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One Standard at a Time: The Journey to NAPRA Compliance

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Presenter Disclosures

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- I have received a speaker's fee for this learning activity

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Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization

Poll Question

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Are you aware of the National Association of Pharmacy Regulatory Authorities (NAPRA) standards for pharmacy sterile compounding that will be adopted into bylaws by the College of Pharmacists of British Columbia?

Learning Objectives

By the end of this session the learner will be able to:

- Explain why the NAPRA Model Standards for Pharmacy Compounding of Non-Hazardous and Hazardous Sterile Preparations have emerged as a priority
- Describe the role of sterility in the development of the NAPRA guidelines
- Describe “controlled areas”, and identify a few key elements of a clean room
- Describe the basic cleaning and disinfection requirements in clean rooms
- Explain what a gloved fingertip sampling is
- Explain what a media fill test is

Outline

- Rationale for the emergence of these standards
- Designated areas for sterile compounding
- Cleaning and Disinfection
- Environmental Sampling
- Hand Hygiene & Garbing
- Gloved Fingertip Sampling
- Media Fill Test

Context

- College of Pharmacists of British Columbia will adopt new standards for sterile compounding into bylaw in July 2022 (extended from May 2021 due to current pandemic)
- 2015 NAPRA model standards for nonhazardous compounding [1] and 2016 hazardous standards [2] were published

WHY?

Why have these NAPRA standards emerged? (1)

- In 2012, the United States had a nationwide meningitis outbreak.[3]
    - More than 200 patients contracted fungal meningitis after receiving methylprednisolone injection contaminated with a brown-black mold (Aspergillus species). [3]

WHY?

Why have these NAPRA standards emerged? (2)

- FDA reported more than 200 adverse events involving 71 compounded products between 1990 and 2012 [3].

- Examples [3]:
  - 14 deaths from contaminated cardioplegia solution
  - 2 patients lost vision due to contaminated eye drops
  - 36 patients developed Pseudomonas bloodstream infection from a heparin/saline flush from prefilled syringe
  - 9 patients died from contaminated parenteral nutrition solution made with non-sterile components

WHY?

Why have these NAPRA standards emerged? (3)

- These cases of contamination shed light on the gap in legislation and identify the need for oversight; compounding pharmacies are to be regulated to standards similar to those used for drug manufacturers to protect the public.

- Key: New model standards focus on *sterility*, which is a shift from only using stability for determining beyond-use dates.

Designated Area for Sterile Compounding

Designated Areas for Sterile Compounding (1)

- Designated spaces for pharmacy sterile compounding are collectively referred to as “controlled areas”[1,2]

- There are 2 types:
  1) Clean Room
     - Connected to anteroom

  2) Segregated Compounding Area (SCA)

Designated Areas for Sterile Compounding (1)

Some details [1,2]

1) Clean Room requirements (key elements):

- A specified level of air cleanliness based on International Organization for Standardization (ISO) standards using high-efficiency particulate air (HEPA) filters
- Specified number of air changes per hour (ACPH)
- Air differential in relation to adjacent rooms
- Preceded by an anteroom

2) Segregated Compounding Area (SCA)

- A space which does not meet the requirements for a clean room as outlined in the standards

Designated Areas for Sterile Compounding (3)

- Hoods, referred to as Primary Engineering Controls (PEC), are located in these spaces.

- Examples:
  - Nonhazardous:
    - Laminar Air Flow Workbenches (LAFW)
  - Hazardous:
    - Biological Safety Cabinets (BSC)

The interior work surface of a horizontal LAFW.

Photo credit: LMPS Quality Team, 2020.

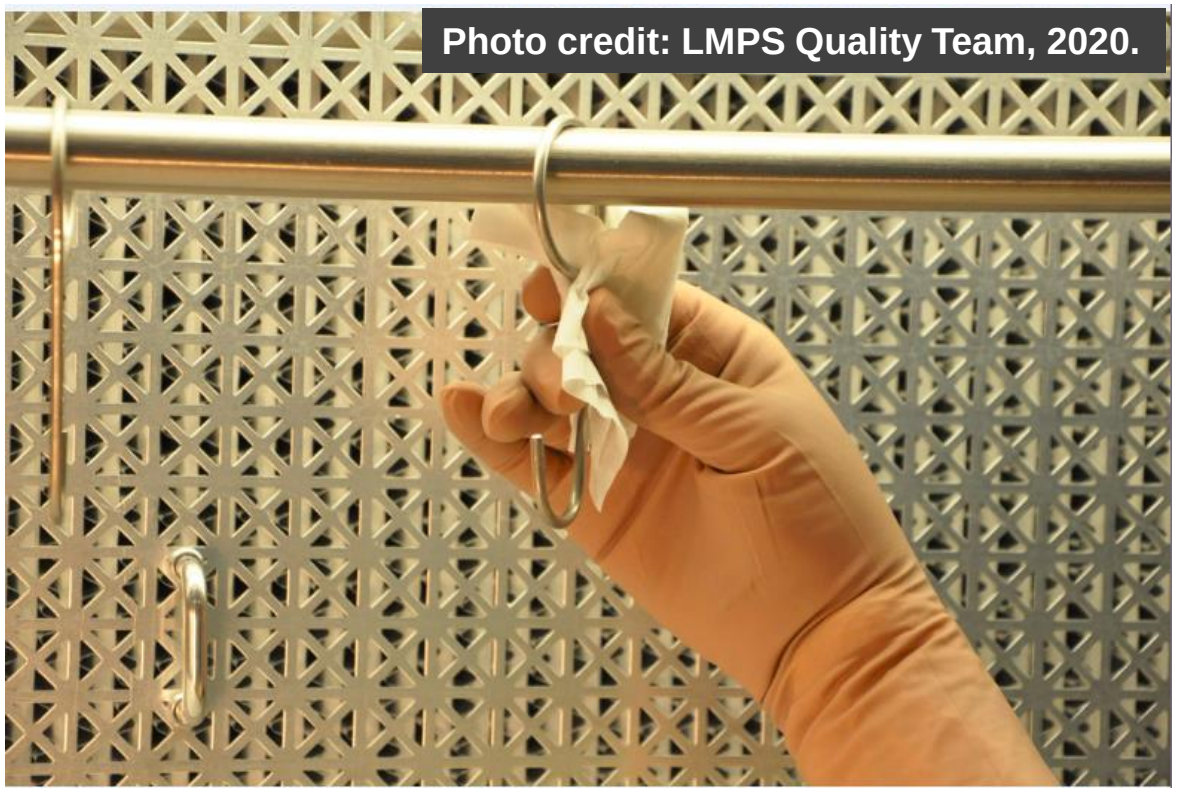
Designated Areas for Sterile Compounding (2)

- ISO Classification for air cleanliness
- Hoods: ISO 5
- Clean room: ISO 7
- Anteroom: ISO 7 (hazardous) or ISO 8 (non-hazardous)

Table 1

Classes of air cleanliness for airborne particulates in clean rooms and clean areas, according to ISO 14644-1	
ISO Class	***Maximum concentration of non-viable particles ≥ 0.5 µm diameter, measured under dynamic operating conditions (particles per m^3 of air)***
3	35.2
4	352
5	3 520
6	35 200
7	352 000
8	3 520 000
ISO = International Organization for Standardization; µm = micrometre; m^3 = cubic metre.	

Image credit: Reference 1,2.



CLEANING & DISINFECTION

Cleaning & Disinfection Requirements (1)

NAPRA standards outline what gets cleaned, how often and with what.

- Regular cleaning of surfaces within controlled areas is mandatory.

- Required:
  - Daily cleaning
  - Weekly cleaning
  - Monthly cleaning

- Cleaning & disinfection:
  - Germicidal detergent
  - Sporicidal
  - Sterile isopropyl alcohol (sterile IPA)

Cleaning & Disinfection Requirements (2)

Cleaning & disinfecting agents [1,2]:

- *Germicidal detergent*
  A washing agent that helps to remove dirt and oil, but also contains compounds which kill microorganisms.

- *Sporicidal*
  An agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Cleaning & Disinfection Requirements (3)

Frequency	Surface
Daily clean, with germicidal detergent	• High touch surfaces: door handles/knobs, telephone/intercoms, light switches, gown hooks • Work surfaces: counter tops, set-up trays, cart surfaces, pass-throughs, sinks (interior and exterior if exposed) • Floor
Weekly as specified	• LAFW, interior: Sterile water, then sporicidal and then sterile 70% IPA • BSC, interior: Decontamination agent of choice, sterile water, sterile 70% IPA
Monthly, with sporicidal	• Hoods, exterior • Carts, all surfaces • Chairs, all surfaces • Refrigerators, interior and exterior • Storage bins, all surfaces • Storage shelves, all surfaces • High touch surfaces: door handles/knobs, telephone/intercoms, light switches, gown hooks

ENVIRONMENTAL SAMPLING

Environmental Sampling Overview (1)

- New standards environment of the controlled areas (clean room and anteroom) to be sampled and inside the hoods (PEC).

Required [1,2]:

- Air sampling (non-viable)
- Non-viable air sampling means counting the number of particulates in the volume of air sampled to determine ISO Class (in contrast to viable sampling, which is to detect presence of microbes)
    - ISO classification = air cleanliness level
    - Hoods (PEC) must be: ISO 5
    - Clean room must be: ISO 7
    - Anteroom (nonhazardous): ISO 7/8
    - Anteroom (hazardous): ISO 7

Environmental Sampling Overview (2)

- NAPRA standards also require use of microbial growth media to conduct air and surface sampling

- The growth media is incubated, and growth is quantified by colony-forming units (CFUs).

- NAPRA has defined contamination levels where action is required in the form of:
  - in-depth investigation,
  - immediate corrective action, and/or
  - preventative action to avoid return to non-compliance.

Environmental Sampling Overview (3)

Requires use of growth media:

- Air sampling (viable), volumetric [1]
  - Samples air by volume into growth media to incubate
    - Areas requiring ISO Class 5 air quality, threshold contamination > 1 CFU/m^3 of air
    - Areas requiring ISO Class 7 air quality, threshold contamination > 10 CFU/m^3 of air
    - Areas requiring ISO Class 8 air quality, threshold contamination > 100 CFU/m^3 of air

- Surface sampling, direct contact [1]
  - Example: Inside work surface of the hood (PEC), on countertop where sterile gloves are opened
    - Areas requiring ISO Class 5 air quality, threshold contamination > 3 CFU/plate
    - Areas requiring ISO Class 7 air quality, threshold contamination > 5 CFU/plate
    - Areas requiring ISO Class 8 air quality, threshold contamination > 100 CFU/plate

Environmental Sampling Overview (4)

Unique to sites for hazardous compounding [2]:

- Hazardous drug contamination sampling
- Example locations, most likely to be contaminated: outside of BSC, floor surrounding BSC, etc.
- Every 6 months, or more

Aseptic Compounding: Personnel Core Competencies

Aseptic Compounding Process

Includes all activities related to completion of compounded sterile preparation (CSP) such as:

- Performing Hand Hygiene
- Garbing
- Cleaning and disinfecting the hood
- Disinfecting supplies and equipment into clean room
- Using aseptic technique to compound sterile preparations in hood
- Verifying, labelling, packaging final preparation

Compounding Personnel

- Possible compounding personnel:
  - Pharmacy technician
  - Pharmacist
  - Pharmacy assistant

- Prepares or supervises the compounding of sterile preparations

Requirements for New Personnel

Any new compounding personnel may begin work in compounding of sterile preparations once they have successfully completed [1]:

- Initial workplace training
- Assessment program

New Personnel
Competency Assessment

- Theoretical Test
  - Knowledge of policies & procedures
  - Aseptic compounding process

- Practical Assessments
  - Gloved Fingertip Sampling
  - Media Fill Test
  - Hand Hygiene & Garbing
  - Cleaning & Disinfection

Current Personnel: Competency Assessment Frequency [2]

For low- & medium- risk level compounders:

- Once a year

For high-risk level compounders [use of non-sterile starting ingredient(s)]:

- Twice a year

Contamination risk levels[82, 83]		
Low	**Medium**	**High**
• Final product compounded using up to 3 "sterile units" • No more than 2 septum punctures at the injection site for each sterile unit • Simple aseptic transfer technique • Drug prepared for one patient (patient-specific dose)	• Final product compounded using 4 or more "sterile units" • Complex manipulations • Prolonged preparation time • Batch preparations (preparing more than one unit of the same composition during one compounding session)	• Non-sterile ingredients or equipment used before terminal sterilization • Non-sterile preparations, containing water, stored for more than 6 hours before terminal sterilization • Improper garbing or gloving by compounding personnel

Image credit: Reference 1,2.

Hand Hygiene & Garbing

- Don garb and perform hand hygiene in an order that proceeds from the dirtiest to cleanest body parts, top to bottom (head and face, feet)

Personnel Assessments using Nutrient Growth Media (for Microbes):

Gloved Fingertip Sampling

Gloved Fingertip Sampling (1)

Purpose:

- Assess aseptic technique with focus on gloved hands.

Process:

- Requires use of agar plates and incubation.
- Agar evaluated for absence or presence of growth.

Gloved Fingertip Sampling(2)

- Two different types of GFS
- Each type has different CFU thresholds
- Microbial growth is indicated by the number of colony-forming units (CFUs)

Gloved Fingertip Sampling (3)
Two types Key Differences

Gloved Fingertip Sampling Types and Compliance Thresholds			
GFS Type	**# of sets**	**When**	**Compliance Threshold (Standard Met)**
Initial GFS	3 sets	After Hand Hygiene & Garbing	Zero CFUs from all plates.
Ongoing GFS	1 set	Immediately after Media Fill Test	*Not more than 3* CFUs from all plates.

Gloved Fingertip Sampling (3)
Growth examples

Presence of growth on a contact plate with 1 CFU.

Presence of growth on an agar paddle side with 2 CFUs

Photo credit: LMPS Quality Team, 2020.

Exercise 1: Count CFUs: presence of Growth

- Review this agar plate for growth.
- How many colony forming units (CFUs) are present?

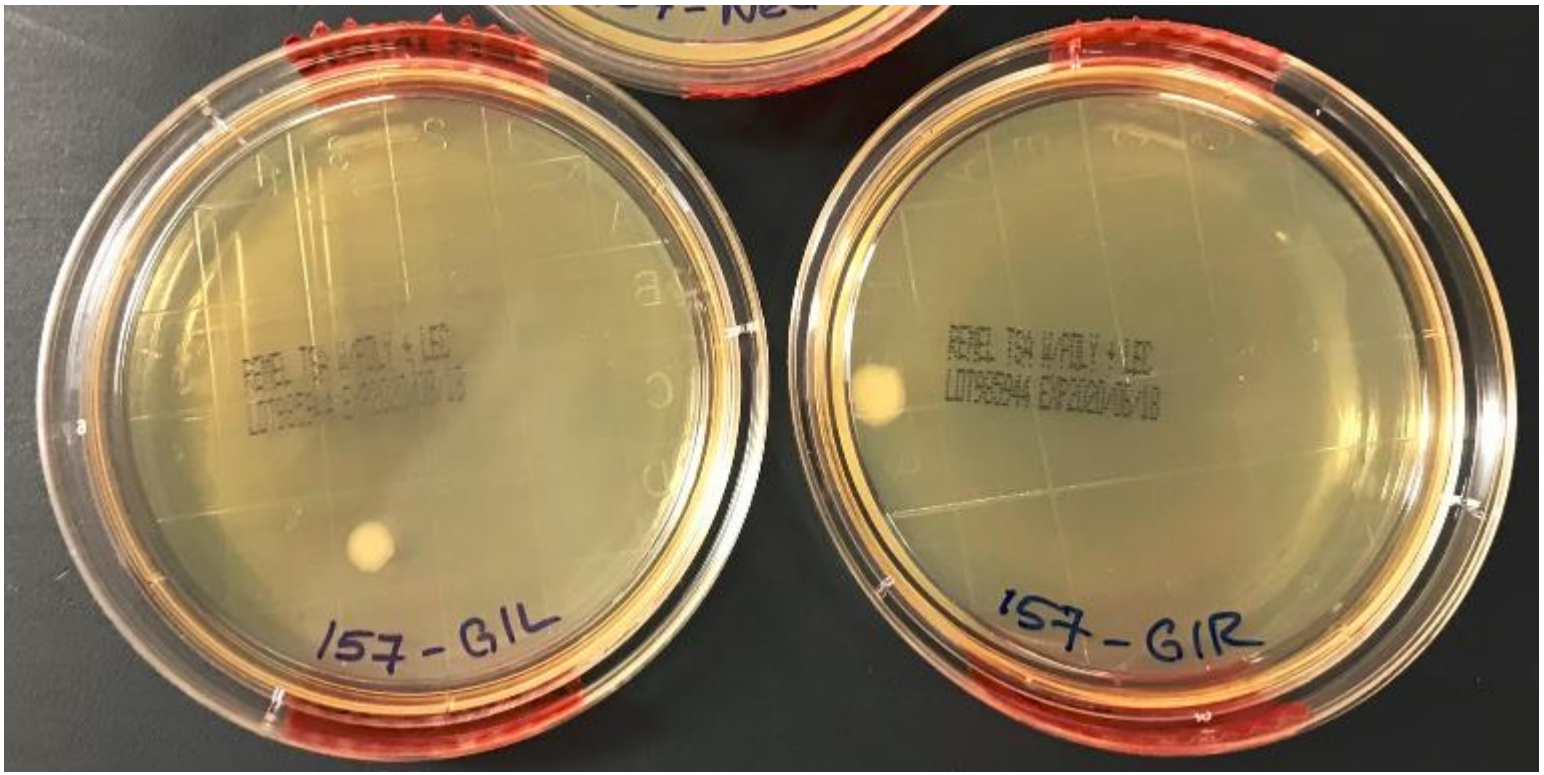


Photo credit: LMPS Quality Team, 2020.

Exercise 2: Count CFUs: presence of Growth

- Review this agar plate for growth.
- How many colony forming units (CFUs) are present?

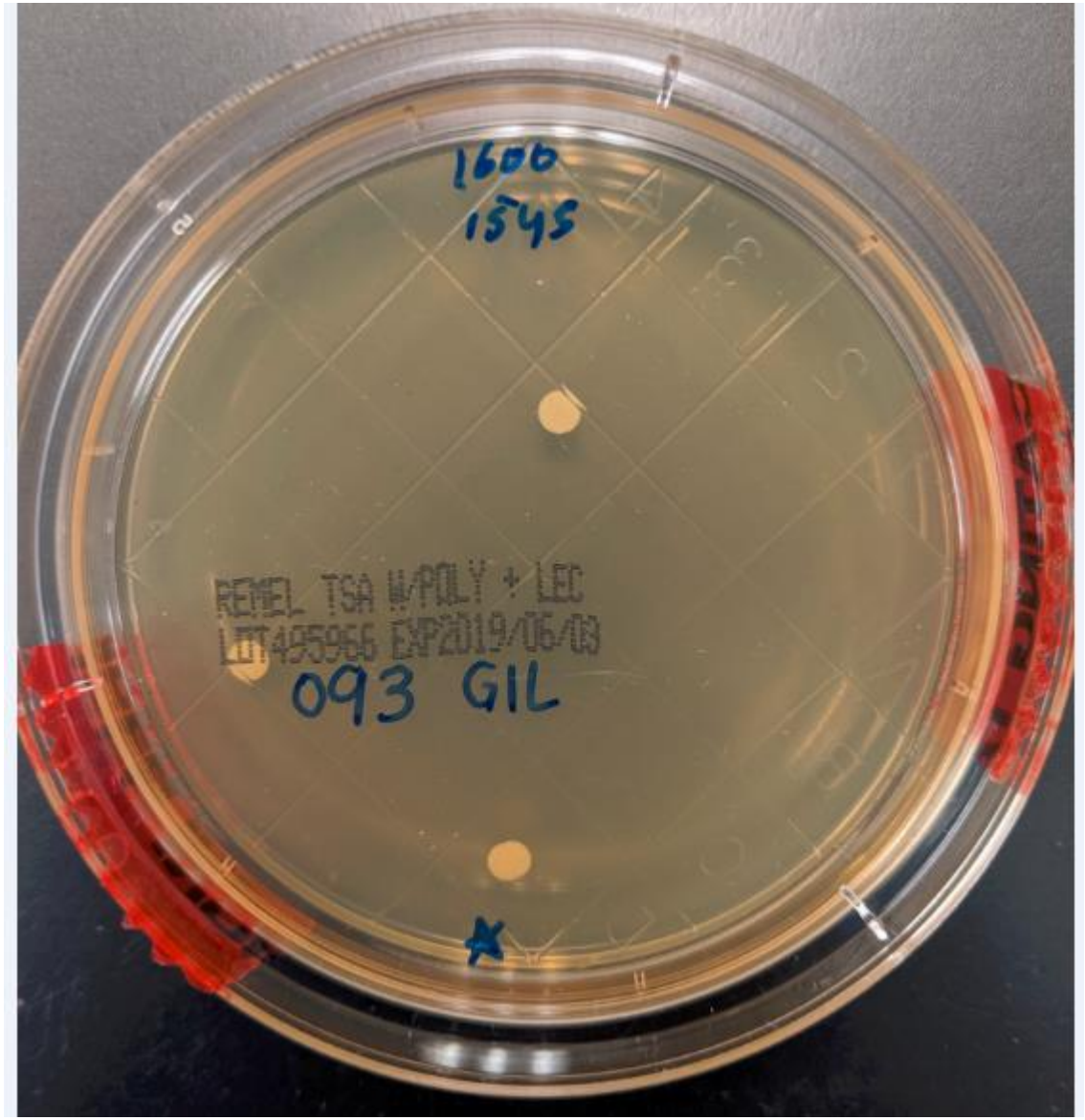


Photo credit: LMPS Quality Team, 2020.

Personnel Assessments using Nutrient Growth Media (for Microbes):

Media Fill Test

Media Fill Test (1)

- Compounding simulation test that assesses sterility of the compounded preparation after manipulation & transfers
- Uses sterile growth media (tryptic soy broth) instead of drugs and diluents.
- Requires use of growth media to evaluate for absence or presence of growth.

Media Fill Test (2)

- Mimics compounding process.
- Requires several manipulations to transfer contents into a single container (e.g. 100 mL IV bag),
- Incubated for 14 days
- Observed for turbidity

Media Fill Test (3)

Growth example

A transparent solution after 14 days of incubation indicates no microbial contamination.

Turbidity after 14 days of incubation indicates microbial contamination

Photo credit: LMPS Quality Team, 2020.

QUESTIONS?

END

References

1. National Association of Pharmacy Regulatory Authorities (NAPRA). Model standards for pharmacy compounding of non-hazardous sterile preparations. Ottawa, ON: NAPRA; 2015 [cited 2020 Oct 18]. Available from: URL: https://napra.ca/sites/default/files/2017-09/Mdl_Stnds_Pharmacy_Compounding_NonHazardous_Sterile_Preparations_Nov2016_Revised_b.pdf
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