiration date along with storage and handling instructions
  - National Drug Code ("NDC") Identifier (if applicable)
  - "Not for resale" and, if the drug is compounded other than pursuant to a prescription, the statement "Office Use Only"
  - Active and inactive ingredient information (if adequate space)
### Compounded Labeling Requirements: Outsourcing Facilities
- **Container**
  - Directions for use, including dosage and administration
  - FDA adverse event reporting contact information
  - Active/inactive ingredient information that cannot fit on label

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### Draft Guidance: Adverse Event Reporting
- **ONLY applies to Outsourcing Facilities**—traditional pharmacies exempt!
- **What to Report:**
  - MUST report all serious, unexpected adverse drug experiences associated with compounded product
  - FDA suggests reporting all serious adverse drug experiences associated with compounded drug products
- **Information to Collect:**
  - Patient information (name, DOB, sex, etc.)
  - Reporter information (name, title, contact info)
  - Drug information (dosage form, lot number, etc.)
  - Adverse event information (death, hospitalization, disability, etc.)

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### Draft Guidance: Adverse Event Reporting
- **When to Report:**
  - Alert Report within 15 days of receipt of adverse event information
  - Within 15 days of new information or at FDA’s request
- **Inspections:**
  - FDA may review all adverse event report records including SOPs during routine inspections
- **Recordkeeping:**
  - Keep adverse event report records for 10 years from report of adverse event

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### What Products Can I Compound?

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### Other Provisions of DQSA
- **"Demonstrable Difficulties" List**
  - FDA must publish a list of drugs or categories of drugs that present "demonstrable difficulties for compounding" that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients.
  - Outsourcing facilities are prohibited from compounding drugs or categories of drugs on this list.
  - FDA has solicited nominations for this list.
- **List of Drug Products Withdrawn or Removed from the Market**
  - 21 C.F.R. 216.24 lists drug products that the FDA has withdrawn or removed from the market because they were found to be unsafe or not effective; no drug product on this list can be compounded.
  - The FDA issued a proposed rule to add 25 more drug products. 73 Fed. Reg. 37687 (July 2, 2014).

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### Other Provisions of DQSA
- **Bulk Drug Substances – Clinical Need List**
  - FDA will publish a list of bulk drug substances for which there is a clinical need that may be used by outsourcing facilities to compound drugs.
  - In Jan. 1999, FDA published a proposed rule proposing to include 20 drugs on the initial bulk drug substances list. 64 Fed. Reg. 996 (Jan. 7, 1999).
  - Before a final rule was published, the Supreme Court issued the Thompson decision; FDA stopped working on the bulk drug substances list.
Other Provisions of DQSA

- Now that the DQSA removed the unconstitutional provisions from 503A, FDA is restarting its efforts to create a list of bulk drug substances. In Dec. 2013, FDA withdrew the 1999 list (that was never finalized), and asked for nominations for a bulk drug substances list. 78 Fed. Reg. 72841 (Dec. 4, 2013).
- FDA issued a notice and revised request for nomination in July 2014 because many of the nominations received in response to the December 2013 notice “either were for a substance that is already the subject of a USP monograph or a component of an-FDA approved drug, were not for bulk drug substances used in compounding as active ingredients, or did not include sufficient information to justify inclusion of the nominated substance on the list.”
- The 503B list has yet to be published.

Pharmacy Compounding Advisory Committee ("PCAC")

- February 2015 Meeting
  - Addressed:
    - Drugs withdrawn or removed from the market for safety reasons
    - Bulk drug substance list under 503A
- June 17-18, 2015 Meeting
  - Follow-up discussions from previous meeting
  - Discussion of specific drugs to be added to the bulk drug substance list under 503A
- Discussion of criteria FDA proposes to use to evaluate drug products or categories of drug products for identification as demonstrably difficult to compound

Issues Outsourcing Facilities Are Facing?

Initial Issues for Outsourcing Facilities

1) Sterile vs. Non-Sterile
2) Animal/Vet
3) Repackaging
4) cGMP Lite?
5) MOU – How does it apply?

Issues

- Sterile v. non-sterile compounding
  - The DQSA’s definition of outsourcing facility includes only facilities engaged in compounding of “sterile” drug products.
  - Compounding means “the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering a drug or bulk drug substance to create a drug.”
  - Subsequent FDA guidance on whether to register as an Outsourcing Facility extended this to non-sterile.
  - FDA has clarified that Outsourcing Facilities can compound non-sterile products. However, the facility must compound at least one sterile product.

What About Animal/Veterinary Use?

- DQSA applies only with respect to “Human Drugs”
  - May 2015, FDA issued Draft Guidance for compounding of animal drugs from bulk drug substances and solicits nomination for Animal Drug Bulk Drug Substance List
  - Comment period is still open
Draft Guidance: Animal Drug Compounding From Bulk Drug Substances

• Applies to state-licensed pharmacies, licensed veterinarians, and Outsourcing Facilities.
• Only applies to animal drug products compounded from bulk drug substances and not drugs compounded from approved new animal or new human drugs.
• If an animal drug is compounded by an outsourcing facility, to satisfy the requirements spelled out in the Draft Guidance the compounded drug must:
  • Be compounded only from bulk drug substances appearing on Appendix A of the Draft Guidance, for which FDA is currently soliciting nominations;
  • Be compounded by or under the direct supervision of a licensed pharmacist;
  • Not be intended for use in food-producing animals;
  • Be compounded in accordance with current good manufacturing practices requirements;
  • Be compounded with bulk drug substances manufactured by an establishment that is registered under section 510 of the FFDCA (21 U.S.C. § 360) and is accompanied by a valid certificate of analysis;
  • Comply with the adverse event reporting requirements, i.e., within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs it compounded from bulk drug substances, the outsourcing facility reports it to FDA, on Form FDA1932a;
  • Not be sold or transferred by an entity other than the outsourcing facility that compounded such drug;
  • Be included, along with all other drugs compounded for animals by an outsourcing facility, on the report required by section 503B of the FFDCA to be submitted to FDA each June and December identifying the drugs made by the outsourcing facility during the previous six-month period;
  • Be accompanied by a prescription or order that states the drug is intended to treat the species and condition(s) for which the substance is listed in Appendix A; and
  • Be labeled in accordance with the Draft Guidance.

Draft Guidance: Animal Drug Compounding From Bulk Drug Substances

• Not be intended for use in food-producing animals;
• Be compounded in accordance with current good manufacturing practices requirements;
• Be compounded with bulk drug substances manufactured by an establishment that is registered under section 510 of the FFDCA (21 U.S.C. § 360) and is accompanied by a valid certificate of analysis;
• Comply with the adverse event reporting requirements, i.e., within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs it compounded from bulk drug substances, the outsourcing facility reports it to FDA, on Form FDA1932a;

The DQSA and FFDCA Section 503A

Where Does Section 503A Stand?

The DQSA and FFDCA Section 503A

• FFDCA Section 503A(a) Prior to the DQSA
  • Compounded drug exempt from FFDCA Sections 501 (cGMP), 502 (directions for use), and 505 (new drug application) if the drug is compounded based on unsolicited receipt of a valid prescription for an identified individual patient if:
    • The drug is compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, OR
    • The drug is compounded:
      • By a licensed pharmacist in limited quantities before the receipt of a valid prescription for such individual patient, AND
      • Based on a history of the licensed pharmacist receiving valid prescriptions for the compounded drug solely within the relationship between the pharmacist and either the ordering physician or the affected patient.

cGMP Issues

• Discrepancies between requirements applied to Outsourcing Facilities and traditional pharmacies conducting the same activities.
• Remember, both 503As and 503Bs can compound a prescription for a patient based on an individual prescription order
  • Repackaging—Differing BUD requirements and labeling
  • Compounding based on individual prescription—USP v. cGMP
  • Adverse event reporting—Applicable to 503Bs, but not 503As
The DQSA and FFDCA Section 503A

**503A Final Guidance**

1. Drug must be compounded for identified, individual patient pursuant to a prescription or a notation that says a compounded product is required – no changes in Guidance.
2. Drug must be (1) compounded pursuant to a prescription or (2) before receiving a prescription if there is a history of compounder receiving past orders – no changes in Guidance.
3. Drug must be compounded in compliance with USP chapters on compounding, using bulk substances that comply with applicable USP or NF monograph.
   - Guidance provides compounded drugs should only contain bulk drug substances that are components of FDA-approved drugs, OR are subject of a USP or NF monograph.
4. Drug must be compounded using bulk drug substances manufactured by registered entity – no changes in Guidance.

The DQSA and FFDCA Section 503A

**FFDCA**

1. Compounded drug exempt from FFDCA Sections 501 (cGMP), 502 (directions for use), and 505 (new drug application) if the drug is compounded based on unsolicited receipt of a valid prescription for an identified individual patient if:
   - The drug is compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, OR
   - The drug is compounded:
     - By a licensed pharmacist in limited quantities before the receipt of a valid prescription for such individual patient, AND
     - Based on a history of the licensed pharmacist receiving valid prescriptions for the compounded drug solely within the relationship between the pharmacist and either the ordering physician or the affected patient.

The DQSA and FFDCA Section 503A

503A exempts a compounder from requirements regarding cGMP, certain labeling provisions, and new drug applications/abbreviated drug applications if compounder complies with 10 conditions.


The DQSA and FFDCA Section 503A

- Exceptions under 503A for pharmacy compounding still exist:
  - Receipt of a valid prescription order that is approved by prescribing practitioner
  - Identified patient
  - Compounded by a licensed pharmacy, Federal facility, or a licensed physician
- 503A still recognizes an exception for compounding in limited quantities before the receipt of a valid prescription
  - Based on historical need

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The DQSA: Traditional Compounding

- Traditional Pharmacy Compounding
  - No FDA registration requirement
  - Still licensed and regulated by State boards
  - Traditionally compounded drugs still eligible for FFDCA Section 502 and 505 exemptions, but only if they are compounded:
    - For an identified patient pursuant to a valid prescription, or
    - In limited quantities in reasonable anticipation of receiving a prescription ("anticipatory compounding")
  - Can no longer make office use prescriptions - valid patient prescription is required.

Traditional Compounding

- So, after all the regulations and red tape, what does that mean for traditional compounding?
  - Traditional compounding pharmacies can still compound prescriptions that will be exempt from FDA regulation
  - Traditional compounding pharmacies do not have to register with FDA
  - Traditional compounding pharmacies will continue to be regulated by state boards of pharmacies
  - AS LONG AS THEY STAY WITHIN THE LINES...

Memorandum of Understanding

- Notice withdraws 1999 draft MOU.
- DQSA requires FDA to publish an MOU that states must sign in order for state-licensed pharmacies to compound beyond a certain threshold.
  - That threshold is 5%. If the MOU is not signed, compounding by entities within the state may not go beyond 5% of total product distributed.
  - If signed, the threshold is 30%.
  - Anything beyond 30% is considered an "inordinate amount" and is prohibited.
  - States are required to investigate complaints regarding: (1) adverse drug experiences, and (2) product quality issues.

Memorandum of Understanding

- They must also notify FDA.
- MOU may be terminated by FDA if state doesn’t comply, but no other specific repercussion.
- FDA proposed that enforcement of 5% rule will not take effect until 180 days after finalization and release of MOU to states (for those states that have not signed the MOU).
- Potential work-around:
  - Definition of a "unit"
  - Use of an agent
  - Acquisitions in key states

With regard to Section 503A, after the DQSA:

a. Prescription drugs can be filled without prescriptions for named patients
b. Prescriptions can be unsolicited
c. Purchase orders are acceptable in place of prescriptions
d. State boards of pharmacy no longer have any jurisdiction.

After the DQSA, 503B Outsourcing Facilities:

a. Can prepare non-sterile compounds as long as they prepare at least one sterile product
b. Must follow USP 797
c. Are inspected by the board(s) of pharmacy in the state(s) in which they are located
d. Cannot fill individual prescriptions for named patients
The Role of USP 795 and 797

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USP 795 and 797 Applicability

- USP 795: Non-sterile Compounding
- USP 797: Sterile Compounding

Section 503A

- Created under the 1997 Food and Drug Administration Modernization Act (FDAMA)
- Addressed only pharmacist compounding as Outsourcing Facilities were not created under the law until the DQSA.

DQSA

- Contained some provisions relative to 503A
- Created 503B Outsourcing Facilities
  - Subject to cGMPs
  - Not the subject of this presentation

FDAMA and USP 795

- FDAMA 503A addressed USP in the context
  - of bulk substances
    - 503A(b)(1)(A)(i)(I)
  - and ingredients other than bulk substances
    - 503A(b)(1)(B)

503A(b)(1)(A)(i)(I)

"(b) Compounded Drug—
(1) ... A drug product may be compounded under subsection (a) if the licensed pharmacist or licensed physician—
(A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the Code of Federal Regulations—
(i) that—
(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and United States Pharmacopoeia chapter on pharmacy compounding..."
503A(b)(1)(B)

- "(B) compounds the drug product using ingredients (other than bulk drug substances) that comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding"
  - Refers to USP 795. USP 797 was first published in 2004.

2015 Guidance Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

- 3. The drug product is compounded in compliance with the United States Pharmacopoeia (USP) chapters on pharmacy compounding⁸ using bulk drug substances, as defined in 21 CFR 207.3(a)(4), that comply with the standards of an applicable USP or National Formulary (NF) monograph, if one exists.
  * After the Modernization Act was enacted in 1997, the USP moved its chapter on pharmacy compounding to chapter <795> and added chapter <797>, which specifically addresses sterile compounding and is referenced in chapter <795>.

- 6. The drug product is compounded using ingredients (other than bulk substances) that comply with the standards of an applicable USP or NF monograph, if one exists, and the USP chapters on pharmacy compounding⁹ (section 503A(b)(1)(B) of the FD&C Act).
  * Id.
  - (* After the Modernization Act was enacted in 1997, the USP moved its chapter on pharmacy compounding to chapter <795> and added chapter <797>, which specifically addresses sterile compounding and is referenced in chapter <795>.

State Compounding Laws

- Most states require pharmacists to adhere to USP 795 when compounding 503A prescriptions.
- ~37 states require pharmacists to adhere to USP 797 when engaged in sterile compounding of prescriptions.

USP 795

- Nonsterile Compounding

General Organization of USP 795

- Definitions
- Categories of Compounding
  - Simple: reconstituting, manipulating
  - Moderate: special procedures or calculations (e.g. morphine suppositories)
  - Complex: Special training, environment, facilities, equipment, procedures
- Responsibilities of the Compounder

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General Organization of USP 795

- Compounding Process
  - Master formulation record
  - Appropriate equipment
  - Clean and sanitized area
  - Appropriate clothing
  - Hygiene
  - Reliable BUD
  - Labeling
  - Others

- Compounding Facilities
  - Space
  - Potable water
  - Plumbing
  - Lighting
  - Ventilation
  - Hazardous drug handling
  - Others

- Compounding Equipment
  - Appropriate equipment
  - Storage
  - Cleaning

- Component Selection, Handling & Storage
  - Source (e.g., USP, chemically pure, analytical reagent grade, ACS certified, etc.)
  - Expiration dates
  - Manufactured product as source
  - Dietary supplements
  - Storage
  - Others

- Stability Criteria & Beyond Use Dating
  - For nonaqueous formulations:
    - The BUD is not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier
  - For water-containing oral formulations:
    - The BUD is not later than 14 days when stored at controlled cold temperatures
  - For water-containing topical/dermal and mucosal liquid and semisolid formulations:
    - The BUD is not later than 30 days

- Packaging and Drug Preparation Containers
  - Suitable and clean materials
  - USP requirements
  - Stored off the floor

- Compounding Documentation
  - Master formulation record
  - Compounding record
  - Standard operating procedures
  - Material safety data sheets file

Outline of Hypothetical SOP for 503A

Monitoring of temperatures in refrigeration units used for medication storage

- Procedure:
  - Refrigeration Unit Monitoring Equipment
  - Temperature ranges
  - Outside Monitoring Company
  - Employee Monitoring Responsibilities
  - Deviation Response
  - Power failure Emergency Response
USP 797

- Sterile Compounding
- Too voluminous to go over in entirety but some highlights are in order.

General Organization of USP 797

- Definitions
- Responsibility of Compounding Personnel
- CSP Microbial Contamination Risk Levels
  - Low Risk
    - Example: single-volume transfers of sterile dosage forms from ampuls, bottles, bags, and vials using sterile syringes with sterile needles.
  - Medium Risk
    - Example: Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions

General Organization of USP 797

- High Risk
  - Example: Nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g., oral) are incorporated or a nonsterile device is employed before terminal sterilization

General Organization of USP 797

- Personnel Training and Evaluation in Aseptic Manipulation Skills
- Immediate-Use CSPs
  - Those situations where there is a need for emergency or immediate patient administration
- Single-Dose and Multiple-Dose Containers

General Organization of USP 797

- Hazardous Drugs as CSPs
- Radiopharmaceuticals as CSPs
- Allergen Extracts as CSPs
- Verification of Compounding Accuracy and Sterility
- Environmental Quality and Control
- Suggested Standard Operating Procedures

General Organization of USP 797

- Elements of Quality Control
- Verification of Automated Compounding Devices (ACDs) for Parenteral Nutrition Compounding
- Finished Preparation release Checks and Tests
General Organization of USP 797

• Storage and Beyond Use Dating
  – Can be determined in a number of ways
  • Consult the manufacturer of a particular product
  • Use appropriate literature sources
  • If not literature or direct testing, assign as in table for 795
  • Predict a theoretical BUD using charts, publications and tables

Conclusion

• Compounding pharmacies must now meet more stringent standards than in the past and may be subject to both FDA and state sanctions.

Under USP 795, for nonaqueous formulations, the beyond use date (BUD) is:

a. Not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier
b. Not later than 30 days
c. Not later than 14 days when stored at controlled cold temperatures
d. Not later than 60 days

Under USP 797, when nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g. oral), are incorporated or a nonsterile device is employed before terminal sterilization, this is considered:

a. Low risk
b. Medium risk
c. High risk

Compounding: The Potential Liabilities: Historical, Current and Future

Tony J. Park, Pharm.D., JD

Current Coverage & Reimbursement

• Provider Enrollment Spectrum – From unrestricted enrollment on one end, to mandatory credentialing on the other.
• Medicare
• Medicaid
• Private Insurance
• Worker’s Compensation
• Accountable Care Organizations
Are Compounded Drugs Even a Covered Benefit?
- Medicare
- Medicaid
- Private Insurance
- Worker’s Compensation
- Accountable Care Organizations

HM COMPOUNDING SERVICES, INC., and HMX SERVICES, LLC, Plaintiffs, v. EXPRESS SCRIPTS, INC., Defendant.
- No. 4:14-CV-1858 JAR.
- United States District Court, E.D. Missouri, Eastern Division.
- July 9, 2015.

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Bases of Reimbursement
- Highest Cost NDC
- Labor
- Degree of Difficulty
- Others

Current Audit Issues
- Desktop Audit
- Direct Beneficiary Communications
- “Mail Order” and/or “Specialty Pharmacy” restrictions
- Overpayment Recoupment

Future Trends in Coverage, Reimbursement and Audits
- Increased scrutiny for compounded drugs, both sterile and nonsterile.
- Creative new ways to justify audit recoupment.
  - Violations of the DQSA.
  - Violations of USP Standards [cGMP ?].
- Outright universal rejection of compounded drugs as a covered benefit.
- Downward pressures on third party reimbursement for drugs. v.2.0
  - Limited # of providers.
  - Race to the bottom dollar.
  - Increase in cash patients.
  - Increase in injury claims based upon manufacturing defects.
Potpourri of other Compounding-Pharmacy related risks:

- Patent Infringement

- Injunction from using Compounded drugs for execution

The following federal legal protections are afforded to compounding pharmacies with regard to third party audits:

- The DQSA expressly includes protections for compounding pharmacies against egregious private third party payor audits.
- The DQSA expressly includes protections for compounding pharmacies against egregious government-sponsored third party payor audits.
- Congress is currently looking into passing new legislation to protect compounding pharmacies against egregious private third party payor audits.
- There are no federal legal protections afforded to compounding pharmacies against any third party payor audits.

Compounded drugs is an entitled benefit according to Medicare.

a. True
b. False

Future trends strongly indicate expansions of compounded drugs as a covered benefit by government and private payors.

a. True
b. False