



**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 SUBCOMMITTEE  
MINUTES**

**DATE:** March 19, 2013

**LOCATION:** DCA Headquarters Building Two  
1747 North Market Blvd Room 186  
Sacramento, CA 95834

**BOARD MEMBERS**

**PRESENT:** Amy Gutierrez, PharmD, Chair  
Randy Kajioka, PharmD, Vice President

**BOARD MEMBERS**

**IN AUDIENCE:** Stanley Weisser, RPh, President

**STAFF**

**PRESENT:** Virginia Herold, Executive Officer  
Robert Ratcliff, Supervising Inspector  
Jeffery Smith, Inspector  
Laura Hendricks, Staff Analyst

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**Call to Order**

Chairperson, Dr. Amy Gutierrez, called the meeting to order at 10:02 a.m.

**I. General Background of Compounding Pharmacies in California**

Dr. Gutierrez reported that sterile compounding is currently in the spotlight. In 2001, the board sponsored legislation and eventually promulgated requirements for pharmacies that compound sterile injectable compounds as part of the board's response to a contaminated compounded medication that killed three patients and injured others in Northern California. Regulation requirements exist for any pharmacy that compounds, and there are additional requirements for pharmacies that do sterile compounding, and even more for pharmacies that do non-sterile to

sterile compounding. Dr. Gutierrez added that the main provisions are in Title 16 California Code of Regulations sections 1735 et seq. and 1751 et seq.

Dr. Gutierrez directed the committee and the public to watch a *60 Minutes* news report on the meningitis outbreak that resulted from the sterile products compounded at The New England Compounding Center (NECC). A link to the video is below.

<http://www.cbsnews.com/video/watch/?id=50142537n>

Dr. Gutierrez conducted a roll call -Dr. Amy Gutierrez and Dr. Randy Kajioaka were present.

Dr. Gutierrez reported that for a number of years California law has authorized a pharmacy to compound for prescriber office use (Business and Professions Code section 4052(a) and (a)(1)). This authority and clarifying regulations that exist in Title 16 California Code of Regulations Section 1735.2 does allow pharmacies to compound larger quantities of non-patient specific medication.

Dr. Gutierrez noted that the question has been for years, “At what point is a pharmacy is no longer compounding medication, but rather manufacturing medication?”

Dr. Gutierrez reported that the FDA is looking at perhaps creating a new classification of compounding – a “nontraditional compounding pharmacy” that would likely be more restrictive than California’s current structure for “prescriber office use”.

Dr. Gutierrez stated that the board is again reopening the discussion in California on compounding and California’s requirements. She referenced a copy of the proposed legislation that was provided in the meeting materials.

Inspectors Robert Ratcliff and Dr. Jeffery Smith provided a PowerPoint presentation giving a general background on sterile compounding and summarizing a survey of sterile compounding pharmacies conducted by the board. The presentation has been provided following the meeting minutes.

During the PowerPoint presentation members of the audience where allowed to informally ask questions from their seats to clarify points of the presentation. Questions included clarifications on the statistics reported, what violations were found in the pharmacies, what type of sterilization technique were being used in the pharmacies and what type of testing was seen in the pharmacies.

Ms. Virginia Herold added that the board is reexamining its processes because there have been two recent national incidents of patient injury and death due to sterile compounding. She reported that the NECC was appropriately licensed to

ship products into California. However, the fact that there were no deaths in California was not a result of any preventative measures taken by the board. Additionally, both the FDA and the NABP are looking at changes needed in regards to sterile compounding.

Ms. Herold reported that the board is reevaluating its process and in doing so is inspecting pharmacies more routinely to find potential problems. These inspections have and will most likely triggered more enforcement actions.

Ms. Herold noted that another piece of the reevaluation process would be determining if California requirements could be improved by comparing them to USP 797.

A member of the public commented that price is not the only reason pharmacies order from companies like NECC, often times it is because there is a shortage of the product.

Mr. Ratcliff responded that when inspections are conducted the inspectors ask what a pharmacist would do if they could not get a product. About half of them answered that they would contact the prescriber and change the therapy.

Dr. Steve Gray from Kaiser commented that his understanding that the goal of this subcommittee meeting was to establish priority items in regards to sterile compounding.

Dr. Doug O'Brien commented that it is frustrating when big companies say that they are registered with the FDA, but it really doesn't mean anything.

Ms. Herold responded that pharmacies should verify with that state regulatory agency when they receive offers from companies selling compounded medications to verify if they are licensed to sell drugs in the state.

Dr. Kajjoka commented that the FDA is overburdened, and therefore it would be beneficial to send out the board's inspectors to non-resident pharmacies.

Dr. Kajjoka commented that while the board's main focus must always be on consumer protection, it is important not to forget that there are drug shortages that have to be addressed.

Dr. Gray noted that there are a lot of facilities other than hospitals that rely on compounding pharmacies to address shortages and the board should take that into consideration when moving forward.

**II. Discussion Regarding California's Amended Compounding Regulations to Take Effect April 1, 2013 – Amendments to 16 California Code of Regulations, Sections 1735.1, 1735.2 and 1751.2**

Dr. Gutierrez referenced the meeting materials provided including the amended compounding regulations that will take effect April 1, 2013.

Discussion:

Dr. Gray noted that further clarification on the regulations was needed and the board should work to educate pharmacies about the requirements.

**III. Discussion Regarding the Introduction of the Board of Pharmacy's Sponsored Legislation on Sterile Compounding, Senate Bill 294 (Emmerson)**

Dr. Gutierrez referenced the meeting materials which provided a copy of the proposed legislation.

Discussion:

Jonathan Nelson from CSHP commented that the tragedy that occurred with NECC was not necessarily representative of sterile compounding facilities as a whole. He also added that CSHP believes that 41.375 is too vague. Mr. Nelson also commented that while nursing schools can receive dangerous drugs to use for education purposes CSHP has found that schools of pharmacies cannot.

Dr. Gray from Kaiser added that schools of pharmacy have expanded their sterile compounding programs, but they cannot get the actually drugs to do the skill based teaching.

Dr. Gray from Kaiser added that the board needs to be very careful in the timing and implementation of this bill.

Ms. Herold responded that there is a lot of interest in this bill and implementation dates can be adjusted as needed.

Mr. Ratcliff responded to Mr. Nelson's comment about schools of pharmacy receiving dangerous drugs for teaching purposes by referencing the definition of laboratory and stated that schools should be able to receive drugs for teaching purposes.

Dr. Gray commented that wholesalers are often hesitant to sell drugs and supplies to schools because they do not have a board license.

Mr. Dan Willis of Grandpa's Compounding Pharmacy asked if the board was going to be requiring inspections for California compounding pharmacies in the same way that it will be required for out of state facilities. Additionally, he asked if there was a set criterion for determining if a facility was manufacturing.

Ms. Herold responded that the determination is left to the FDA to regulate manufacturing. She added that there have been three attempts in the past to work with the industry and the FDA to determine the threshold for manufacturing.

Mr. Willis of Grandpa's Compounding Pharmacy asked if the board had considered creating a specialty license type for compounding, not just sterile compounding.

Ms. Herold responded that the board believes that the practice of pharmacy includes general, patient specific compounding and this type of compounding should not require a specialty license.

Ms. Herold commented that the FDA is grappling with how to address the issue of shortages. The concern is that if drugs cannot be obtained from a compounding pharmacy than people without the necessary education and sterile environment will begin doing it themselves.

Dr. Gray from Kaiser suggested that the board carefully consider the actions it will take in regards to compounding so that it does not have to retract its laws in the same way that Louisiana and Tennessee recently had to.

Ms. Herold noted that in the case of NECC both the FDA and the Massachusetts Board of Pharmacy had inspected the facility and found issues with sterility, but the way the cases were settled the information was not disclosed across state lines.

A member of the public asked for clarification on when a product would need to be recalled.

Mr. Ratcliff reported that a product needs to be recalled after it is dispensed.

A member of the public noted that this legislation does not address if a recall is required for things such as a typo on the label.

The board recessed for a lunch break at 10:53 a.m. and reconvened at 12:38 p.m.

#### **IV. Discussion Regarding USP's 797 Standards and Regulation Requirements of the Board of Pharmacy**

Dr. Gutierrez referred to the meeting materials which included a side-by-side comparison of USP 797 and California State Law was provided.

Discussion:

Mr. Rick Roads from University Compounding Pharmacy asked for clarification on “what constitutes a batch” and “what type of sterility testing is required”.

Mr. Ratcliff and Dr. Gutierrez answered that these questions would be answered in a presentation later in the meeting.

Dr. Kajioka added that the board was hesitant on being too prescriptive and choose to rely on the expertise of the pharmacist-in-charge (PIC) to create a validation process to determine what percentage of their products need to be tested.

Dr. Gray from Kaiser and CSHP commented that the batch number provided in USP was arbitrary and that defining a batch is a much more complex issue than just providing a number threshold.

A member of the public from University Compounding Pharmacy provided that there are patients that need drugs immediately and waiting for sterility testing results is not an option.

Ms. Herold provided that a patient should be informed if they are receiving a high risk compounded drug.

Dr. Kajioka added that there are many different scenarios that happen when compounding, and there are times that a medication cannot wait to be tested before it is dispensed to a patient. He added that the board is working with the industry to address the challenges they face without compromising public safety.

Ms. Lynn Paulson from the University of California recommended that the board create a definition of a batch. She added that the reason USP choose 25 is because if you have batches smaller than 25 you should be testing 100% of the product.

**V. Discussion Regarding “Batches”**

Discussion:

Mr. Ratcliff noted that a batch is defined differently depending on where you look. He defines a batch as anything beyond making medications for more than one patient.

Dr. Gray from Kaiser commented that you cannot define a batch without defining when it will be used and the purpose of defining a batch is to determine if a product will be tested before it is dispensed.

Dr. Gray asked for clarification on who would be the custodian of the informed consent if a patient was required to give consent prior to receiving compounded drug.

Ms. Herold provided that informed consent is a complicated issue, but the public is trusting in the drug supply chain and should know if they are receiving a compounded product.

Dr. Kajjoka commented that you do not always have the intention to use a compounded drug and often times a patient may not be conscious to give informed consent.

Kath Furgby, RPh, provided that it isn't only compounded drugs that pose a problem, she has seen an increase in the number of recall notices being issued for manufactured product.

Ms. Paulson referenced a sheet from USP 71 that outlines what percent of the product you need to test based on the number of doses being made and the beyond use date.

Dr. Kajjoka clarified that the beyond use date isn't the manufacture expiration date; it is how long you can keep a drug at room temperature.

Dr. Doug O'Brien from Kaiser commented that USP defines the beyond use date as how long you can store a product before you administer it to a patient. He also added that low risk and medium risk products do not require end use testing under USP 797. Additionally, USP 797 defines high risk products in wider terms than California does.

Dr. William Zolner from Eagle Analytical Services clarified that under USP 797 all sterile compounds require testing if they are stored beyond the specified time limit. It doesn't matter if it is high, medium or low risk product. He added that in his opinion batch size is irrelevant, because even if you only make one product and you keep it too long it can become non-sterile.

Mr. Dan Willis of Grandpa's Compounding Pharmacy provided that the only way to know if everything is sterile is if you test everything. The problem is that this can prohibit patients from receiving the product they need in a timely manner. He also added that his pharmacy has patients sign a consent form if they release it before test results come back. Mr. Willis also commented that high risk might be better defined by how it is administered i.e. topical vs. injectable.

Maria Serpa from Sutter Health asked the board to help the industry by making their definitions very clear. She also commented that in the hospital pharmacy setting the term batch is used differently, and recommended that hospital and community pharmacies might consider using a different term than batch.

Dr. William Zolner from Eagle Analytical Services provided a PowerPoint presentation on the process of sterility testing. The presentation has been provided after the meeting minutes.

Doctor Thomas Kupiec from Analytical Research Laboratories provided a presentation via phone. His presentation covered testing and quality control methods. Mr. Kupiec highlighted that you cannot test quality into a product, a test will only tell you if a product is sterile it will not make it sterile. Mr. Kupiec added that a test will only indicate that the products a client sent in for testing are sterile; there is still a statistical probability that other products not tested could be contaminated. Mr. Kupiec commented that if a pharmacy is conducting its own sterility testing they need to be sure that the test really works by testing a product that the pharmacy knows is contaminated to make sure the test detects the contamination.

## **VI. Discussion of the Board of Pharmacy's Questions and Answers Document on Compounding**

Dr. Gutierrez asked for public comment on the Board's Questions and Answers (Q&As) Document.

Mr. Damon Jones from Mcguff Pharmaceuticals Inc. noted that ancillary supplies have not been included in the regulation.

Dr. Gray from Kaiser requested that the board add in ancillary supplies to the master formula to encourage consistency.

Dr. William Zolner from Eagle Analytical Services commented that his company requires a formula worksheet to be sent to in for every potency test they conduct. He also added that in his opinion there needs to be more detailed instructions regarding how you process the ingredients to ensure you get a consistent product no matter who processed it.

Dr. Kajjoka commented that there should be a level of inherent knowledge assumed when creating instructions

Maria Serpa from Sutter Health asked the board not to be too restrictive in their requirements for formula worksheets.

Dr. Gray recommended that the board solicit more public comments on end product evaluation.

Jonathan Nelson from CSHP commented that their organization has gotten a lot of feedback on the Q&A's.

## **VII. General Discussion**

Dr. Gutierrez asked for public comment on this agenda item.

Dr. Gray from Kaiser commented that pharmacists are becoming more involved in experimental therapies, such as cellular therapies. He requests that the board considers this when making compounding decisions.



Mr. Joe Percelli from University Compounding Pharmacy recommended the board create a specialty license for compounding pharmacies. He also recommended that the PIC of out-of-state pharmacies be licenses in California, or be required to sign a self-assessment from.

Dr. William Zolner from Eagle Analytical Services offered to work with the board to develop a webinar training series on sterile compounding for inspectors.

### **VIII. Closing Comments**

No additional committee or public comments were provided.

### **X. Public Comment on Items Not on the Agenda/Agenda Items For Future Meetings**

No additional committee or public comments were provided.

Dr. Guterrez adjourned the meeting at 3:15 p.m.

Sterile Compounding Inspection Report  
Sterile Compounding Committee  
March 19, 2013



CALIFORNIA STATE  
BOARD OF PHARMACY

# Overview

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- ▶ Sterile Compounding Requirements for Resident and Non-Resident Pharmacies
- ▶ Total Number of Licensed Pharmacies by Type
- ▶ Recent Sterile Compounding Inspection Findings from 35 licensed pharmacies
- ▶ Recent Sterile Compounding Inspection Findings from 21 hospital pharmacies
- ▶ Recent FDA Inspection Findings from 4 pharmacies- Issues Identified with California Law



# Requirements for California Sterile Compounding License

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The following may compound injectable sterile drug products in California:

- ▶ A pharmacy that is specially licensed with the board as a sterile compounding pharmacy, or
- ▶ a pharmacy that is operated by an entity that is licensed by the board or the State Department of Health Services and has a current accreditation from the Joint Commission on Accreditation of Healthcare Organizations or another accreditation agency approved by the board. The following private accreditation agencies have been approved by the board:
  - ▶ Accreditation Commission for Health Care, Inc. (ACHC) through February 2014,
  - ▶ Community Health Accreditation Program (CHAP) through February 2014,
  - ▶ Det Norske Veritas (DNV) through July 2013,
  - ▶ Pharmacy Compounding Accreditation Board (PCAB) through February 2014, or
  - ▶ American Osteopathic Association Healthcare Facilities Accreditation Program (HFAP) through February 2014.
- ▶ A license to compound injectable sterile drug products may not be issued until the location is inspected by the board and found to be in compliance with Article 7.5 of Chapter 9, of Division 2 of the Business and Professions Code and regulations adopted by the board.



# Requirements for Non-Resident Sterile Compounding License

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Effective July 1, 2003, a nonresident pharmacy may not compound injectable sterile drug products for shipment into California unless:

1. The nonresident pharmacy is licensed with the board as an injectable sterile drug compounding nonresident pharmacy, **OR:**
2. The nonresident pharmacy is operated by an entity that is licensed as a hospital, home health agency, or a skilled nursing facility, and has a current accreditation from the Joint Commission on Accreditation of Healthcare Organizations, or another accreditation agency approved by the board. The following private accreditation agencies have been approved by the board:
  - ▶ Accreditation Commission for Health Care, Inc. (ACHC) through February 2014,
  - ▶ Community Health Accreditation Program (CHAP) through February 2014,
  - ▶ Det Norske Veritas (DNV) through July 2013,
  - ▶ Pharmacy Compounding Accreditation Board (PCAB) through February 2014, or
  - ▶ American Osteopathic Association Healthcare Facilities Accreditation Program (HFAP) through February 2014.



# State Pharmacy Licenses- March 2013

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Total California licensed pharmacies= 6898

License Type	Total
Community Pharmacy (PHE)	6409
Hospital Pharmacy (HPE)	489
Sterile Compounding (LSC)*	270
Centralized Hospital Packaging	0

\*LSC licensed is in addition to a community or hospital pharmacy license



# Non Resident Pharmacy Licenses- March 2013

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License Type	Total
Non-Resident Pharmacy	478
Non-Resident Sterile Compounding License	92

\*Sterile Compounding license is in addition to a pharmacy license

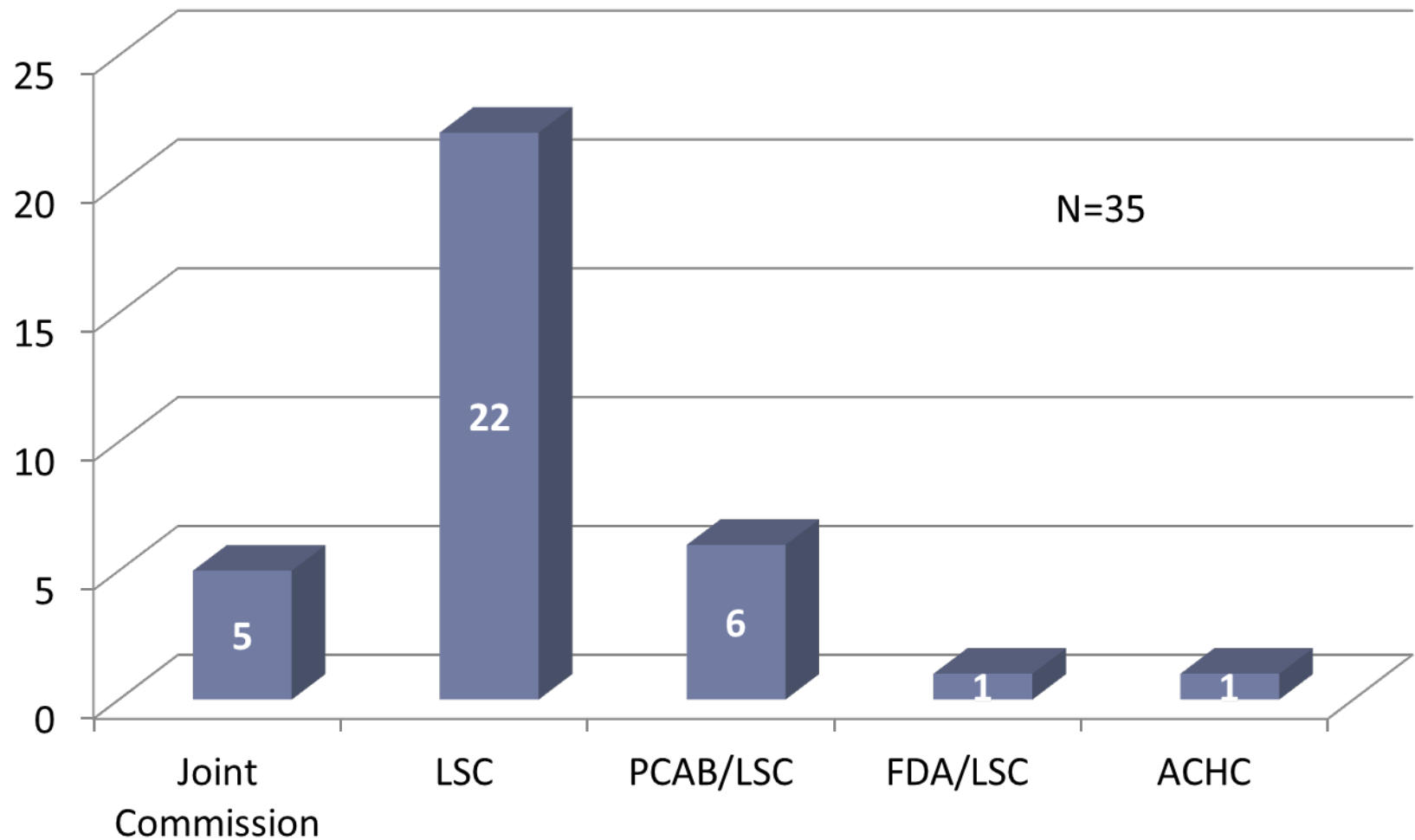


# Recent BOP Sterile Compounding Inspection Results

35 pharmacies – all located within California

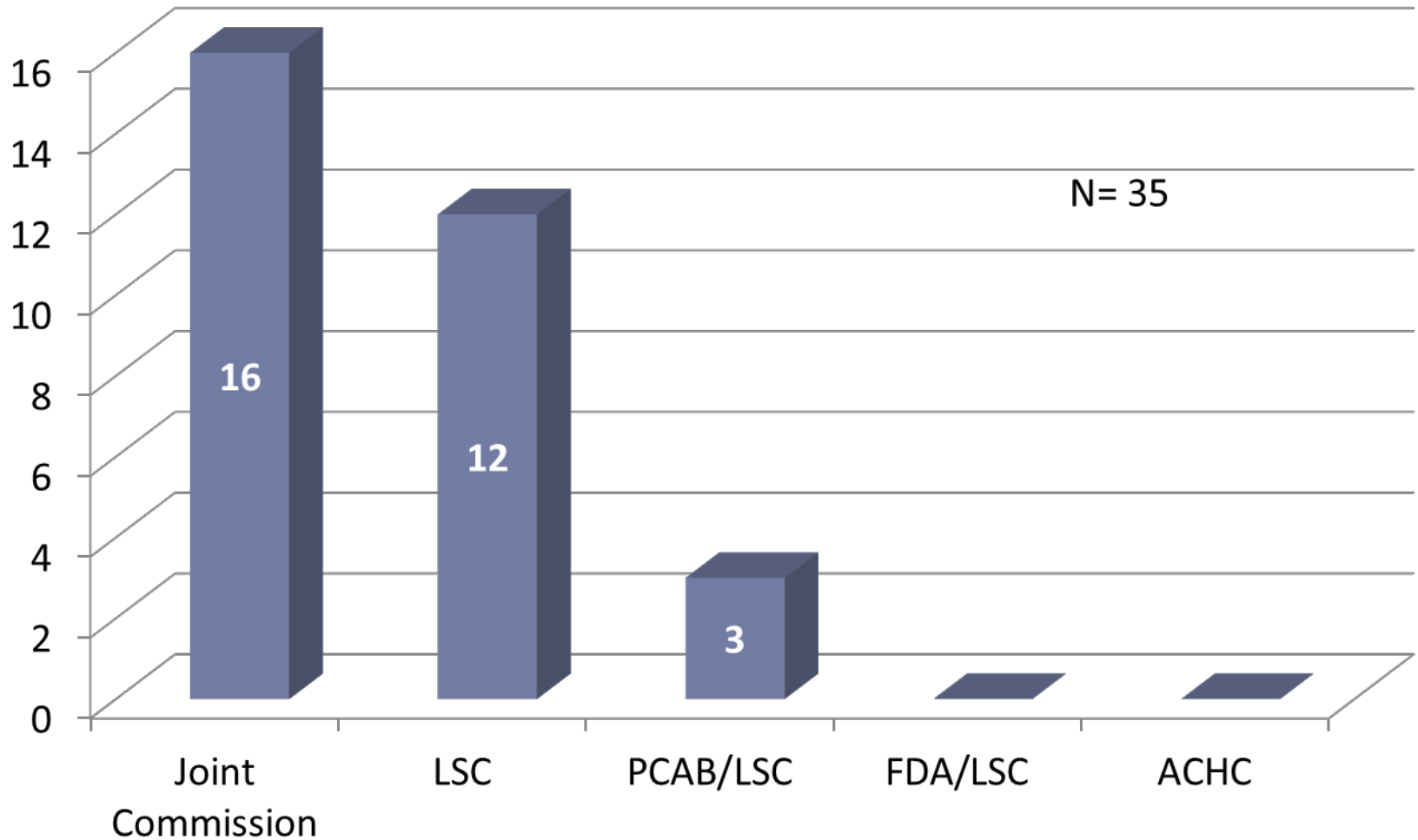


# Recent Inspections- By Accreditation Type



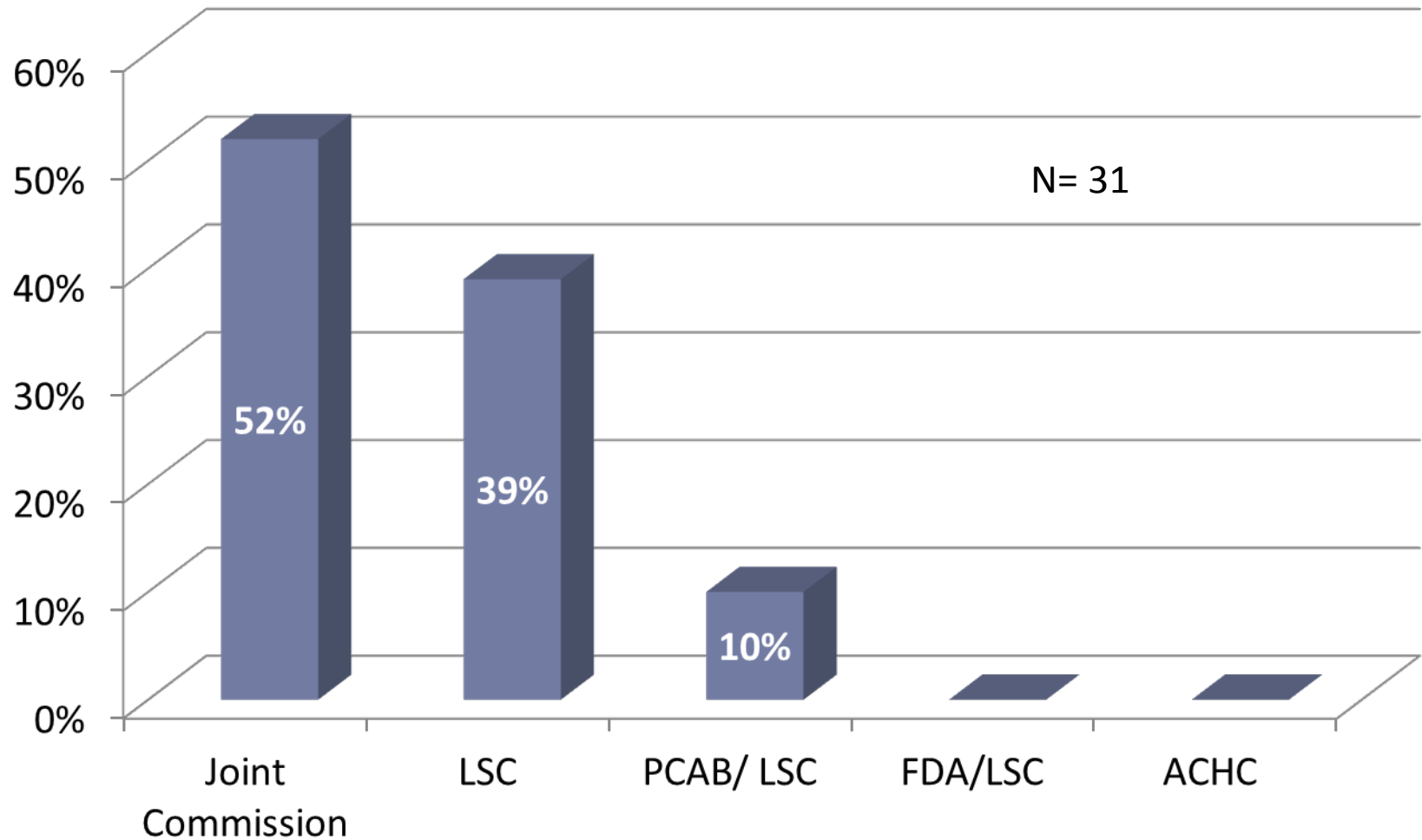
# Corrections Issued for Recent Inspections By Accreditation Type

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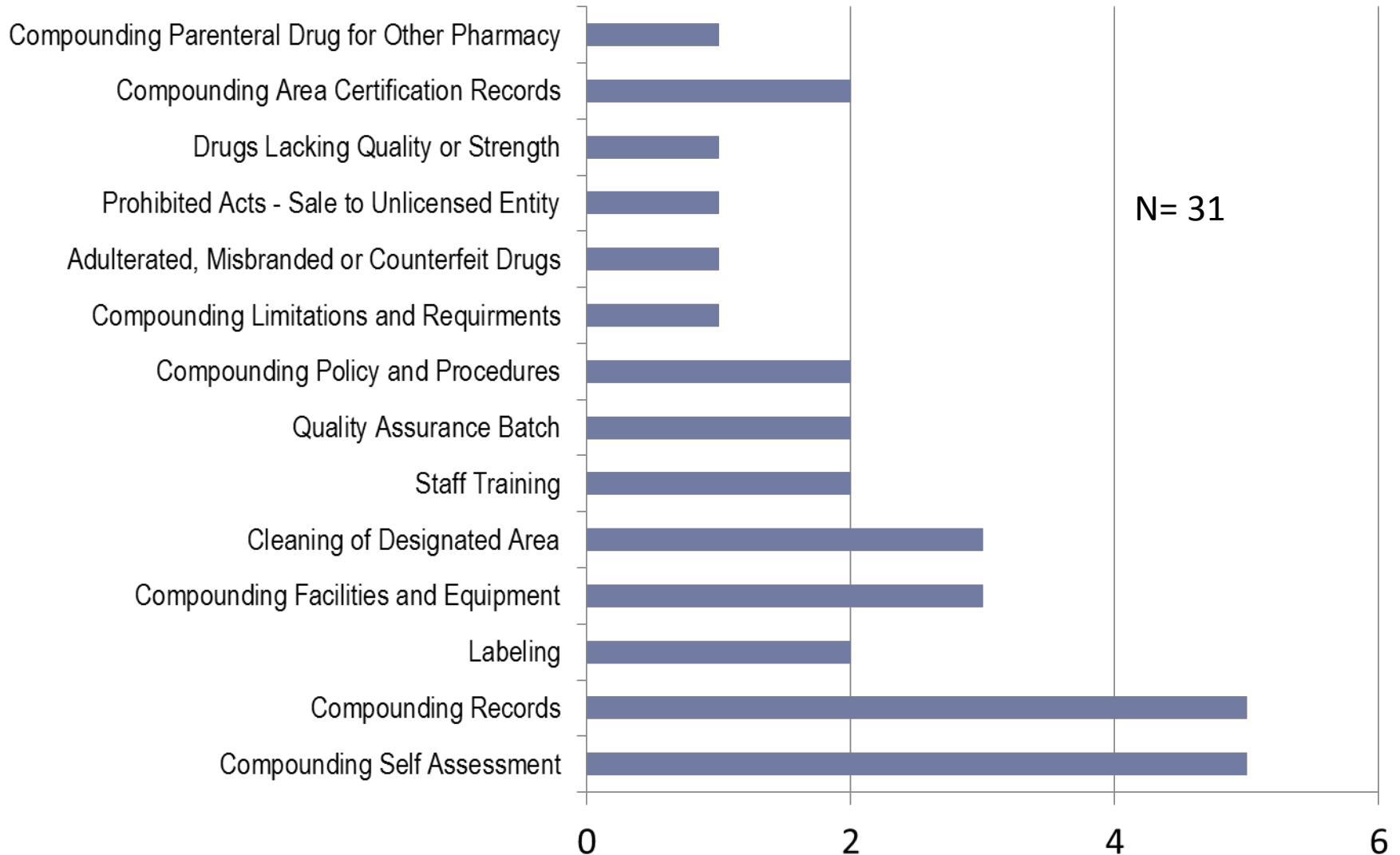


# Total Corrections Issued Percentage By Accreditation Type

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# Consolidated Inspection Report Citation Data



Survey Element N= 35		Total
Number with LSC License		29
Patient Type	Human/Animal	21/2
	Human & Animal	12
Self Reported to be USP 797 Compliant		30 / 5
Accredited		12
High Risk Compounding		21
Ships Compounded Product Out of State		13
Compounds Non Patient Specific Product		16
Hood Certification	3 month	1
	6 month	31
	12 month	3
Viable Air Counts		21
Surface Testing		11
Fingertip Testing		10
Sterility		30
Pyrogen		24

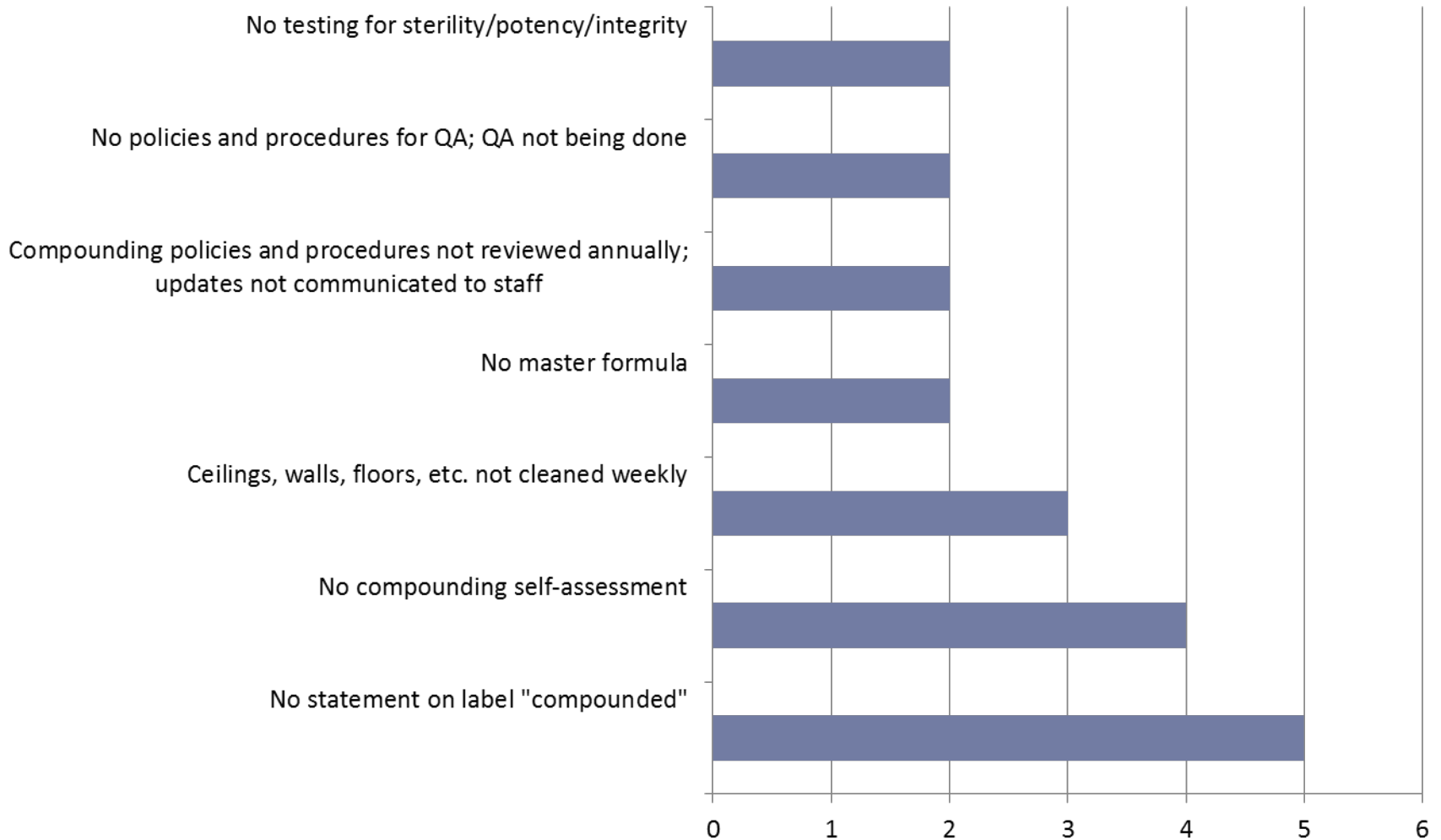
# State BOP Recent Hospital Pharmacy Inspections

21 Hospital Pharmacies

# Hospital Pharmacy Inspection Findings

## Top 7 Findings

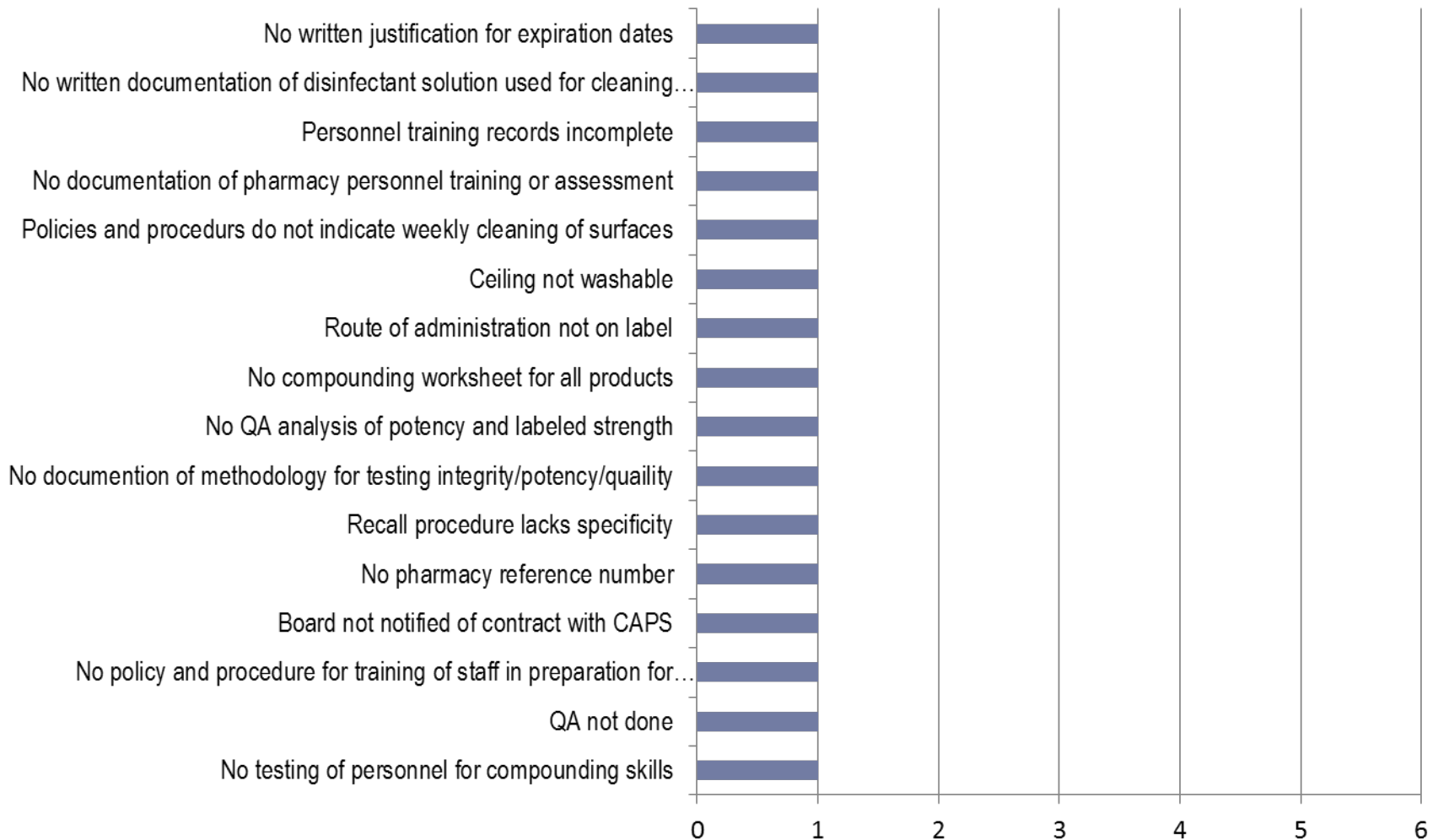
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# Hospital Pharmacy Inspection Findings

## Additional Findings

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Recent FDA Inspection Findings  
Items Identified with California law non-compliance

Four Independent Non-Resident Pharmacies Surveyed from  
Target 30 List

Count of Findings	Description of Findings	Notes
3	Batch produced sterile injectable products compounded from one or more non-sterile ingredients subject to end product testing	All products not tested, or partially tested or product not tested in final container
1	Expiration date may not be longer than the shortest expiration date of ingredient	
1	No sterile product shall be compounded if it is known, or reasonably should be known, that the compounding environment fails to meet criteria.	Viable air samples from hood exceeded action levels but no action taken
1	Expiration dating	90 day dating for all intrathecal medication without adequate stability data tested with stability-indicating methods)
1	Compounding record - documentation of equipment	
1	Compounding record - documentation of manufacturer and lot number	



**CALIFORNIA BOARD OF PHARMACY  
INSPECTOR PRESENTATION**

WILLIAM J ZOLNER, PHD  
EAGLE ANALYTICAL SERVICES / PCCA  
HOUSTON, TEXAS

# CALIFORNIA BOARD OF PHARMACY

## **PRESENTATION GOALS - Explain:**

- **Who We Are - Eagle Analytical Services / Bill Zolner**
- **What we do**
- **General Comments on Sterility of Compounded Preparations**
- **Comments on USP<71> Sterility Tests**
- **USP<71> Sterility Tests Procedure**
- **USP<85> Bacterial Endotoxins Test**
- **Questions**

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William J Zolner, PhD

Chemical Engineering, 1971 Northeastern University, Boston MA

25 yrs in the Analytical Instrument Industry

Air Pollution, Chemical & Petrochemical, Pharmaceutical, Food & Beverage,  
Water, Oil & Gas, and Medical Industries

Engineering, Quality, Manufacturing, Quality, Business Management

Lean Manufacturing, Six-Sigma, QbD, PAT

11 yrs at Eagle Analytical Services – Compounding Pharmacies

Chief Scientific Officer

Written papers on Quality Control in Compounding Pharmacy (IJPC)

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## EAGLE ANALYTICAL SERVICES INC.

- A PCCA Company
- Founded 11 years ago to help compounding pharmacies comply with USP<797> and new State compounding regulations
- Test For:
  - Sterility
    - USP<71> Sterility Tests Protocols
    - ScanRDI Test Protocol
  - Bacterial Endotoxins
    - USP<85> Bacterial Endotoxin Test Turbidimetric Protocol
  - Potency of active ingredients (HP
    - HPLC, UPLC, UV, FTIR, Wet chemistry, +
  - Particulates in Injectables
  - Help pharmacists establish Beyond Use Dates for their Preparations

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## PROCEDURE FOR SAMPLE SUBMISSION:

- Fill out a Sample Submission Form (Paper or OnLine)
- Send sample (usually overnight ) to Eagle
- We check in Sample, Assign a Test Sample ID, Specify Tests Required
  - All information sent scanned into database
  - Sample receipt and status presented on line (after registration)
- Eagle Guidance on Sample Size for Sterility “USP <71> and proper quality control procedures dictate the number of articles and amount of product necessary for a statistically valid sterility test procedure. In general, the more product furnished for analysis the higher the probability of detecting a non-sterile item. The following requirements are indicative of the sample size needed to perform an analysis, not the amount that would satisfy a statistically valid sampling procedure. If possible, a sample size sufficiently large to represent the sample, packaged in the final delivery container, allows for the best chance in obtaining a valid sterility test.”

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## GENERAL COMMENTS ON STERILITY OF COMPOUNDED PREPARATIONS

- A. You cannot Test Sterility into a Compounded Sterile Preparation
- B. You must make the Preparation Sterile using a “Sterile Process”
- C. Current Guidelines on Sterility:
  - A. Determine initial bio-burden
  - B. Design a “Sterility Process” to eliminate this bio-burden +
  - C. Monitor the “Sterility Process” to insure it remains in control
  - D. Use Sterility Testing as a confirmation that process is working
  - E. QbD, PAT, Parametric Release



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## USP<71> STERILITY TESTS (From the Introduction to the Monograph)

”These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures”

### Three Fundamental Problems:

- Sampling plan is insufficient to meet requirements implied by the title of the test
- Test was designed primarily for manufacturing operations
- Test involves recovery and recognition of microbial contamination in the sample, should it exist.. There are well documented VBNC (Viable But Not Culturable) organisms.

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- Other currently available alternate technologies that do not require growth offer the opportunity to dramatically improve the sensitivity and ease of use.  
(Moldenhauer & Sutton, Toward an Improved Sterility Test, PDA Journal, Vol 58:6, 2004)
- FDA has recently issued updated sterility test procedures for biological materials that do not specify USP<71>

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## USP<71> Sterility Tests

### Procedure Summary:

- If possible, filter the sample through a 0.45 micron filter.
- Wash filter with approved fluid to remove potentially interfering substances
- Put half the filter in Soybean Casein digest medium
  - Fungi and aerobic bacteria
  - Incubate 14 days at 20-25 C
- Put half the filter in Fluid Thioglycollate Medium
  - Anaerobic and aerobic bacteria
  - Incubate 14 days at 30-35 C
- If cannot filter (suspensions, some oils, insoluble items)
  - Inject directly in two above media (not more than 10% of the media volume)
  - Incubate for 14 days

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- If cannot determine if turbidity is from sample or growth
  - Remove 1mL + from each media and inject in 100mL of same media
  - Incubate for 4 additional days at specified temperatures
- At conclusion of incubation, inspect both media for turbidity, or growth of microorganisms. Positive growth in either media indicates the sample is non sterile and fails the test.
- Retesting requirements:
  - Laboratory error, facility or procedure
  - Growth shown in negative controls
  - After identifying the microorganism, it is shown that “growth of this species may be ascribed unequivocally to faults with respect to the material and or the technique used in conducting the sterility test procedure”

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Question: How much of my preparation do I need to send for Sterility Testing:

USP<71> Tables

Injectables

< 100 containers	10% or 4 (whichever is more)
100-500 containers	10 containers
> 500 containers	2% or 20 (whichever is less)

Non-injectables

< 200 containers	5% or 2 (whichever is more)
> 200 containers	10 containers

(See USP<71> tables for more detail)

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## USP<85> Bacterial Endotoxin Test

- Bacterial Endotoxins - The lipopolysaccharide complex associated with the outer membrane of Gram-negative pathogens
- i.e. Come from dead gram negative bacterial (E coli)

In compounded preparations they come from four (4) areas:

- Water used in compounding
- From equipment that has not been properly depyrogenated
- When non sterile preparations are sterilized without the removal of the pathogens. (i.e. steam sterilization, gamma ray)
- From the chemicals used in the compounding process

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## The Bacterial Endotoxin Test

Eagle uses a Turbidimetric Technique – Gel clot test

Gel Clot – a lysate from the blood of the horseshoe crab is added to the sample

If the mixture forms a clot, then endotoxins are present

Turbidimetric test - add lysate to the sample and monitor the rate that the sample clots – Performed in an incubating spectrophotometer

- Most sensitive test available - 0.001 EU/mL

- Performed in duplicate

- Duplicate Enhancement / inhibition tests done on each sample

Add known amount of endotoxin to your sample

Valid tests if the endotoxin is recovered

If endotoxin cannot be recovered, sample is diluted and test is re-run

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BET Procedure





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