



California State Board of Pharmacy

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STATE AND CONSUMER SERVICES AGENCY

DEPARTMENT OF CONSUMER AFFAIRS

GOVERNOR EDMUND G. BROWN JR.

**STATE BOARD OF PHARMACY
DEPARTMENT OF CONSUMER AFFAIRS
COMPOUNDING REGULATION SUBCOMMITTEE
MINUTES**

DATE: January 4, 2012

LOCATION: Department of Consumer Affairs
First Floor Hearing Room
1625 N. Market Boulevard
Sacramento, CA 95834

SUBCOMMITTEE MEMBERS

PRESENT: Randy Kajjoka, PharmD, Chair
Anil Badlani, RPh

STAFF

PRESENT: Virginia Herold, Executive Officer
Anne Sodergren, Assistant Executive Officer
Robert Ratcliff, Supervising Inspector
Janice Dang, Supervising Inspector
Carolyn Klein, Legislation and Regulation Manager
Tessa Miller, Staff Analyst

Call to Order

Subcommittee Chair Randy Kajjoka called the meeting to order at 10:08 a.m.

Discussion Including Questions and Answers from Hospital Pharmacies and the Public on the Board's Implementation of 16 California Code of Regulations Sections 1735-1735.8, Pharmacies That Compound, and Sections 1751-1751.8, Pharmacies That Compound Sterile Injectable Medications

1. Overview of the Regulations

Executive Officer Virginia Herold provided an overview of the origins of the compounding regulations as well as a review of the timeline for evolution of the regulations. A copy of the presentation is attached, following this meeting summary.

Ms. Herold discussed that the new regulations were initiated in response to a letter from the Department of Health Services in July 2002 asking for collaboration with the board

to develop comments to the FDA on differentiating between compounding and manufacturing. She provided that in 2004 the board formed a workgroup which developed a legislative proposal as well as regulation proposals in 2005. Ms. Herold explained that this ultimately led to the board's final approval in 2009 and implementation of the regulations effective July 6, 2010.

There was no subcommittee discussion or public comment.

2. Requirements of the Regulation

Lead Supervising Inspector Bob Ratcliff provided a presentation on the requirements of the compounding regulations. A copy of this presentation is attached, following this meeting summary.

Dr. Ratcliff provided an overview of California Code of Regulations section 1735 and highlighted various definitions, requirements and limitations from the section.

Dr. Ratcliff also provided some historical perspective on the compounding regulations and discussed that California Pharmacy Law has had quality assurance requirements since at least 1993.

Dr. Ratcliff stated that effective January 1, 2012, the board's enforcement staff is implementing more aggressive enforcement of the compounding requirements. Specifically, he added that the board is reviewing and looking for the completed self-assessment, proper documentation, and adherence to the quality assurance program.

Public Comments

Katy Marconi sought clarification on the requirement for qualitative analysis.

Dr. Ratcliff provided that the pharmacist-in-charge is responsible for developing a policy and procedure that explains how to determine how and when qualitative and quantitative analysis is to be conducted.

3. Questions and Answers

a. What does quality assurance (QA) assessment of compounding require?

Chair Kajioka discussed that the pharmacist-in-charge, using his or her professional judgment, is to determine the component of the QA program and to ensure that the program is being utilized. He discussed that there should be a rationale behind why there is less structured QA for a particular medication.

Subcommittee Member Neil Badlani emphasized that the main goal is to ensure that pharmacies have QA policies and procedures in place.

Supervising Inspector Janice Dang discussed that the board's inspectors are looking to ensure that a QA program is in place. She discussed that generally, there should be a structured QA process in place for medication that is compounded routinely or periodically. Dr. Dang provided that the board's inspectors will look at what is being tested and the results of those tests. She added that test results and records should be organized and kept together in one place.

Public Comment

A member of the public provided comment on the evolution of compounding and the compounding requirements. He reviewed the difference between manufacturing and compounding. He discussed that quantitative analysis is an unrealistic expectation for hospital pharmacies providing immediate use doses and should not be required.

Chair Kajioka provided that the regulation covers both sterile to sterile compounding as well as non-sterile to sterile compounding. He stated that quantitative testing is more geared towards non-sterile to sterile compounding.

Ms. Herold discussed that the requirements of the regulation apply to all types of compounding in all settings. She advised that quantitative analysis is not required for every product. Ms. Herold explained that the pharmacist-in-charge needs to develop a plan and determine when and why analysis is not being conducted for certain products.

Katy Marconi provided comment on quantitative analysis and discussed that this area is highly scientific. She discussed risks involved with non-sterile to sterile compounding and suggested that the regulations be more specific in this area.

Chuck Snipes, representing Davis Compounding Solutions, discussed that the regulation specifies that mixing from manufacturers' bottles is not considered compounding.

Discussion continued. The importance of developing and following a QA program was emphasized.

Steve Gray, representing Kaiser Permanente, provided some historical background on this issue and the use of the term "end product evaluation." He suggested potential products and criteria that can be used to determine when to conduct quantitative analysis including narrow therapeutic index drugs, situations when the pharmacist-in-charge is not confident in the certificate of analysis for ingredients, and when there is no quantitative analysis available for a product.

Dr. Gray discussed that there is a need for education materials on what pharmacies should include in their QA programs, how information should be documented, and what inspectors will be looking for during inspection.

Jenny Partridge provided comment in support of the regulations. She cautioned pharmacies from overcomplicating the issue and discussed that the regulation simply requires each pharmacy to develop and document a QA program.

Dr. Dang again discussed that testing is not required for every product. She provided that pharmacists-in-charge need to develop a QA program and ensure that products are being tested according to their program.

b. Sterile injectable labeling requirements (§ 1751.2): Labeling of compounds that are Cytotoxic/chemotherapy

Chair Kajioka provided that § 1751.2 (d) requires that all cytotoxic agents bear a special label which states “Chemotherapy – Dispose of Properly.” He discussed that this issue may require a regulation change as the board has received comments that chemotherapy labels are generating anxiety for patients. Chair Kajioka reviewed the following potential amendments to the language:

- Option A: All cytotoxic agents shall bear a special label which states “~~Chemotherapy~~ Cytotoxic product – Dispose of Properly.”
- Option B: All cytotoxic agents shall bear a special label which states “Chemotherapy – Dispose of Properly” or “Cytotoxic product – Dispose of Properly.”

Chair Kajioka provided comment in support of option B and discussed that he prefers that pharmacists-in-charge have flexibility in this area. He discussed that nursing staff have different training requirements for chemotherapy and cytotoxic products.

Ms. Herold provided that this provision has been in effect since at least 1995 and should be reevaluated.

Public Comment

Steve Gray provided comment in support of option B. He asked whether the board’s enforcement staff will exercise discretion in this area until a regulation change is made.

Chair Kajioka provided that the subcommittee is recommending to the board that enforcement discretion be applied in this area.

c. Equipment used in Compounding

Chair Kajioka provided that the board’s compounding Q&A document (available on the board’s website) was too broad in its initial definition of equipment that must be recorded whenever a product is compounded. He stated that the subcommittee is recommending to the board an amendment to § 1735.3(a)(7) to read:

- The equipment used in compounding the drug product. For purposes of this section, equipment means items that must be calibrated or maintained.

Chair Kajioka provided that the subcommittee is also recommending that the equipment be required in the master formula rather than in the daily logs/compounding record as currently required.

Ms. Herold clarified that an amendment to § 1735.2 9(d) is needed in order to require that equipment be recorded in the master formula.

Inspector Jeff Smith discussed that documenting the equipment in a compounding record is useful when identifying the source of a problem in cases involving equipment malfunction. He clarified that it is rare for equipment to malfunction.

Chair Kajioka discussed that equipment malfunction was considered by the subcommittee. He provided comment in support of the subcommittee's recommendation and discussed that equipment is typically calibrated daily and tested frequently.

Dr. Dang discussed that it is a good investigative tool to have the equipment specified in the daily log. She discussed that the master formula specifies what type of equipment is to be used; whereas, the daily log indicates which piece of equipment was used (i.e. hood A vs. hood B).

Public Comment

Katy Marconi provided comment in support of the subcommittee's recommendation. She cautioned the board from requiring additional recording requirements.

Steve Gray asked whether every piece of equipment would have to be recorded if a pharmacy's QA program indicated that all equipment would be tested in the event a problem is identified.

Dr. Dang indicated that she will need to evaluate this question further.

Rich Sakai provided comment in support of the subcommittee's recommendation and provided evidence in support of the recommendation. He stated that although the master formula will not identify the exact piece of equipment used, it will narrow down what type of equipment should be reviewed. Dr. Sakai added that contamination is usually a result of employee error and not necessarily contamination of a piece of equipment.

- d. Only the component compounds used in a compounded product need to be recorded (see § 1735.3(6)), this does not include equipment and supplies.

Chair Kajioka reviewed current § 1735.3(a)(6) regarding the recording of the manufacturer and lot number of each product. He discussed that during its review, the subcommittee discovered that the expiration date of the components has been left out of the recording in this section and should be amended in.

Ms. Herold provided that this change will require an amendment to the regulation.

Public Comment

Steve Gray, representing Kaiser Permanente, provided comment in opposition to adding the expiration date as a recording requirement. He discussed that expiration dates can be traced by lot number. He also stated that adding additional recording requirements increases the chance for human error.

Dr. Gray expressed concern regarding the definition of components and stated that this should include more than active ingredients and diluents.

Dr. Ratcliff strongly recommended that expiration date be included as a recording requirement. He stated that this will highly impact general compounding that's done in community pharmacies as well as the board's investigations in this area.

Ms. Herold discussed that cases involving expired product usually result in a citation and fine and in some serious cases formal discipline.

Katy Marconi spoke in opposition to requiring the expiration date. She discussed that this will be burdensome and will not help to improve patient safety.

Rita Shane, representing the Cedars-Sinai Medical Center, discussed that expiration dating is required by three different agencies. She questioned why compounded medication is the sole focus for expiration dating. She suggested that the board conduct random spot checks of all products on pharmacy shelves.

Ms. Herold clarified that the board does conduct random spot checks, usually whenever an inspection is performed.

Dennis McAllister, representing Medco, spoke in opposition to the proposed requirement for recording the expiration date and discussed that this requirement should not burden the entire profession.

Dr. Dang discussed that the board's inspectors actively look at inventory for expiration dating. She indicated that lot numbers are not readily retrievable and are only helpful in the event of a recall.

Dr. Dang and Dr. Ratcliff spoke in support of the proposal and discussed that it is a needed tool for the board's investigations.

Chair Kajioka confirmed that this requirement adds value to quality compounding.

Dr. Shane provided that a compounding pharmacy's policies and procedures should detail how dating is determined and should address expiration of a product prior to the end use date.

Dr. Shane asked for consideration by the board to exempt acute care hospitals accredited by the Joint Commission as they are already required not to utilize or dispense expired products.

Chair Kajioka provided that this request can be considered by the board at a future meeting.

Bruce Vinson, representing Cedars-Sinai Medical Center, provided comment on non-sterile products which are often purchased in bulk containers and can be evaluated for expiration dating during an investigation.

Ms. Herold discussed that cases regarding expiration dating are prevalent in all settings and are not unique to compounding pharmacies.

The board recessed for a lunch break at 12:30 p.m. and reconvened at 1:45 p.m.

- e. In the interests of patient safety when compounding stock solutions from nonsterile to sterile ingredients, do the stock solutions need to undergo sterility and pyrogen testing?

Chair Kajioka reviewed § 1751.7(c):

1751.7(c) Batch-produced sterile injectable drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility and pyrogens and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens.

Chair Kajioka provided that there is a concern regarding the definition of a "batch-produced" sterile injectable drug product and an "end product" that requires testing for sterility and pyrogens.

Chair Kajioka provided that many compounding pharmacies are compounding a stock solution made from one or more non-sterile ingredients. He stated that the stock solution is used over a period of time to compound multiple prescriptions by withdrawing an amount from the stock solution to be compounded with other non-sterile or sterile ingredients as prescriptions are received.

Chair Kajioka provided that the compounding pharmacies are filtering the stock solution and the final compounded drug product that has the additional ingredients added. He stated that the compounding pharmacy considers the product with all the ingredients to be the “end product.” Chair Kajioka explained that the compounding pharmacy is also considering, once the stock solution is filtered, it is sterile and does not consider it to be a non-sterile ingredient, even though it is not tested to confirm sterility.

Chair Kajioka provided that because the compounding pharmacy is adding additional ingredients with an amount from the stock solution as they receive a prescription, the compounding pharmacy does not consider the final compounded drug as being “batch produced” and therefore, not subject to end-product testing for sterility and pyrogens. He stated that this practice of compounding can result in multiple patients being affected by a stock solution that is not tested to confirm sterility.

Dr. Dang clarified that the stock solution is considered the end product which needs to be tested for sterility and pyrogens.

Chair Kajioka provided that the subcommittee needs to discuss and determine its interpretation of the regulations regarding end-product testing of non-sterile to sterile injectable compounds and whether this requires sterility and pyrogen testing of stock solutions.

Chair Kajioka reviewed the following possible amendment:

1751.7(c) Batch-produced sterile injectable drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility and pyrogens and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens. Additionally, stock solutions compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility and pyrogens and shall be quarantined until the product testing confirms sterility and acceptable levels of pyrogens.

Chair Kajioka provided comment on his interpretation of the end product. He stated that the end product is not the final product. Chair Kajioka discussed that it is dangerous to not test a stock solution that may be used for multiple patients. He stated that this possible amendment is being implemented to be proactive in the interest of consumer protection.

Mr. Badlani discussed that additional discussion in this area regarding storage and sterility of stock solutions is needed.

Public Comment

Kent Martyn provided comment regarding the sterilization process. He discussed that testing of the solution may not be required every time when there is a validated process in place.

Steve Gray, representing Kaiser Permanente, provided comment on the importance of testing stock solutions and encouraged additional discussion in this area.

Jerra Banworth discussed that the Doc's Pharmacy incident occurred prior to the implementation of the current regulations. She provided comment in opposition to stock solution testing and expressed concern that the final end product is not being tested.

Discussion continued regarding end product testing and the requirements in this area.

Chair Kajjoka requested that additional comments be submitted to the executive officer for possible discussion at a future board meeting.

Presentation

Dr. Shane provided a presentation on sterile compounding and related safety strategies in hospital pharmacies to ensure patient safety. A copy of the presentation is attached, following this meeting summary.

Dr. Shane provided an overview of hospital patient-specific sterile compounded medications using sterile products and offered the following proposed definition:

- Hospital patient-specific sterile compounded medications using sterile products: Medications compounded using sterile products for an individual patient based on a physician order (prescription) intended to be administered within 24 hours.

Dr. Shane discussed that medications prepared and not administered due to changes in patients' conditions could be used if sterility and stability standards are met.

Dr. Shane reviewed a proposal to the board for an exemption to the recording requirements under Section 1735.3 (a)(6) and (7) for patient-specific compounded medications for use within 24 hours. She discussed that patient-specific sterile compounded medications should not require the recording of manufacturer and lot numbers for the following reasons:

- Hospitals use sterile products in compounding (sterile to sterile).
- Handwritten documentation for patient-specific medications delays timely delivery of critical medications.
- Harmful events related to sterile compounding have not been shown to result from drug recalls but rather from contamination and human errors.
- Critical medications that are on shortage are being discarded even though considered sterile and stable based on national standards.
- Quarantining and removal of all recalled products would ensure patient safety and timely follow-up and action.

Example: 1 dose of vancomycin 1.5 gram prepared for patient A, discontinued and used for patient B on the same day or within 14 days if refrigerated per USP 797.

Dr. Shane discussed that complying with the documentation requirements often takes longer than the time it takes to prepare the compounded medication.

Dr. Shane provided that she supports the recording of lot number and manufacturer for compounding of batches or sterile products from non-sterile ingredients.

Discussion

Chair Kajioka expressed concern that failure to record the required elements may lead to serious medication errors. He discussed that information regarding the manufacturer and lot number can assist pharmacies to quickly and accurately respond to errors and recalls.

Public Comment

Katy Marconi discussed that it takes a considerable amount of time to meet the recording requirements, even when using compounding technology. She recommended that the board consider an exemption from Sections 1735 and 1751 for inpatient hospitals that do not compound sterile product from non-sterile product that are accredited by the Joint Commission or an accrediting body recognized by the Centers of Medicare and Medicaid Services.

Rich Sakai provided comment on the challenges in complying with the regulation and cautioned the board that these extra recording requirements may result in unintended consequences that may result in decreased patient safety.

A member of the public provided comment on financial considerations for the practice of pharmacy. He stated that these considerations cannot be dismissed.

Steve Gray, representing Kaiser Permanente, also provided comment regarding the financial considerations in this area. He discussed that the benefit and value of the recording requirements should be evaluated against the risks and costs. Dr. Gray urged the subcommittee to consider the unintended consequences and recommend to the board that the recording requirements be reconsidered, because the board supported such unit dose repackaging and because of the implementation of the board's compounding regulation.

Chair Kajioka discussed that as the regulation has been in place for some time now, the board needs to begin enforcement of the requirements. He stated that the board can revisit and make modifications and improvements in the future.

Ms. Herold suggested that the board consider AB 1370 (Solorio) regarding centralized hospital drug distribution in the event the regulation is reconsidered.

Jenny Partridge asked whether policies and procedures are required for non-sterile compounding of a mouth wash.

Dr. Dang discussed that the requirements in Section 1735 apply for all compounding.

Steve Gray, representing Kaiser Permanente, requested that the board consider enforcement discretion for hospitals that commit to remove all recalled product from stock in response to a recall.

Dr. Ratcliff expressed concern regarding Dr. Gray's suggestion and stated that this may be an underground regulation.

Chair Kajioka provided a recap of the meeting and stated that the discussion from today's meeting will be presented to the board.

Public Comments on Items Not on the Agenda

David Smith discussed the costs involved in maintaining a sterile compounding license in California. He expressed concern that non-resident pharmacies that compound are not inspected by the board. Mr. Smith requested that the board reconsider issuing sterile compounding licenses to non-resident pharmacies.

The meeting was adjourned at 4:12 p.m.

Compounding Requirements

From 2002 through 2006

Compounding Vs Manufacturing

- July 2002, Department of Health Services sends letter asking to work with the board to develop comments to the FDA on differentiating between compounding and manufacturing

2004

- Workgroup On Compounding Formed
- Meetings:
 - March 3
 - June 9
 - Sept. 22
 - Dec. 1

Purpose of Work Group

- Define where mfg starts and pharmacy compounding ends
- Fill the gap between existing board regulations that focus on physical conditions for compounding, procedures and record keeping and
- Fill the void by establishing criteria for quality, strength and end product testing of the compounded product

Outcomes

- January 2005
Legislative proposal & regulation proposals
 - Establish requirements for all pharmacies that compound
 - Professional relationship between prescriber and patient must exist
 - Permit central fill compounding
 - Labeling requirements
 - Quality assurance for products
 - Requirements for facilities
 - Stored according to US Pharmacopeia

Legislation

- 2005 AB 595 (Negrete-McLeod)
Dropped by the board at the end of the session.

Regulation History

Origins

- 2004 Work group on Compounding develops statutory and regulation changes
- Legislation introduced in 2005
- Legislation died in the fall of 2006
- Board begins working on compounding regulations in January 2007 at its Licensing Committee Meetings

2007

- March – Licensing Committee discusses draft regulations
- May – Licensing Committee reviews regulation subdivision by subdivision
- July – Licensing Committee recommends initiation of rulemaking during board meeting

2008

- January: Board has regulation hearing on proposed requirements. No final action taken
- April: Start new notice based on comments from January
- August 22: new notice begins.
- October: Reg. hearing: Board meeting forms subcommittee to review comments

2009

- January Board Meeting: Board modifies text to specify 2 hours for non recording of lot number and mfg.
- April Board Meeting: board discusses three options: exempt for 24 hours or 12 hours or 2 hours
Board amends language to 24 hours and releases for (final) 15- day comment
- May: Final 15 day comment period

2009

- July 2009 Board Meeting: board approves language and adopts

2010

- January 6: OAL approves rulemaking
- July 6: Regulations take effect

Compounding

Bob Ratcliff
Supervising Inspector
CA State Board of Pharmacy

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- A long journey
 - Started on March 3, 2004
 - First of many meetings of Compounding Workgroup
 - Workgroup made up of board members, board staff, and stakeholders
 - Concluded December 10, 2009
 - Approval by Office of Administrative Law of regulations for pharmacy compounding

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- FDA's closer scrutiny of pharmacy compounding
 - Manufacturing
 - Compounding

 - Repealed existing CCR 1716.1 & 1716.2
 - New CCR 1735 et seq
 - Applies to general compounding and sterile injectable compounding

CCR 1735 et seq

- Defines what compounding is (1735)
- Definition of terms (1735.1)
- Compounding limitations (1735.2)
 - No anticipatory compounding
 - Compound in advance based on necessity to provide continuity of care
 - Master formula record

Master Formula Record

- Required for all compounded products
 - Active and inactive ingredients used
 - Process and/or procedure used
 - Quality review of each step
 - Post-compounding process or procedures
 - Expiration dating requirements
- Prescription document itself may be used for pharmacy that does not routinely compound

Self Assessment

- Two sections
 - 1st applicable to all compounding
 - 2nd sterile injectable compounding
- Must be completed before any compounding is performed

Records for Each Compounded Product

- Master formula record
- Date compounded
- Identity of who compounded
- Identity of RPH the reviewed final product
- Quantity of each component
- Manufacturer and lot number of each component
- Equipment Used

Records for Each Compounded Product

- Pharmacy assigned reference or lot number for the compounded product
- Expiration date of final product
- Quantity or amount of product compounded

Records for Each Compounded Product

- Exempt from previous requirements are sterile products compounded on a one-time basis for administration within 24 hours to an inpatient in a health care facility licensed under H&S 1250
- Chemicals, drug products, & components
 - Obtain from reliable supplier
 - Retain any available certificates of purity/analysis

Labeling

- B&P 4076 plus
 - Generic name of principal active ingredients
 - Statement the drug has been compounded
 - On container or
 - On receipt provided to patient
 - Unit dose products or too small/impractical for full compliance
 - Name(s) of active ingredients
 - Concentration or strength
 - Volume or weight
 - Pharmacy reference or lot number
 - Expiration date

Policies and Procedures

- Written policy and procedure manual
 - Procurement procedures
 - Method for formulation and compounding
 - Facilities and equipment
 - Cleaning
 - Maintenance
 - Operation
 - PIC review on annual basis and update as needed
 - Recall plan for dispensed compounded product

Compounding Facilities and Equipment

- Written documentation regarding facilities and equipment necessary for safe and accurate compounding
 - Equipment
 - Storage
 - Use
 - Maintenance
 - Calibration, if required
 - Prior to use
 - Written documentation

Training of Staff

- Written documentation to demonstrate staff have skills and training required
- Develop and maintain on-going competency evaluation process
- Demonstrate knowledge about process and procedures used in compounding prior compounding any drug product

Quality Assurance P&P's

- Designed to monitor and ensure integrity, potency, quality, and labeled strength
- Procedures for verification, monitoring, and review of adequacy of process
- Standards for qualitative and quantitative analysis for integrity, potency, quality, and labeled strength – retained and collated with compounding record and master formula
- Action to be taken if compounded product falls below minimum standards for integrity, potency, quality, and labeled strength

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Records of training and demonstrated competence shall be available for each individual and shall be retained for three years beyond the period of employment.

The pharmacist-in-charge shall be responsible to insure the continuing competence of pharmacy personnel engaged in compounding parenteral solutions.

1751.6. Disposal of Waste Material

Pharmacies providing parenteral services shall have written policies and procedures for the disposal of infectious materials and/or materials containing cytotoxic residues. The procedures shall include cleanup of spills and shall be in conformance with local health jurisdiction. The pharmacy shall ensure the return of such materials or shall communicate the proper destruction of such materials to the caregiver.

1751.7. Quality Assurance

There shall be a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications.

The Quality Assurance Program shall include at least the following:

(a) Cleaning and sanitization of the parenteral medication preparation area.

(b) Written documentation that the end product has been tested on a sampling basis for microbial contamination and steps taken in the event that testing for contamination proves positive.

(c) If manufacturing of parenteral products is performed using non-sterile chemicals, extensive end product testing must be documented prior to the release of product from quarantine. This process must include testing for sterility and pyrogens.

(d) The storage of compounded parenteral products in the pharmacy and periodic documentation of refrigerator temperature.

(e) Steps to be taken in the event of a drug recall.

(f) Written justification of the chosen expiration dates for compounded parenteral products.

1751.8. Policies and Procedures

Written policies and procedures associated with the pharmacy's preparation and dispensing of parenteral products shall include, but not be limited to:

(a) Compounding and labeling of intravenous admixtures.

(b) Administration of intravenous therapy.

(c) Equipment and supplies.

(d) Training of staff, patient and caregiver.

(e) Procedures for handling cytotoxic agents.

(f) Quality assurance program.

(g) Recordkeeping requirements.

Quality Assurance P&P's

- **1735.5. Compounding Policies and Procedures** (Effective 07/06/10)
- (a) Any pharmacy engaged in compounding shall maintain a written policy and procedure manual for compounding that establishes procurement procedures, methodologies for the formulation and compounding of drugs, facilities and equipment cleaning, maintenance, operation, and other standard operating procedures related to compounding.
- (b) The policy and procedure manual shall be reviewed on an annual basis by the pharmacist-in-charge and shall be updated whenever changes in processes are implemented.
- (c) The policy and procedure manual shall include the following:
 - (1) Procedures for notifying staff assigned to compounding duties of any changes in processes or to the policy and procedure manual.
 - (2) Documentation of a plan for recall of a dispensed compounded drug product where subsequent verification demonstrates the potential for adverse effects with continued use of a compounded drug product.
 - (3) The procedures for maintaining, storing, calibrating, cleaning, and disinfecting equipment used in compounding, and for training on these procedures as part of the staff training and competency evaluation process.
 - **(4) Documentation of the methodology used to test integrity, potency, quality, and labeled strength of compounded drug products.**
 - (5) Documentation of the methodology used to determine appropriate expiration dates for compounded drug products.

Quality Assurance P&P's

- **1735.8. Compounding Quality Assurance (Effective 07/06/10)**
- **(a) Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the integrity, potency, quality, and labeled strength of compounded drug products.**
- (b) The quality assurance plan shall include written procedures for verification, monitoring, and review of the adequacy of the compounding processes and shall also include written documentation of review of those processes by qualified pharmacy personnel.
- **(c) The quality assurance plan shall include written standards for qualitative and quantitative integrity, potency, quality, and labeled strength analysis of compounded drug products. All qualitative and quantitative analysis reports for compounded drug products shall be retained by the pharmacy and collated with the compounding record and master formula.**
- (d) The quality assurance plan shall include a written procedure for scheduled action in the event any compounded drug product is ever discovered to be below minimum standards for integrity, potency, quality, or labeled strength.

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(2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years.

(Amended 9-29-2004; Operative 10-29-2004)

1751.6. Disposal of Waste Material

Pharmacies compounding sterile injectable products shall have written policies and procedures for the disposal of infectious materials and/or materials containing cytotoxic residues. The procedures shall include cleanup of spills and shall be in conformance with local health jurisdiction.

(Amended 9-29-2004; Operative 10-29-2004)

1751.7. Quality Assurance and Process Validation

(a) There shall be a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications. The Quality Assurance Program shall include at least the following:

(1) Cleaning and sanitization of the parenteral medication preparation area.

(2) The storage of compounded sterile injectable products in the pharmacy and periodic documentation of refrigerator temperature.

(3) Actions to be taken in the event of a drug recall.

(4) Written justification of the chosen expiration dates for compounded sterile injectable products.

(b) Each individual involved in the preparation of sterile injectable products must successfully complete a validation process on technique before being allowed to prepare sterile injectable products. The validation process shall be carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The validation process shall be representative of all types of manipulations, products and batch sizes the individual is expected to prepare. The same personnel, procedures, equipment, and materials are involved. Completed medium samples must be incubated. If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated. Personnel competency must be revalidated at least every twelve months, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile injectable drug products is repaired or replaced, the facility is modified in a manner that affects airflow or traffic patterns, or whenever improper aseptic techniques are observed. Revalidation must be documented.

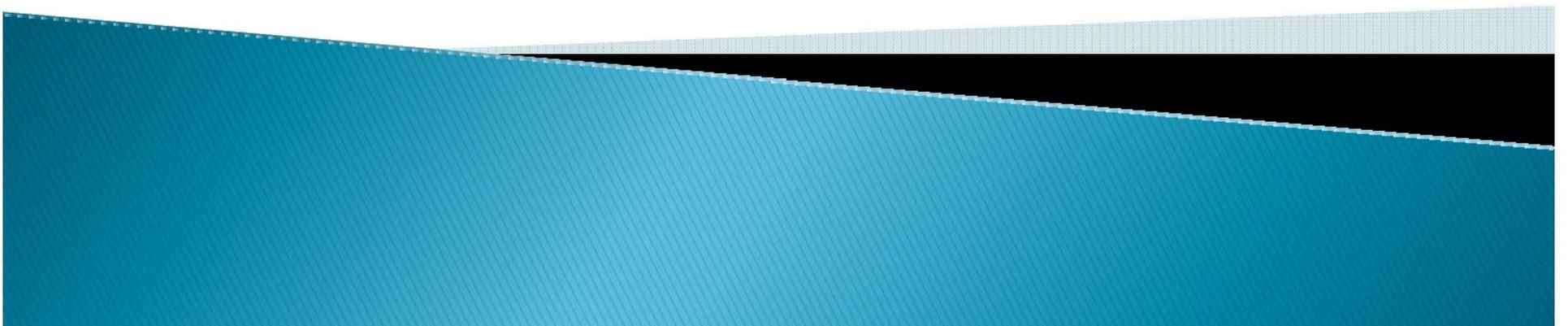
(c) Batch produced sterile injectable drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility and pyrogens and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens.

(Amended 9-29-2004; Operative 10-29-2004)

Implementation

- Regulation becomes effective in six months – July 2010
- **Board will do compliance checks and education for six months – until Jan. 2011**

Sterile Compounding Subcommittee

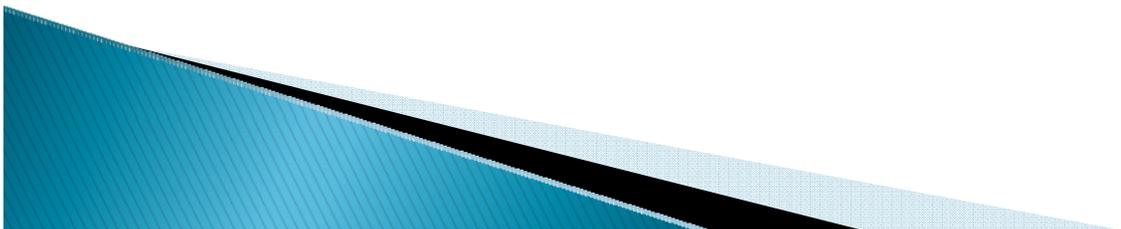


Goal and Objectives

Goal: Collaborate on strategies to prevent harm associated with sterile compounding in the hospital setting and ensure sterile compounded medications are available to treat patients

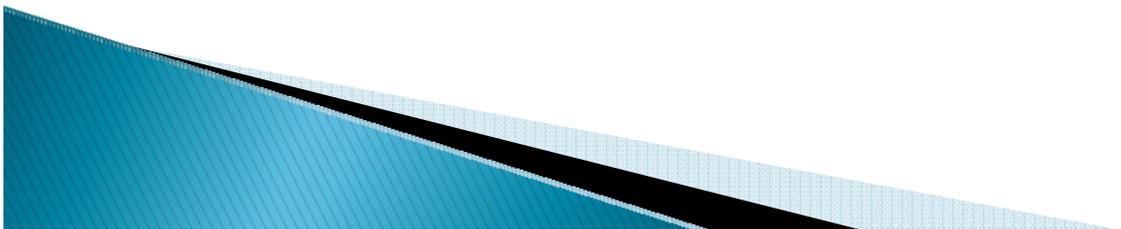
Objectives:

- Review definitions for hospital patient-specific (and non-patient specific) sterile compounding, components and equipment based on August and October meetings
- Review standards supporting sterility and stability of hospital patient-specific sterile compounding beyond 24 hours
- Provide rationale for exempting hospital patient-specific sterile compounding from documentation of manufacturer and lot number
- Provide recommendations regarding quantitative analysis
- Replace the term “chemotherapy” with “cytotoxic” for labeling of medications



Proposed Definitions and Interpretations

- ▶ **Hospital Patient–Specific Sterile Compounded Medications using Sterile Products:**
 - Definition: Medications compounded using sterile products for an individual patient based on a physician order (prescription) intended to be administered within 24 hours. (1735.3. (a) (6))
 - Interpretation: Medications prepared and not administered due to changes in patients’ conditions could be used if sterility and stability standards are met.



Sterility and Stability of Sterile Compounded Medications

<u>Sterility:</u> USP 797 National Standards Defines storage until the IV infusion begins <u>Stability:</u> Mfr info, published compendium and literature				CaBOP Supply Mfr, Lot #, & Exp Date Must be Logged <u>to</u> <u>Reuse</u> Admixtures (Needles, Syringes, Tubing)
<u>Storage until infusion begins</u>	<u>Room Temp</u>	<u>Refrig</u>	<u>Frozen</u>	
Immediate Use	1 hr	1 hr	N/A	
Low Risk \leq 2 adds; BUD < 12 (non-clean room)	12 hrs	12 hrs	12 hrs	
Low Risk \leq 2 adds (IV Clean Room)	48 hrs	14 days	45 days	<u>24 hours</u> No reuse
Medium Risk > 2 adds, chemo, TPN	30 hrs	9 days	45 days	<u>24 hours</u> No reuse
High Risk-non-sterile	24 hrs	3 days	45 days	<u>24 hours</u> No reuse

Proposed Definitions and Interpretations

- **Hospital Non-Patient Specific Sterile Compounding**
 - Compounding of medications in anticipation of physicians' orders
- ▶ **Components: 1735.3. (a) (5) and (6)**
 - Medications used to compound sterile products (excludes needles, syringes, etc)
- ▶ **Equipment: 1735.3 (a) (7)**
 - Interpretation: Items used in compounding that require calibration or maintenance per manufacturer's guidelines excluding laminar airflow hoods and biosafety cabinets with required certification



Rationale for Exemption of Hospital Patient Specific– Sterile Compounding

- ▶ Hospital patient–specific sterile compounded medications should not require the recording of mfr and lot numbers because:
 1. Hospitals use sterile products in compounding (sterile to sterile).
 2. Handwritten documentation for patient–specific medications delays timely delivery of critical medications.
 3. Harmful events related to sterile compounding have not been shown to result from drug recalls but rather from contamination and human errors.
 4. Critical medications that are on shortage are being discarded even though considered sterile and stable based on national standards.
 5. Quarantining and removal of all recalled products would ensure patient safety and timely follow–up and action.
- 

Time and Motion Evaluation of Compounding and Manual Recording of Mfrs and Lot #s

Compounding IV
with electrolytes
and vitamins

- 5 minutes

Documentation of
manufacturers and
lot numbers

- 3 minutes 51 seconds – represents 77% increase in time
- Each lot # is 7–10 characters

Pharmacist
checking of
documentation of
manufacturers and
lot numbers

- 2 minutes 30 seconds – time to document and pharmacist check of documentation is > than time to compound the medication

6:21
min

1 Month of Drug Shortages involving Medications used in Sterile Compounding



242 Shortages in 2011

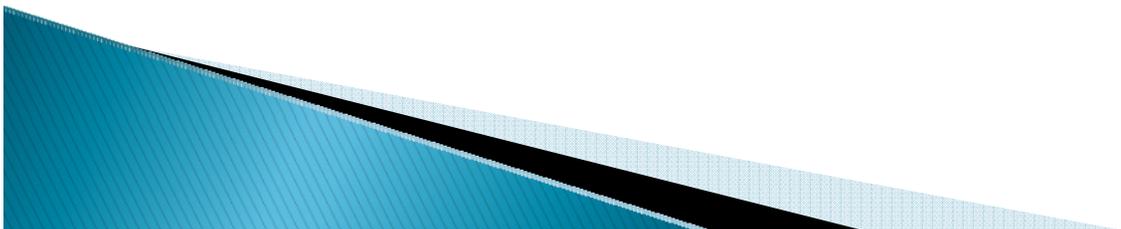
Hospital Management of Recalls

Hospital Recall Survey

- 99% (73 / 74) of hospitals would recall all compounded products not yet administered unless they could verify that they had not received the recalled ingredient
- One hospital is recording mfr and lot #

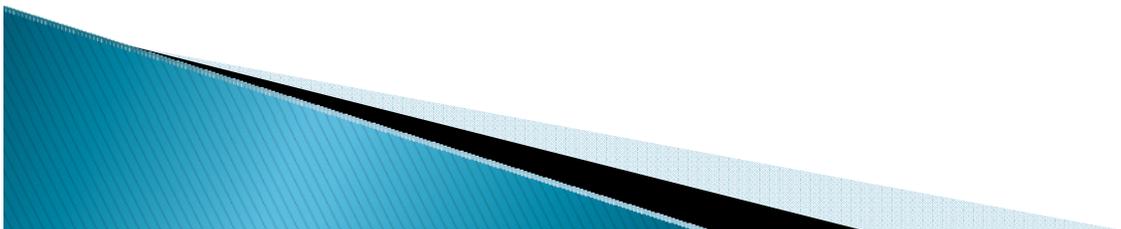
Recommendation

- Adopt current practice (stated above) to ensure timely removal and quarantining of recalled products



Hospital Requirements Related to Expiration Date

- ▶ Prior to dispensing or compounding, medications are checked to ensure that they are not expired
- ▶ Hospitals are required to check all areas where medications are stored monthly to ensure the absence of medications that are expired
 - CDPH, CMS Conditions of Participation, The Joint Commission
- ▶ Requiring documentation of expiration dates will increase time required to prepare product and distract focus from ensuring accuracy, safety and absence of contamination



Ensuring Safety of Complex Sterile Products

High-risk therapies

Chemotherapy
High-alert medications
Patient controlled analgesia (PCA)

High-risk routes

Epidural
Intrathecal
Ophthalmic

High-risk populations

Pediatrics
Dose considerations
Volume considerations
Preservatives
Critical Care

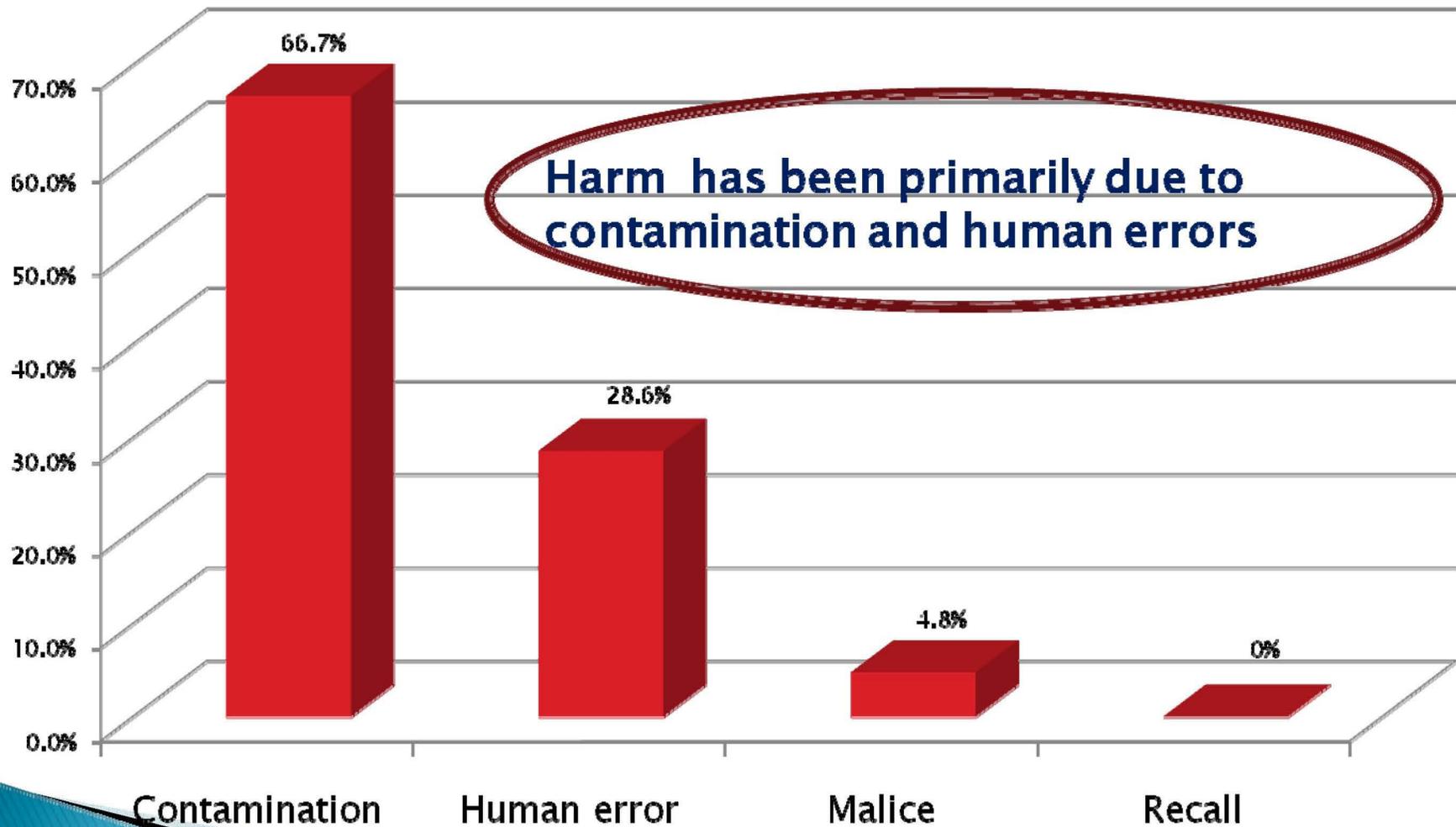
TPNs

Multiple additives
Compatibilities
Use of automated compounders
Order entry

Multiple independent checks performed to ensure safe, accurate compounding

U.S. Publicly Reported Events Associated with Sterile Compounding

Analysis of Causes of Harmful Patient Events



Harm has been primarily due to contamination and human errors

Alabama TPN Contamination

- ▶ Six Alabama Hospitals used an outsource pharmacy to compound TPNs
- ▶ 17 *Serratia marcescens* bloodstream infections due to contaminated TPNs
- ▶ 9 possible deaths due to the bloodstream infections
- ▶ Use of non-sterile powder to prepare amino acids

Centers for Disease Control and Prevention (CDC) and United States Pharmacopeia (USP);
Compounding Total Parenteral Nutrition Preparations: A 2011 Investigation of a Bacterial
Outbreak Webinar, September 20, 2011.



Alabama TPN–Compounding with Non–Sterile Powder

USP Pharmacopeial Education

Compounding of 15% Amino Acid Solution

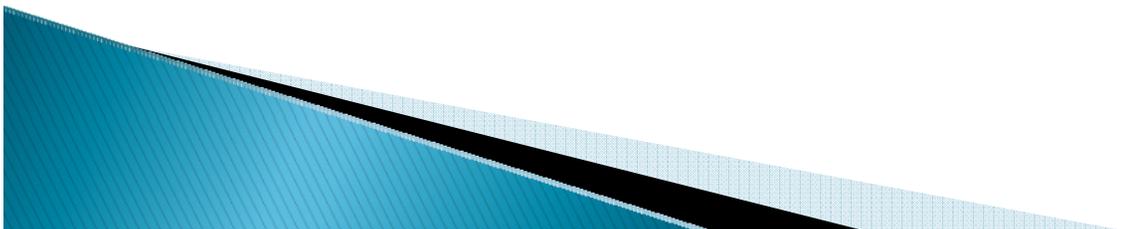


- ❑ Bulk amino acid powders
 - Nonsterile
- ❑ Sterile water in large mixing container
- ❑ 80–100 L batches
- ❑ On occasion, compounded 1–2 days prior to filtration

- Utilized tap water to rinse mixing containers
- Insufficient sampling of amino acid solution (non–sterile) for sterility testing
- Did not follow USP 797

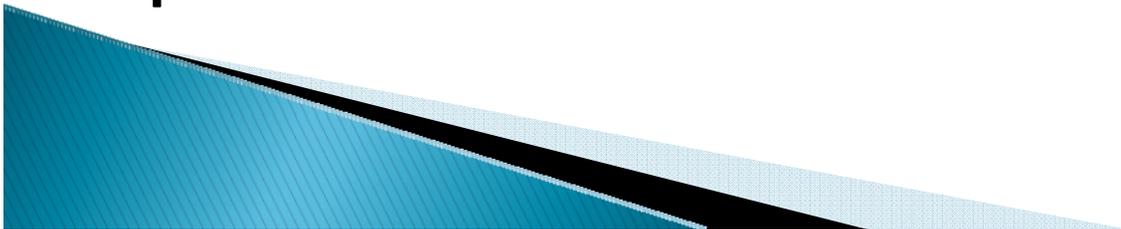
Avastin (bevacizumab) Intravitreal Injection Contamination

- ▶ Cluster of streptococcal endophthalmitis infections
- ▶ Preparation of Avastin 1 mg syringes from 100mg preservative-free, single-dose vial
- ▶ Compounding pharmacy (FL)
- ▶ Hospitals (TN, CA)
- ▶ 21 patients experienced blindness or partial loss of vision



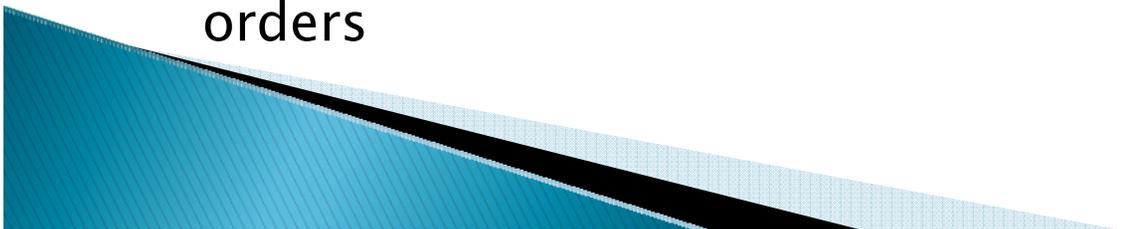
USP 797

- ▶ National standards for sterile compounding to ensure the highest quality
- ▶ Surveyed by CDPH
- ▶ Has been adopted by hospital pharmacies
- ▶ Dating of sterile compounded products is defined by USP based on risk levels which are determined by the level of complexity to prepare compounded products
- ▶ **Main Goals: Sterility and safety of compounded products**



Hospital Sterile Compounding Recommendations

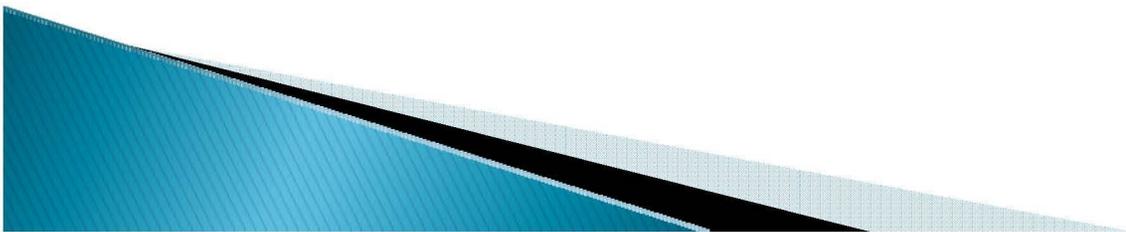
1. Exempt “Hospital Patient–Specific Compounded Medications” from requiring documentation of mfr and lot number
 - Definition of “Hospital Patient–Specific Compounded Medications”: Medications compounded using sterile products for an individual patient based on a physician order (prescription) intended to be given within 24 hours
 - Interpretation: Medications prepared and not administered due to changes in patients’ condition could be used if sterility and stability standards are met
2. Continue to record manufacturer and lot number for medications for non–patient specific compounding and non–sterile compounded products
 - Definition of “Non–Patient–Specific Compounded Medications”: Compounding of medications in anticipation of physicians’ orders



Hospital Sterile Compounding Recommendations

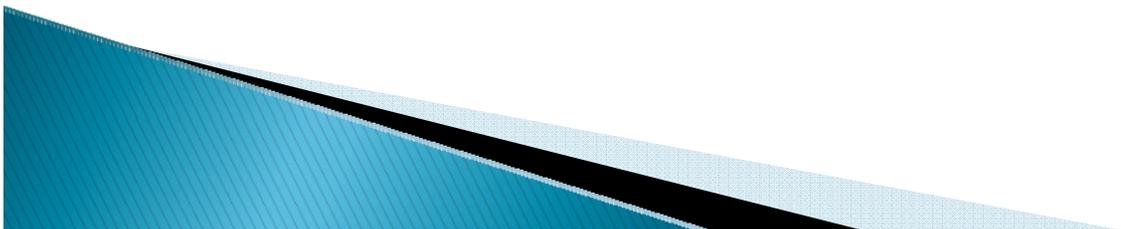
3. **“Component” & “Equipment” 1735.3. (a) (5)–(7)**
 - **“Component”**: Medications used for sterile product compounding (excludes needles, syringes, etc)
 - **“Equipment”**: Items used in compounding that require calibration or maintenance per manufacturer’s guidelines excluding laminar airflow hoods and biosafety cabinets with required certification
 4. **Quantitative analysis**
 - Reserve for sterile products compounded from non–sterile ingredients
 5. **Labeling of Cytotoxic Agents as “Chemotherapy”**
 - All cytotoxic agents shall bear a label which states “cytotoxic” rather than “chemotherapy” as currently stated in Compounding Regulations. 1751.2.(d)
- 

Additional Slides for Reference



1735.3. Records of Compounded Products

- ▶ (a) For each compounded drug product, the pharmacy records shall include:
- ▶ (6) The manufacturer and lot number of each component. If the manufacturer name is demonstrably unavailable, the name of the supplier may be substituted. Exempt from the requirements in this paragraph are sterile products compounded on a one-time basis for administration within twenty-four hours to an inpatient in a health care facility ...
- ▶ (7) The equipment used in compounding



California Hospital Survey of Sterile Compounding Practices N=38

USP 797

- 94 % following USP 797
- 6% implemented the majority of components and working towards facility renovation

Safety Strategies

- 100% double checking of chemotherapy
- Safety measures for pediatric sterile products include: certified Individuals, double checking, verifying weight based dosing

Training

- Formal Training Programs for pharmacists and technicians including ASHP training and written exam

Drug Shortages

- 100% of hospitals significantly impacted by drug shortages

Error Prevention

- Errors have been intercepted by double checks
- Causes of errors include calculations, CPOE, computer system errors

Hospital Pharmacy Computer Systems

- Commercial systems do not have the ability to support documentation of lot number and manufacturer N=22

Sterile Compounding Processes in Ambulatory and Hospital Settings

Ambulatory Setting

- ▶ One compounded prescription generally represents multiple days' supply of medications

Home Infusion

- ▶ One prescription is compounded for multiple days at the same time

Hospital Setting

- ▶ One prescription represents multiple days of medications that are generally compounded multiple times per day for the duration of treatment
- ▶ Safety strategies

Sterile Compounding and Implications of Drug Shortages and Wastage

Approx. 900 sterile products prepared/day based on over 5000 orders/day



95 sterile products wasted per day due to 24 hour dating*
Significant environmental impact



49% of medications wasted are drugs that are in shortage



Types of drugs wasted that are on shortage: antibiotics, heart failure meds, critical care meds, chemotherapy, antivirals

Drug Shortages have a significant impact on availability of injectable drugs

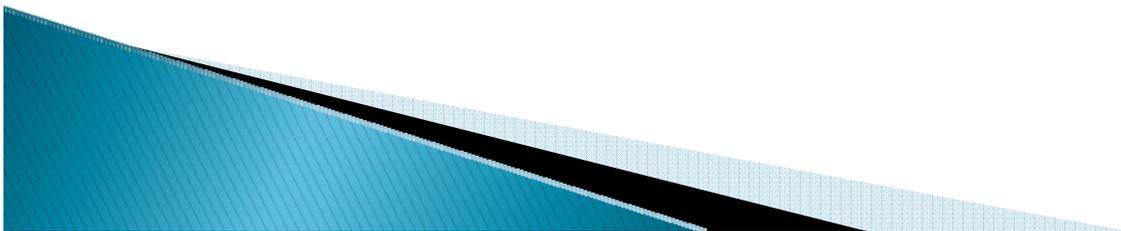


243 Drug Shortages YTD of which 95% are injectable drugs

*does not include sterile products wasted in patient care areas

Challenges Associated with Quantitative and Labeled Strength Analysis (1735.8.)

- ▶ Overfill volume for commercially manufactured intravenous solutions ranges from 2%–34% (source:3 IV manufacturers)
 - Overfill varies within a batch and amongst different volumes of IV fluids
- ▶ As a result, an analysis of potency of medication will almost always be less than what is labeled
- ▶ Many products cannot be quantitatively assayed



CERTIFICATE OF ANALYSIS

SAMPLE INFORMATION

Customer: Cedars-Sinai Medical Center
Received: June 3Q 2011
Description: AMIODARONE 1MG/ML IND5W
Lot Number: 110629ivr03
Sample #: W-1-4

Storage: Room Temperature
Amount/ Device: Amiodarone 500m

RESULTS

Test	Specification
Potency/Purity ¹	90.0 -110.0 %

AUTHORIZATION AND WARRANTY

Medications Labeled as Chemotherapy

1751.2.d. All cytotoxic agents shall bear a label
“Chemotherapy–Dispose of Properly”

Medication	Category/Use
Ganciclovir	Antiviral used for CMV prevention/treatment in transplant pts
Infliximab	Biologic used to treat Crohn’s disease, rheumatoid arthritis
Flucytosine	Antifungal therapy used for meningitis
Foscarnet	Antiviral agent used for CMV retinitis and HSV
Leuprolide	Gonadotropin–releasing hormone agonist used for endometriosis
	Keratinocyte growth factor used for oral mucositis