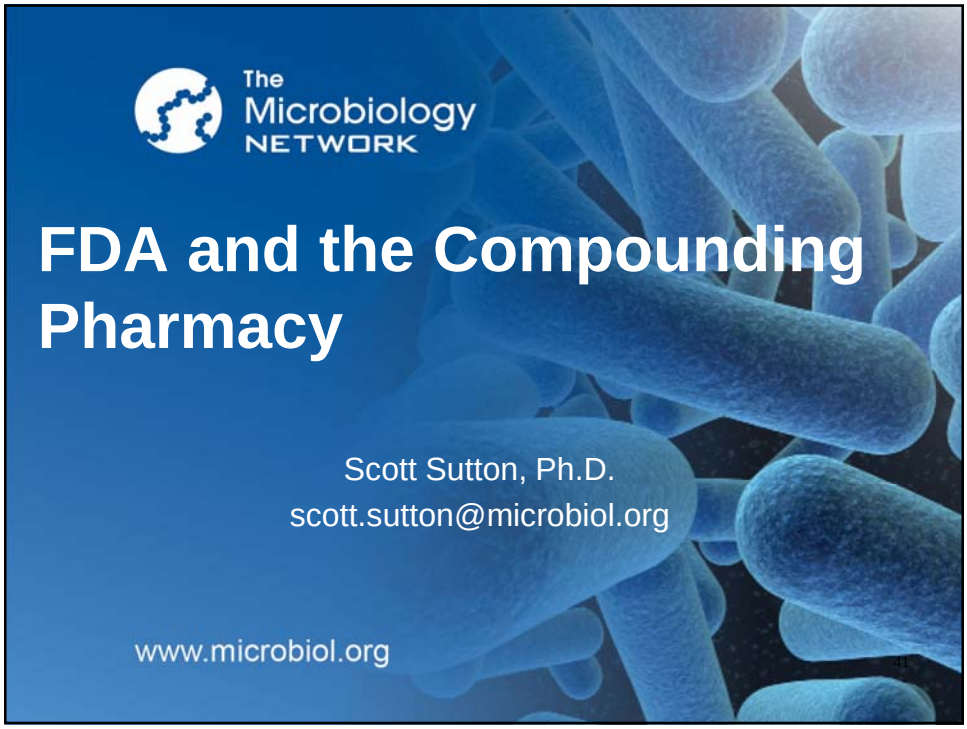

Overview of Presentation

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- H.R. 3204 – Outsourcing Facility
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BioNeutral Group

- Disinfection and sterilization is a timely topic for Compounding Pharmacies
- BioNeutral launched our YGIENE 206 Sporicidal/Disinfectant earlier this year
- Good success:
  - Research facilities
  - GMP pharmaceutical manufacturing
  - Compounding pharmacies

BIONEUTRAL™ Advanced Infection Control

YGIENE 206 Sporicidal/Disinfectant

- Oxidative chemistry (H_2O_2+PAA)
  - "Kills most" in 90 – 120 seconds
  - "Kills all" – fastest EPA registered sterilant(20 min.)
- Excellent materials compatibility
  - Gentle on stainless steel and other surfaces
  - Relatively pH neutral (4 -5)
  - Environmentally friendly
- Contact Ray Dunning – 440 799 7701
  Ray.d@bioneutral.com

BIONEUTRAL™ Advanced Infection Control

Disclaimer

- I am making this presentation as an independent agent
- I am not making this presentation as a representative of USP, PDA, PMF or any other organization with which I am currently associated.
- The views expressed in this presentation are offered as mine alone.

Overview of Presentation

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FDA

Table 1. Issues in Compounding Pharmacies Identified by FDA 483 Observations*

	SOPs to Prevent Microbial Contamination Non-existent or Not Followed	Inadequate/ Improper EM	Stability Program	Inadequate Gowning	Batch Release	Validation of Sterilization	Lab Procedures: Testing/ Contract Lab Control
Anazaohealth	1*	4	8	5	3	2	11
Avella of Deer Valley	3	2	.	1	6	4	.
Balanced Solutions Compounding	3	4	9	6	1, 7	5	.
CAPS (Central Admixture Pharmacy Services) (Chicago)	.	2	7	3	1	6	.
CAPS (Homewood, AL)	6	6	9, 12	4	1, 2	.	11
CAPS (Kansas City)	2	3	.	2	4	.	1
CAPS (Livonia)	3, 5	.	.	.	6	.	.
College Pharmacy, Inc	.	1	5	.	2, 6	4	2
Compounding Shop, The	1	2	11	9	4, 10	5	4
Drugs Are Us	.	1	3	2	.	.	.
Foundation C							
Home Int							
IV Solutio							
Lee Pharr							
Lowlyn P							
Medaus							
Medi-Far Center							
NECC							
Nora Apo Therapie							
Oakdell P							
Olympia Phar							
Pentac Health	8	.	6	2	.	1	5
PharMEDium Services (Cleveland)	5	.	10, 11	.	3, 9	3	2, 3, 9
PharMEDium Services (Edison, NJ)	5	.	4	1	3	.	2
PharMEDium Services (Memphis, TN)	3	.	8, 12	.	5, 7	6	4, 5
PharMEDium Services (Sugarland, TX)	3	8	6, 7, 9	2	4, 5	.	4
Portage Pharmacy	1	3	10, 11	4	2, 6, 7, 8	.	9, 12
Specialty Compounding	1	3	5	2	7	4	6
Triangle Compounding	4	3	.	.	.	2	.
University Pharmacy	4	5	6	.	2	3	.
Wedgewood Village Pharmacy	.	.	.	1	3, 10	4	3, 9

Sutton, S. 2013. GMP and Compounding Pharmacies. *Amer Pharm Rev.* 16(3):48-59.

http://www.americanpharmaceuticalreview.com/Featured-Articles/135985-GMP-and-Compounding-Pharmacies/

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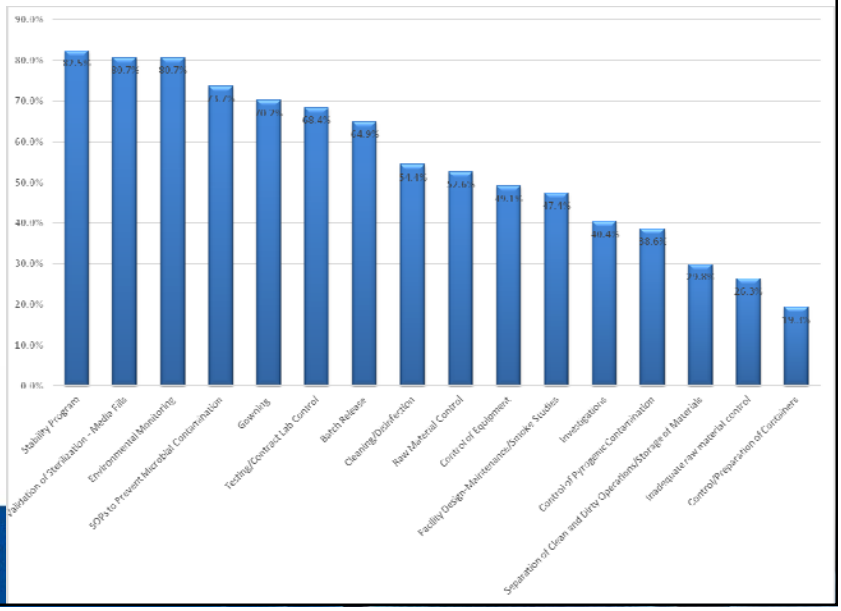
Frequent 483 Citations



The Press

Table 2. Compounding Pharmacies and Microbial Contamination in the News[a]

2012	• 33 people across 7 states contracted fungal endophthalmitis leading to the recall of 6 months' worth of all compounded batches from Franck's Pharmacy. This pharmacy also produces veterinary products (40% of 2000 sales). http://news.vin.com/VINNews.aspx?articleId=22724 • Oto-Ease ear lubricant (a non-sterile product) was recalled due to potentially pathogenic microbial contamination. http://outbreaknews.com/2012/07/14/oto-ease%C2%AE-ear-lubricant-recalled-due-microbial-contamination/ • As of February 4, 2014 687 patients contracted fungal meningitis after receiving methyl-Prednisolone acetate injection prepared by NECC (the current crisis related to compounding pharmacies) http://www.cdc.gov/hai/outbreaks/meningitis-map.html (numbers updated regularly)
2011	• 9 patients died of the 10 total taken ill in Alabama when parenteral nutrition solutions that were administered were contaminated with *Serratia marcescens* during compounding using non-sterile components to prepare amino acids. The compounding pharmacy, Medi IV, was found to have the same strain of *S. marcescens* in the tap water faucet and the compounding equipment. http://www.npr.org/blogs/health/2011/03/30/134984222/nine-dead-in-ala-after-iv-treatment • 16 people in Florida and Tennessee infected when a compounding pharmacy in Hollywood, CA repackaged Avastin for off-label eye injections. Contaminated intra-ocular injections for age-related macular degeneration resulted in blindness for some. http://www.nytimes.com/2011/08/31/health/31drug.html?_r=3&
2007	• Eight cases of *Sphingomonas paucimobilis* bloodstream infections were associated with contaminated intravenous fentanyl. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2660711/
2005	• Up to 25 patients in New Jersey and California contracted *Serratia marcescens* infections due to contaminated magnesium sulfate prepared by Pharmedium, a compounding pharmacy located in Lake Forest, IL. http://www.ncbi.nlm.nih.gov/pubmed/17682984 • 6 cases of postsurgical endophthalmitis were reported due a compounded trypan blue ophthalmic injection contaminated with *Pseudomonas aeruginosa* and *Burkholderia cepacia*. This was recalled by the compounding pharmacy Custom-RX of Richfield, MN. http://cid.oxfordjournals.org/content/48/11/1580.long • 16 patients died in Virginia after exposure to cardioplegia solution from 2 lots contaminated with gram-negative rods. This product was made by Central Admixture Pharmacy Services, Inc. (CAPS), a subsidiary of B. Braun Medical located in Maryland (also see 1998 incident below). http://richmond.legalexaminer.com/defective-and-dangerous-products/cluster-of-heart-surgery-patient-deaths-linked-to-contaminated-cardioplegia-made-by-a-compounding-pharmacy.aspx?googleid=211240 • *Pseudomonas putida* septicemia was reported in a special care nursery due to contaminated flush solutions prepared in a hospital pharmacy. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1248510/ • 36 cases of *Pseudomonas fluorescens* bloodstream infections were associated with a heparin/saline flush. From the MMWR Report: "To produce its heparin/saline flush, IV Flush ordered heparin powder and sent it to a compounding pharmacy, where a concentrated heparin solution was made. This concentrated solution was then returned to IV Flush, where it was added to bags of saline solution, from which the syringes were filled." IV Flush was located in Rowlett, Texas while the affected patients were in four states across the country. A later research paper identified potentially 89 cases. http://www.ncbi.nlm.nih.gov/pubmed/16960559 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm http://cid.oxfordjournals.org/content/47/11/1372.full
2004	• 36 patients developed *Pseudomonas* bloodstream infections after receiving heparin/saline flushes from multiple lots of preloaded syringes by Pinnacle Medical Supply of Rowlett, TX. These infections occurred in Missouri, New York, Texas, and Michigan. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm • 2 patients reported with life-threatening sepsis caused by *Burkholderia cepacia* from contaminated intravenous flush solutions that had been shipped across state lines. http://pediatrics.aappublications.org/content/118/1/e212.long • 16 patients were reported with Hepatitis C virus infections from a contaminated radiopharmaceutical used in myocardial perfusion studies. http://www.ncbi.nlm.nih.gov/pubmed/17062864
2003	• Bacteria contamination with *Burkholderia cepacia* was found in at least 2 batches of a compounded inhalant solution used by 10,000 patients nationwide with chronic lung diseases. Med 4 Home (Kansas City, MO) did only a partial recall of the batches, which totaled more than 1-million doses. http://www.upitnas.com/2003/04/18/news_pf/Business/Uncrns_pharmacy_runs.shtml
2002	• MMWR reported on *Exophiala (Wangiella) dermatitidis* infections from contaminated injectable methyl-Prednisolone prepared by a compounding pharmacy, one patient died. NOTE that this report describes fungal meningitis from a steroid spinal injection. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5140a1.htm • Injectable methylprednisolone and bacitilan was recalled by FDA recommendation because of contamination with *Penicillium* mold, *Methylobacterium*, and/or *Mycobacterium chelonae*. This recall was later expanded to all products of Urgent Care Pharmacy due to poor manufacturing quality. http://scienceblog.com/community/older/archives/M/1/fda0779.htm
2001	• 11 patients contracted *Serratia marcescens* infections following the injection of betamethasone compounded at a community pharmacy in California. http://www.ncbi.nlm.nih.gov/pubmed/16941362 • 4 children contracted *Enterobacter cloacae* infections from IV ranitidine compounded in a hospital pharmacy. http://www.ncbi.nlm.nih.gov/pubmed/12802028 • 13 patients (3 Fatalities) came down with bacterial meningitis after receiving contaminated betamethasone shots prepared by Docs Pharmacy in California. http://www.ashp.org/import/News/PharmacyNews/NewsArticle.aspx?id=1125 http://www.sfgate.com/health/article/Steroid-meningitis-echoes-local-incident-3975723.php • MedAlert Pulmonary Services of California was forced to recall five lots of Albuterol (an inhalant) due to contamination by *Serratia liquefaciens*. http://www.thefreelibrary.com/Latter+triggers+recall+for+compounding+pharmacy.-a0184031332 http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2002/ucm1451444.htm
1999	• Survey of compounded Alprostadil formulations from a variety of sources showed contamination in 18% of samples tested. http://www.ijpc.com/abstracts/abstract.cfm?ABS=484
1998	• 11 children became septic in California and 10 tested positive for *Enterobacter cloacae* bloodstream infections associated with contaminated prefilled saline syringes from CAPS, Braun-McGaw of Detroit, MI. (see also 2005 incident above). http://www.cdc.gov/mmwr/preview/mmwrhtml/00055644.htm
1990	• Four patients died of an *Enterobacter* infection from a filter-sterilized cardioplegia solution (a parenteral with high potential for bacteremia) compounded in a Nebraska hospital. In this episode five bottles of the solution tested were nonsterile, several subsequent bottles tested were sterile, and another 93 bottles were dispensed without being tested. http://drugtopics.modernmedicine.com/drugtopics/Health+System+News/USP-drug-safety-review-Requirements-for-compoundin/ArticleStandard/Article/detail/359826 • 2 patients lost their vision after becoming infected by *Pseudomonas aeruginosa* found in Indomethacin eye drops compounded in a Pennsylvania drug store. http://drugtopics.modernmedicine.com/drugtopics/Health+System+News/USP-drug-safety-review-Requirements-for-compoundin/ArticleStandard/Article/detail/359826

[a]All links confirmed 2/12/13.

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Stability Program

- A lack of data supporting the potency, sterility (or occasionally any data whatsoever) of the preparation that might be stored for over a year.
- Clearly this is a GCP concern (well beyond BUD as described in <797>) as well as a GMP concern for compounding manufacturers

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Validation of Sterilization - Media Fills

- Terminally sterilized preparations were not subjected to a validated sterilization cycle in an autoclave
- Or an aseptic fill operations not validated by a relevant media fill (simulated aseptic fill).

<797> discusses this consideration in the section "Verification of Compounding Accuracy and Sterility – Sterilization Methods – Sterilization of High-Rick Level CSPs by Steam" where it is stated "The description of steam sterilization conditions and duration for specific CSPs is included in written documentation in the compounding facility. The effectiveness of steam sterilization is verified using appropriate biological indicators (see Biological Indicators <1035>) or other confirmation methods (see Sterilization and Sterility Assurance of Compendial Articles <1211> or Sterility Tests <71>)

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Inadequate/Improper Environmental Monitoring

- Wide range of issues with environmental monitoring (EM) from insufficient frequency, failure to qualify sampling sites, failure to trend data, failure to respond to excursions, etc).
- This area is one of divergence between GCP (<795>, <797> and <1163>) and GMP as the expectations of GMP are designed to address manufacturing facilities, not the compounding pharmacy.

SOPs to Prevent Microbial Contamination Non-existent or Not Followed

- Wide range of specific issues such as
  - failure to have a qualified sanitization (or in some cases any sanitization) program
  - failure to have cleaning/sanitization procedure
  - having procedures but ignoring them in practice, *etc*.

This is clearly both a GCP and GMP issue as there are multiple references in both <795> and <797> to activities designed to control, monitor and minimize microbial contamination.

Inadequate Gowning

- Lack of critical pieces of gowns (hairnet, beard covers, foot covers, etc)
- Having gaps in gowns
- Poor gowning technique
- Poor aseptic technique with gowns.

This GCP concern is covered in USP<797> section “Additional Personnel Requirements – Personnel Cleansing and Garbing”

Lab Procedures: Testing/ Contract Lab Control

- Poor or non-compliant performance of required testing
  - Potency Testing
  - Sterility Testing
    - Method Suitability
    - Inadequate sample volume
    - Inadequate incubation duration
    - Incorrect incubation temperatures
    - Incorrect growth media
- Poor oversight of testing labs

Batch Release

Release of sterile product under improper conditions without either potency testing, sterility testing, or perhaps any testing whatsoever to confirm the preparation's strength, purity, quality or safety.

Inadequate Cleaning/Disinfection

- Manufacturing equipment or the facility cleanliness and the failure of the pharmacy to ensure that there was no carry-over of preparations from one batch to the next
- Failure to confirm that the disinfection of the aseptic area and PEC were actually working.

The GCP requirements for this issue are discussed in USP <797> in the sections "Cleaning and Disinfecting the Compounding Area"

Control of Equipment

Failure of the pharmacy to ensure that the equipment used for compounding was fit for its intended use.

This GCP topic is discussed in the section “Elements of Quality Control – Equipment” where it is stated “…equipment, apparatus, and devices used to compound a CSP be consistently capable of operating properly and within acceptable tolerance limits. Written procedures outlining required equipment calibration, annual maintenance, monitoring for proper function, and controlled procedures for use of the equipment and specified time frames for these activities are established and followed.”

Inadequate Facility / Smoke Studies

These observations dealt with adequacy of design and qualification studies to ensure the facility is meeting expectations for air balance and air flow in aseptic areas.

USP <797> does expect air pressure differentials of 0.02 to 0.05-inch water column between rooms providing physical separation in the aseptic core and that “In situ air pattern analysis via smoke studies should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions” (see section “Facility Design and Environmental Controls).

Investigations

Inadequate response to problems or errors

- In process (for example environmental monitoring excursions)
- Finished product (failure of potency or sterility testing)
- Field complaints

USP <797> states “When action levels are exceeded, an investigation into the source of the contamination shall be conducted.” (see section Environmental Monitoring - Action Limits, Documentation, and Data Evaluation) and “Positive sterility test results should prompt a rapid and systematic investigation of aseptic technique, environmental control, and other sterility assurance controls to identify sources of contamination and correct problems in the methods or processes” (see section Finished Preparation Release Checks and Tests – Sterility Tests).

Control of Pyrogenic Contamination

USP <797> addresses this specific topic in “Verification of Compounding Accuracy and Sterility – Depyrogenation by Dry Heat where it is stated “The description of the dry heat depyrogenation cycle and duration for specific load items shall be included in written documentation in the compounding facility. The effectiveness of the dry heat depyrogenation cycle shall be verified using endotoxin challenge vials (ECVs). The bacterial endotoxin test should be performed on the ECVs to verify the cycle is capable of achieving a 3 log reduction in endotoxin.

Bacterial Endotoxin Levels are addressed as a finished product specification in the <797> section “Finished Preparation Release Checks and Tests – Bacterial Endotoxin (Pyrogen) Testing”

483 Topic Issue	Frequency
Stability Program	82.5%
Validation of Sterilization - Media Fills	80.7%
Inadequate/ Improper Environmental Monitoring	80.7%
SOPs to Prevent Microbial Contamination Non-existent or Not Followed	73.7%
Inadequate Gowning	70.2%
Lab Procedures: Testing/ Contract Lab Control	68.4%
Batch Release	64.9%
Inadequate Cleaning/ Disinfection	54.4%
Control of Equipment	52.6%
Inadequate Facility / Smoke Studies	49.1%
Investigations	47.4%
Control of Pyrogenic Contamination	40.4%
QAU Not Effective/ Production SOPs not followed/effective	38.6%
Separation of Clean and Dirty Operations/Storage of Materials	29.8%
Inadequate raw material control	26.3%
Container Preparation	19.3%
SOP/Control of Production	14.0%
Safeguard Against Penicillin/ Cephalosporine Cross Contamination	12.3%
Records not Available	14.0%
Labelling Issues	7.0%
Personnel not Trained/ Inadequate	8.8%
Obvious Product Contamination (Micro/Particulate)	5.3%
Change Control	3.5%

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H.R. 3204

Establishes “Outsourcing Facilities”

- Pay an annual registration fee of $15,000
- Not be allowed to compound drugs that
  - Have had their approval withdrawn
  - Are on a safety list that FDA would be charged with creating and maintaining
  - Or are likely to lead to adverse events.
- The drugs would have to be clearly labelled as a compounded drug.
- Be required to report twice a year on the drugs compounded during the last 6 months. Adverse events would need to be reported to FDA within 15 days.

H.R. 3204 (cont)

Establishes “Outsourcing Facilities”

- Be required to submit to FDA inspections on a schedule that would be determined by FDA considering
  - Facility’s recall history
  - Facility’s compliance history
  - The risk of the drugs compounded by the facility.
- Be subject to significant penalties for failing to pay registration or reinspection fees.

H.R. 3204 (cont)

Pharmacies that do not register as outsourcing facilities may be prohibited from compounding drug products without a valid prescription.

Overview of Presentation

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Know the Requirements

- USP <797> is under revision
- Outsourcing Facilities may face a combination of GCP and GMP
  - Review 21 CFR 211
  - Know USP <795>, <797> and <1163>
  - Have your facility in a state of control
  - Have your processes in a state of control
  - Have your testing and stability in line with expectations

Facility Control

- Physical Barriers/Design
- HVAC
- Water
- Cleaning
- Sanitization
- Monitoring

Process Control

- Incoming materials
  - Actives
  - Excipients
  - Water
  - Containers
- Equipment
- Process steps
- Hold times
- Filling conditions

Testing

- Performed in-house
- Contracted
  - You are responsible for the quality of the work you contract – it is your preparation (product)
- Sterility Testing a particular concern

Sterility Testing

- Two separate tests
  - Membrane Filtration
  - Direct Transfer
- 20 Units, 2 media & temperatures
- Requires Growth
  - Incubation period - 14 days

Moldenhauer, J and S. Sutton. 2004. Towards an Improved Sterility Test. *PDA J of Science and Technology* 58(6):284-286.

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Membrane Filtration

- Filter required amount of product through two filters
- Neutralize/Rinse
  - 3 100 mL volumes suggested
  - Formulations for dilution fluids suggested
- One filter into Soybean Casein Digest Broth (SCDB or TSB) – incubate at 20-25^{o}C for 14 days
- One filter into Fluid Thioglycollate Medium (FTM) – incubate at 30-35^{o}C for 14 days

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Direct Inoculation

- Place required amount of product into sufficient recovery medium (with neutralizers?)
  - Soybean Casein Digest Broth (SCDB or TSB) – incubate at 20-25°C for 14 days
  - Fluid Thioglycollate Medium (FTM) – incubate at 30-35°C for 14 days

Method Suitability Test

Can we neutralize any antimicrobial properties of the medication?

Use specified challenge organisms

Use specified total amounts of products

Review of Presentation

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Thank you for your attention

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