CONTEC HEALTHCARE

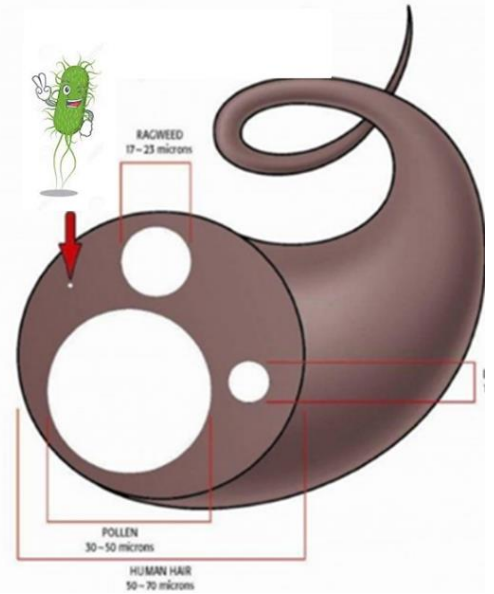
Strategies for Control of Microbial and Hazardous Drug Residues

Mark Wiencek, Ph.D

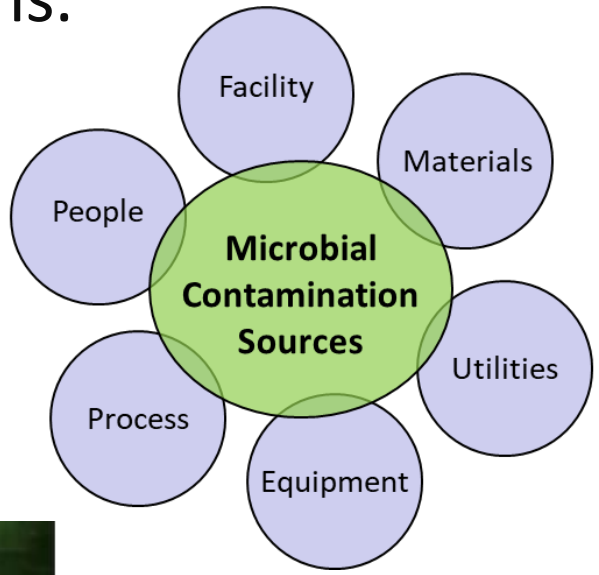
Learning Objectives

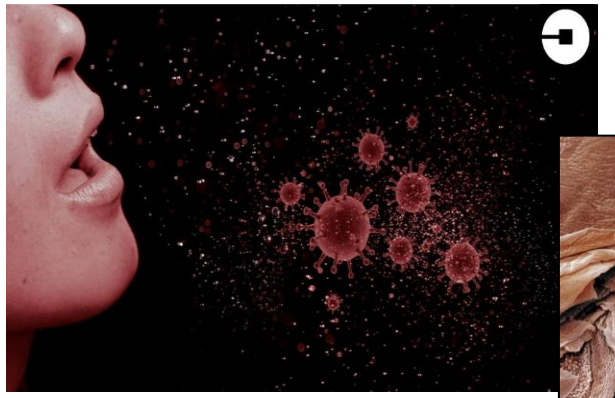
- Distinguish the possible sources for contamination of microorganisms and hazardous drug (HD) residues in a cleanroom.
- Identify the chemical agents and processes for disinfection of microbes and decontamination of HD residues.
- Discuss the methods used to sample for microbial contamination and HD residues and how the results can be interpreted.

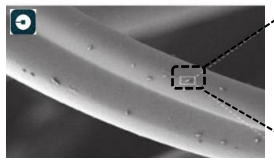
Germs Prefer to Uber®

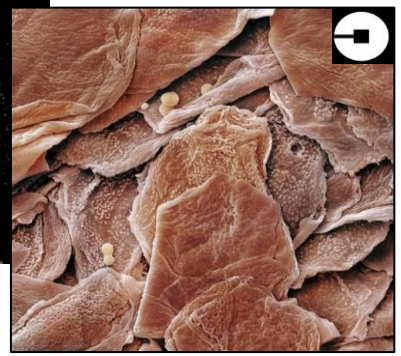


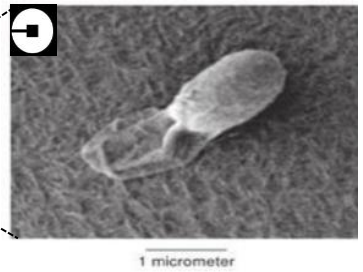
- Germs are tiny. Microscopic!
- Ubering on particles and surfaces increases chance to find moisture and nutrients.
- Many possible sources of microbes into cleanrooms.
- <u>One</u> source is the most common.







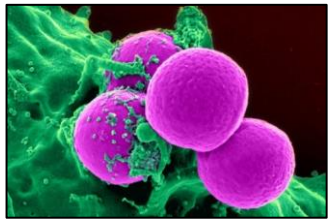




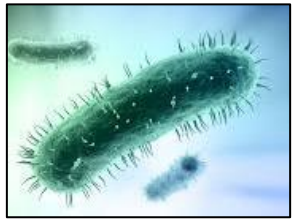
Heston, Charles. Solyent Green. 1973.

Microbes Recovered From Cleanrooms

- From humans:
  - Bacteria (Gram-positive cocci)

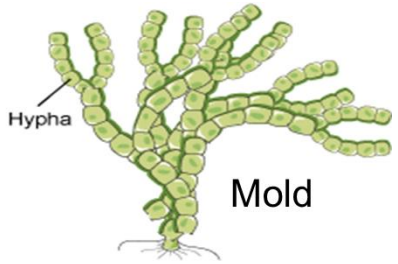


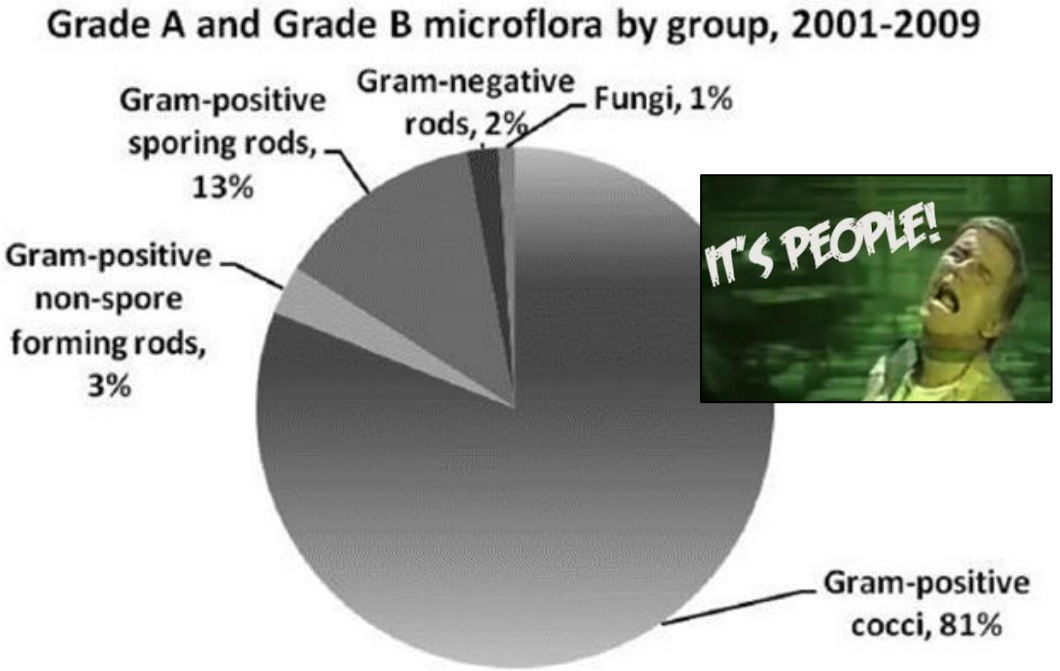
- From water/moisture:
  - Bacteria (Gram-negative rods)



- From dirt/cardboard/outside world:
  - Bacterial endospores, fungi (mold)

Bacterial spores = Nature's Gobstoppers





Sandle, Tim. PDA Journal of Pharmaceutical Science and Technology 65.4 (2011): 392-403.

MODEL STANDARDS FOR PHARMACY COMPOUNDING OF NON-HAZARDOUS STERILE PREPARATIONS

NAPRA and Disinfection

Material Transfer into Cleanroom

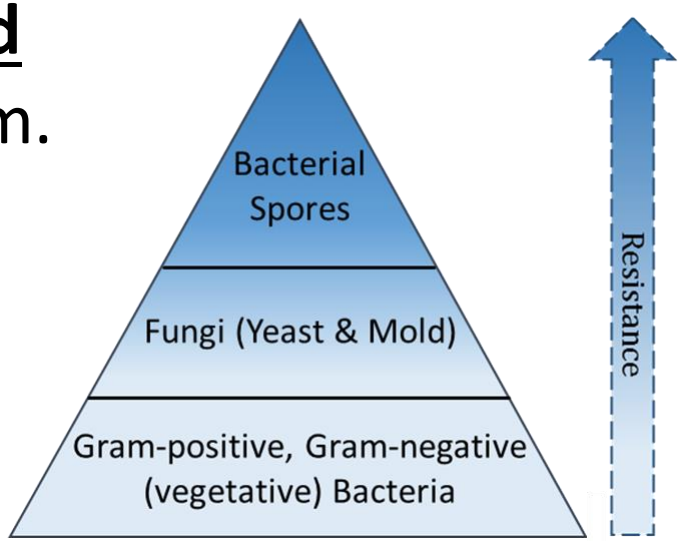
- "To limit the presence of dust and particles in the anteroom, supplies **must** be removed from cardboard boxes outside the anteroom and disinfected with a sporicidal agent before being moved into the anteroom."
- "Cardboard has been found to harbour mould spores, so the product **must** then be wiped with a sporicidal agent."

MODEL STANDARDS FOR PHARMACY COMPOUNDING OF NON-HAZARDOUS STERILE PREPARATIONS

NAPRA and Disinfection

In the Cleanroom

- Use of a germicidal disinfectant detergent is **required** to disinfect all surfaces in a clean room and anteroom.
- Use of an alternative disinfectant in the rotation is unnecessary. However, the daily use of a germicidal disinfectant should be augmented with weekly (or monthly) use of a sporicidal agent



What Is a “Germicidal Disinfectant Detergent?

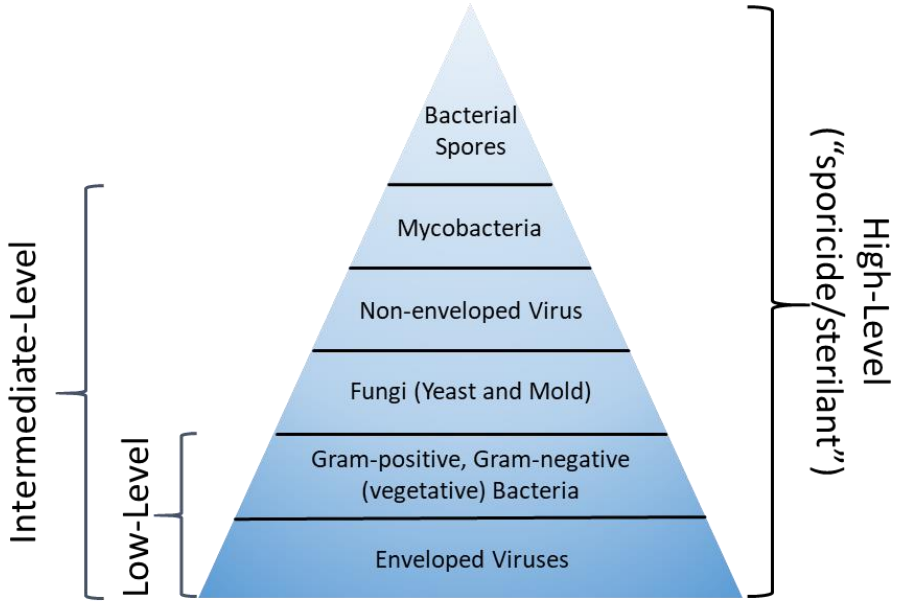
- Health Canada, EPA do not regulate products that only clean
- Most disinfectants also can be used as cleaners
- Germicidal Disinfectant Detergent = One-Step Disinfectant
  - Disinfectants are reactive and non-specific
  - Will react with dirt, debris, and microbes (dead or alive)
  - Some products can be formulated with detergents to help clean and kill in the presence of light-moderate soiling

Health Canada, EPA Defines One-Step Disinfectant:

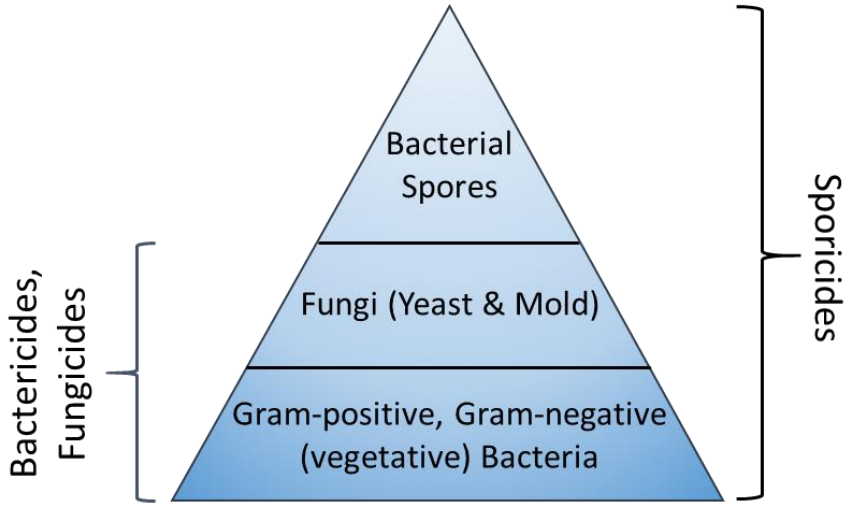
One-Step Disinfectant	a substance, or mixture of substances, that has been tested and found to be effective in the presence of a 5% organic soil load and therefore, may be used without a pre-cleaning step for visibly clean surfaces.

Hierarchy of Susceptibility to Disinfectants

Healthcare, Public Health



Cleanrooms



Low, Intermediate

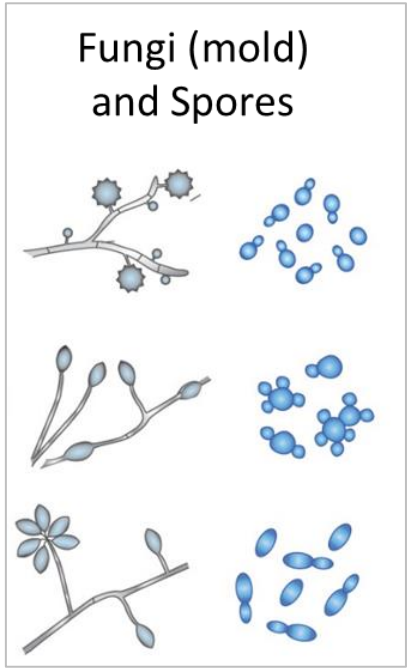
- Hydrogen peroxide
- Phenolic compounds
- Quaternary Ammonium Compounds
- Combos

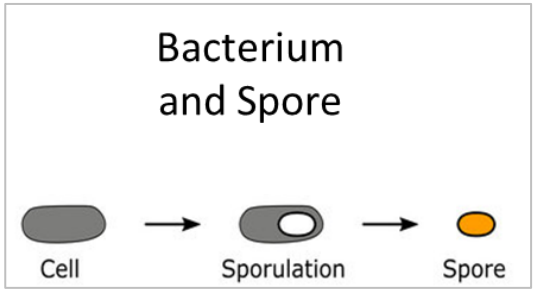
High (sporicides, some also can be "sterilants")

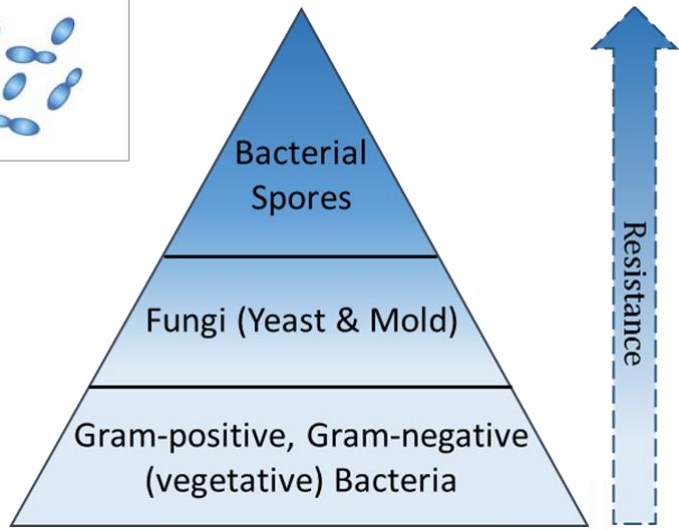
- Peracetic acid + Hydrogen Peroxide
- Hydrogen Peroxide
- Sodium Hypochlorite

What Is a Sporicidal Disinfectant?

- NAPRA, USP, FDA:
  - "A chemical or physical agent that destroys bacterial and fungal spores…"
- Health Canada and EPA:
  - Allows claims of surface disinfection (≤ 10 min.) only against spores of *Closteroides difficile* (C-diff)
  - Allows immersion claims as a "sterilant" against spores of *Clostridium sporogenes* and *Bacillus subtilis*
  - Considers "fungicides" to be effective against all types of fungi and their spores







Sterile 70% IPA as a Disinfectant?

Not recommended

- “IPA isn't an acceptable ingredient in Health Canada's hard-surface disinfectant monograph”*
  - No DIN #, microbes, wet contact times listed on packaging

- Yet, current versions of NAPRA compounding standards refers to 70% IPA as a disinfectant

Active Ingredient:	
Isopropyl Alcohol CAS# 67-63-0	70.0%
Other Ingredients:	
*Water	30.0%
Total:	100.0%
*USP Water for Injection	

- New USP <797> now avoids that term

*https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/disinfectants/hard-surface-disinfectants-monograph-revised.html

Sterile 70% IPA Does What?

70% IPA or EtOH formulations do exhibit some antimicrobial properties

- Health Canada, FDA have approved hand sanitizers (hand rubs) based on IPA
- But…products that ***sanitize*** or ***disinfect*** inanimate surfaces require Health Canada, EPA registration
- New Chapter of <797> is careful to say:
  - **Hands must be *sanitized* with alcohol-based hand rub…**
  - **Application of sterile 70% IPA to gloves must occur…**
  - **…items must be cleaned and wiped with sterile 70% IPA…**
  - **Critical sites…must be wiped with sterile 70% IPA…**

Environmental Monitoring

Environmental Monitoring (EM)

#1. Because NAPRA says we **Must**!

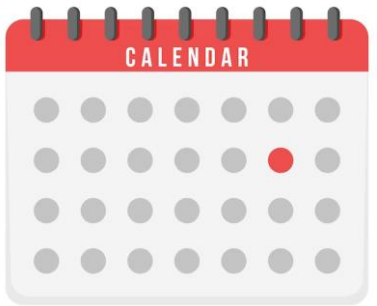
Why do we need to sample?

- The hygienic state of a cleanroom is in constant flux
  - Contamination **increases** from people, fresh air, and supplies
  - Contamination **decreases** from air filtration, natural die-off, cleaning and disinfection

- Results from sampling help:
  - Understand the flux
  - Support certifications
  - Establish normal baseline and seasonal variations
  - Determine impacts from changes in personnel and procedures

7.3.2.3 Environmental verification

- The plan for sampling air (for viable and non-viable particles) and surfaces **must** be established…
  - sampling site diagram
  - type of sampling to be done
  - sampling methods to be used
  - number of samples to be obtained at each site
  - frequency of sampling
  - number of colony-forming units (CFUs) triggering action



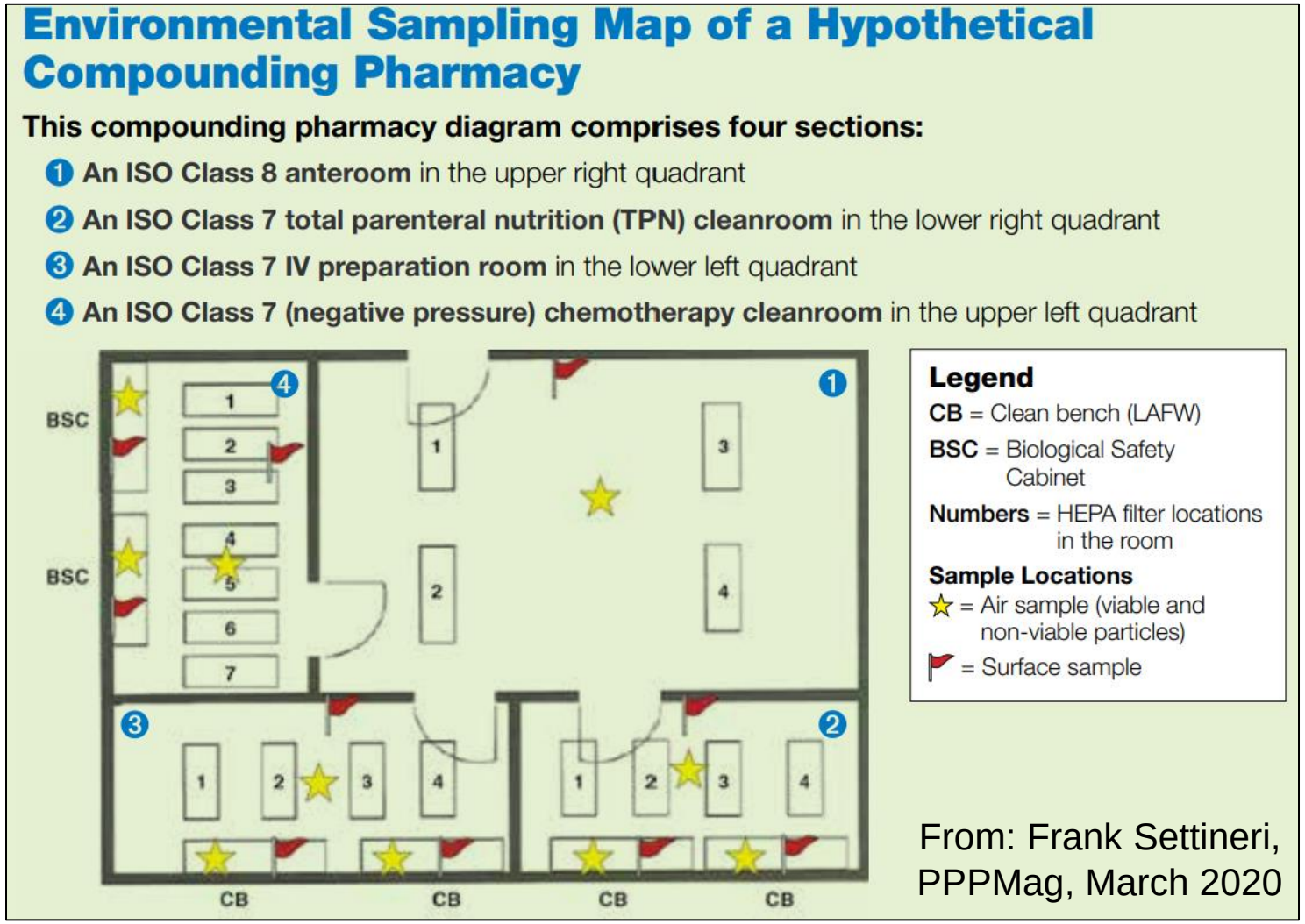
7.3.2.3 Environmental verification

- "**Must**" sample air and surface every 6 months.
- Or if new equipment, maintenance, excursions…
- During the first few months of sampling, the sterile compounding supervisor should ensure that samples are obtained more frequently than the minimum 6-month interval, to create a baseline for comparison.
- If there is growth of any viable particles obtained via air sampling, surface sampling or GFS, the genus of the microorganism **must** be identified. Corrective and preventive actions (e.g., cleaning, disinfecting) will be based on this information."

Environmental Sampling

Develop a Sampling Diagram / Map*

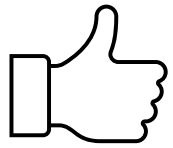
Make a unique code to for each location for easy reference by lab

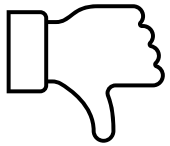


From: Frank Settineri, PPPMag, March 2020

What Makes a Good EM Report?

Test	Organism(s)
Bacterial Surface Sample w/ Genus ID SOP: 12-02 Cfu Raw Count: 11 Corrected Count: 11 cfu/25 cm^2	Micrococcus species 6 CFU Bacillus species 5 CFU
ACCEPTABLE ✓	





SURFACE CULTURE REPORT

Lab ID-Version‡ Location	Sample Size/ Report Unit	Medium	Dilution Factor	Bacterial/ Fungal ID	Colony Counts
[redacted]	Size: 1 sample Unit: 1 sample	TSA	1	Bacteria ✓ X ? Bacillus Gram positive cocci Gram positive rods Staphylococcus Coagulase (-)	2 5 5 1
Comments: Spreading bacterial colonies present. Results may be affected.					

Trending Analyses

If NAPRA/ISO has pass/fail criteria, why trend?

- NAPRA says you **Must**:
  - "The sterile compounding supervisor **must** analyze the data obtained and the trends observed with respect to the microbial load."
- Documentation for audits
- Changes in personnel, seasons, supplies, disinfectants and processes
- Forensics for excursions
- Less challenging to decipher data with higher frequency of sampling

Another Way to Trend

From USP <1116>: Microbiological Control and Monitoring of Aseptic Processing Environments

- The number of samples that show any growth (**contamination recovery rates**) may be as useful as focusing on the number of CFU.
  - Avoids the messy math from zero CFU results
- USP <1116> also provides Table 3 for suggested initial contamination recovery rates in aseptic environments.

Table 3. Suggested Initial Contamination Recovery Rates in Aseptic Environments[a]

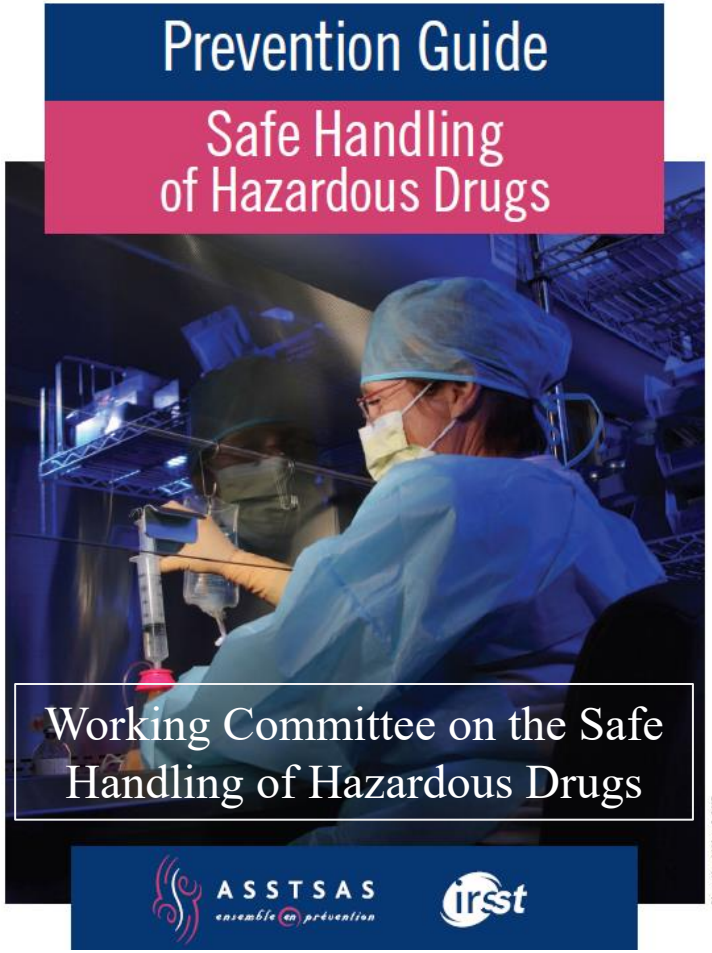
Room Classification	Active Air Sample (%)	Settle Plate (9 cm) 4 h Expo-sure (%)	Contact Plate or Swab (%)	Glove or Garment (%)
Isolator/Closed RABS (ISO 5 or better)	<0.1	<0.1	<0.1	<0.1
ISO 5	<1	<1	<1	<1
ISO 6	<3	<3	<3	<3
ISO 7	<5	<5	<5	<5
ISO 8	<10	<10	<10	<10

Hazardous Drugs

Guidance Documents for Hazardous Drugs

NAPRA ANORP

MODEL STANDARDS FOR PHARMACY COMPOUNDING OF HAZARDOUS STERILE PREPARATIONS



ASSTSAS

Joint Sector-based Association for Health and Occupational Safety for the Social Sector

JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Practice Issues

J Oncol Pharm Practice
2023, Vol. 29(2) 401–412

Safe handling of hazardous drugs

Kardi Kennedy[1], Kathy Vu[2,3,4], Nadia Coakley[5,6], Jennifer Daley-Morris[7], Leta Forbes[8], Renee Hartzell[9] and Darrilyn Lessels[10]

2019

USP General Chapter <800>
Hazardous Drugs – Handling in Healthcare Settings

Reprinted from USP 42—NF 37

What are Hazardous Drugs?

- NIOSH lists common HDs
  - 2016 List + 2018-19 Addenda = 239 drugs in Groups/Tables 1, 2, 3
  - 2020 (Draft) = 230 drugs in Groups/Tables 1, 2

NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016

NIOSH List of Hazardous Drugs in Healthcare Settings, 2020

- Your facility should create an HD list based on NIOSH, Drug IFU criteria
  - Establish the appropriate hierarchy of controls based on an assessment of risk

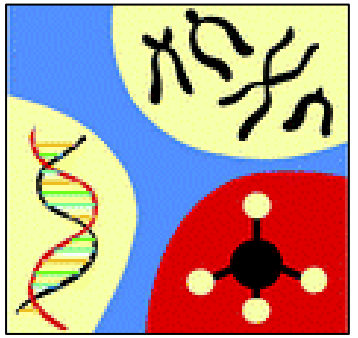
What are Hazardous Drugs?

Characteristics according to NIOSH	Definitions **Source of Table: ASSTSAS**
Carcinogenic (GDT)*	Applies to any substance or agent capable of promoting or causing the development of a cancer or a lesion which could be the starting point of a cancer. Quasi-synonym: carcinogen, cancerogen The terms "carcinogenic" and "oncogenic" should not be confused. "Carcinogenic" is used to refer solely to malignant tumours, while "oncogenic" is used to refer to both benign and malignant tumours.
Teratogenic (GDT)*	Applies to substances capable of causing congenital malformations due to an action on the embryo.
Genotoxic (ASHP)	Applies to substances with the ability to damage the genetic material (DNA) and cause mutations.
Reproductive Toxicity (ASHP)	Applies to substances affecting fertility (e.g., miscarriages, late fetal death, infertility).
Organ Toxicity at Low Dose (ASHP)	Applies to substances with a toxic effect on an organ or on health at a low dose (e.g. liver damage, local necrosis of exposed tissue, etc.).
Similar Drugs (ASHP)	Applies to substances whose structure and toxicity are similar to those of a drug declared hazardous based on one of the above criteria.

* GDT: Grand dictionnaire terminologique (French/English terminology database)

Health Risks from Exposure to HDs

- Genotoxic effects
  - Chromosomal aberrations: 17-study meta-analysis
  - Micronuclei: 24-study meta-analysis
- Cancer occurrence
  - 1.5-fold increase in non-melanoma skin cancer (pharmacy techs)
  - Increase in acute leukemia (nurses)
  - 3.27-fold increase in all cancer types (nurses)
- Adverse reproductive outcomes
  - 1.4-fold increase in infertility
  - 2- to 3.5-fold increase in miscarriage
  - 2.56-fold increase in learning disabilities in offspring

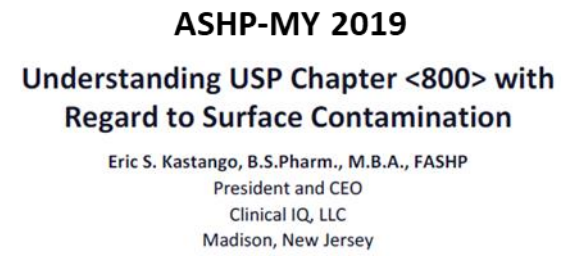


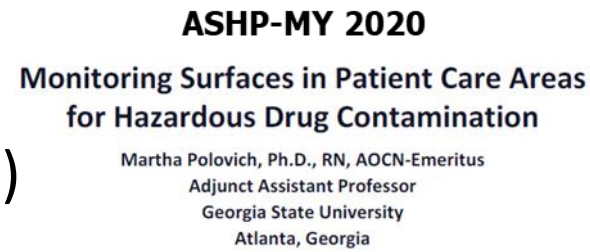
Hansen J, Olsen JH. *Scand J Work Environ Health*. 1994; 20(1):22-6. Roussel C et al. *Mutat Res*. 2019; 781:207-17. Skov T et al. *Br J Ind Med*. 1992; 49:855-61. Suspiro A, Prista J. *Toxicol Lett*. 2011; 207:42-52. Villarini M et al. *Mutat Res*. 2016; 770:35-45.

Lawson CC et al. *Am J Obstet Gynecol*. 2012; 206:327.e1-8. Martin S. *Oncol Nurs Forum*. 2005; 32:425.

Evidence of Exposure to HDs

- 1999
  - 75% of pharmacies and 65% of infusion suites had measurable amounts of cyclophosphamide, ifosfamide and fluorouracil[1]
- 2010
  - 75% of pharmacies and 43% of infusion suites had measurable amounts of the above drugs and paclitaxel and cytrabine[2]
- Excretion of drugs and drug metabolites in:
  - Urine of health care workers (>100 studies since 1992)
  - Contamination on external vial surfaces (<15 studies since 1992)
  - Workplace surface contamination (>100 studies since 1994)





[1]Connor, T, *et al. American Journal of Health-System Pharmacy* 56.14 (1999): 1427-1432.

[2]Connor, T, *et al. Journal of occupational and environmental medicine* 52.10 (2010): 1019-1027.

How Does the HD Get Out of the Bag?

- In the Pharmacy
  - Concentrated or RTU drugs arrive in bulk packaging
  - Compounders dilute concentrates, reconstitute powders, dispense into small containers/unit doses
- In the Location of Administration
  - Hospital
  - Clinic
  - Home

Medication Circuit

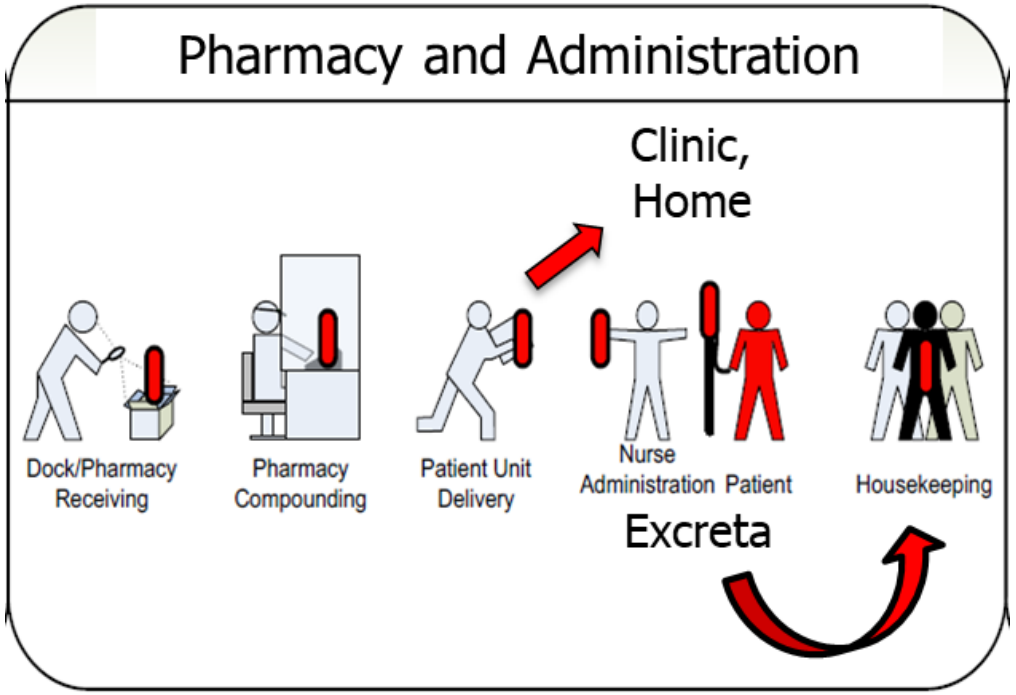
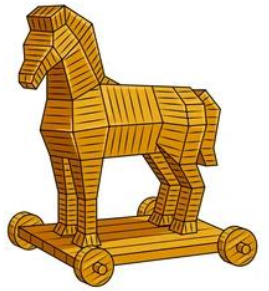


Image Courtesy of Fred Massoomi

Drug Vials – A Trojan Horse for Pharmacies?



Cisplatin Contamination Observed on the Outside of Drug Vials

OLLE NYGREN[1]*, BENGT GUSTAVSSON[2], LENA STRÖM[2] and ARNE FRIBERG[3]

Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: Results of three studies

THOMAS H. CONNOR, PAUL J. M. SESSINK, BRUCE R. HARRISON, JACK R. PRETTY, BYRON G. PETERS, RAUL M. ALFARO, APPIE BILOS, GWENDOLYN BECKMANN, MICHAEL R. BING, LAKISHA M. ANDERSON, AND ROBERT DECHRISTOFORO

Cyclophosphamide Contamination Observed on the External Surfaces of Drug Vials and the Efficacy of Cleaning on Vial Contamination

KARINE TOUZIN[1]*, JEAN-FRANÇOIS BUSSIÈRES[1], ÉRIC LANGLOIS[2], MICHEL LEFEBVRE[2] and CLAUDE GALLANT[3]

Cytotoxic Drug Contamination on the Outside of Vials Delivered to a Hospital Pharmacy

H. J. MASON*, J. MORTON, S. J. GARFITT, S. IQBAL and K. JONES

External contamination of commercial containers by antineoplastic agents: a literature review

Delphine Hilliquin,[1] Cynthia Tanguay ,[1] Jean-François Bussières[1,2]

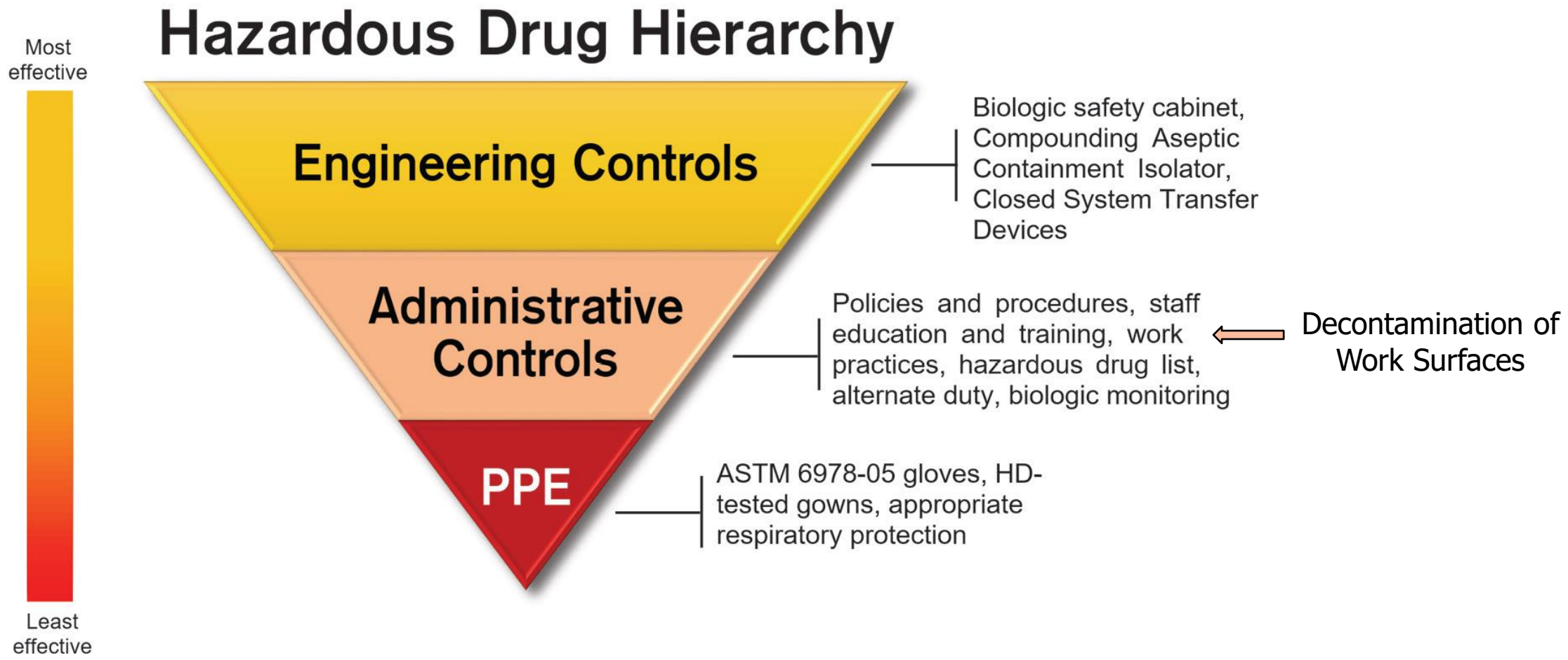
Table 1 Contamination found on the exterior of commercial vials per drug

Drug (n studies)	Manufacturers (n)	Positive containers (n/N (%))	Maximum concentration (ng/vial)
Cyclophosphamide (n=15)	5	545/967 (56.4%)	69 819
Cytarabine (n=1)	2	4/11 (36.4%)	32.35
Docetaxel (n=1)	1	33/33 (100%)	ND
Doxorubicin (n=2)	6	73/91 (80.2%)	4.05
Epirubicin (n=1)	5	3/15 (20%)	17.3
Etoposide (n=2)	3	204/207 (98.6%)	1890.6
Fluorouracil (n=7)	6	386/727 (53.1%)	150 000
Gemcitabine (n=1)	5	3/15 (20%)	3.54
Ifosfamide (n=6)	3	300/901 (33.3%)	1705
Irinotecan (n=1)	7	7/27 (25.9%)	145.14
Methotrexate (n=6)	4	22/146 (15.1%)	15 000
Platinum* (n=9)	9	799/1099 (72.7%)	4719
Vincristine (n=1)	2	0/9 (0%)	ND

*Carboplatin, cisplatin and oxaliplatin were grouped.
ND, not determined.

Hilliquin, *et al.* (2020). External contamination of commercial containers by antineoplastic agents: a literature review. EJHP, 27(5), 313-314.

NIOSH Hierarchy of Controls for HDs



Eisenberg, S. and Klein, C., 2021. Safe Handling of Hazardous Drugs in Home Infusion. *Journal of Infusion Nursing*, *44*(3), pp.137-146.

NAPRA ANORP

MODEL STANDARDS FOR PHARMACY COMPOUNDING OF HAZARDOUS STERILE PREPARATIONS

5.3.4.2 Surface decontamination, deactivation and disinfection

"Cleaning and disinfecting procedures **must** be strictly adhered to in the clean room and the anteroom."

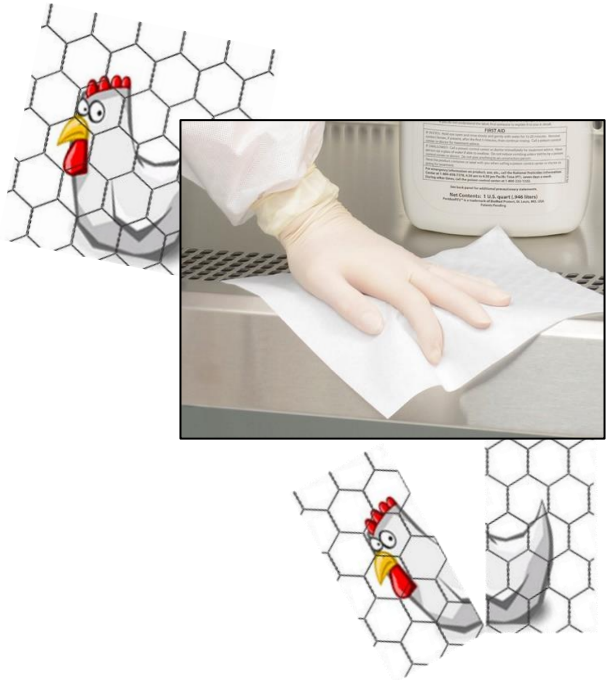
"…cleaning of the premises and equipment **must** also eliminate chemical contamination from the hazardous products used.

NAPRA ANORP

MODEL STANDARDS FOR PHARMACY COMPOUNDING OF HAZARDOUS STERILE PREPARATIONS

Decontamination

- “Decontamination involves the transfer of a hazardous drug contaminant from a fixed surface (e.g., counter, bag of solution) to a disposable surface (e.g., wipe, cloth).”
- “The wipe is then contained and discarded as hazardous waste”
- “On its own, sterile 70% isopropyl alcohol cannot be used to decontaminate hazardous drugs and may in fact spread any chemical contamination that is present to other surfaces.”



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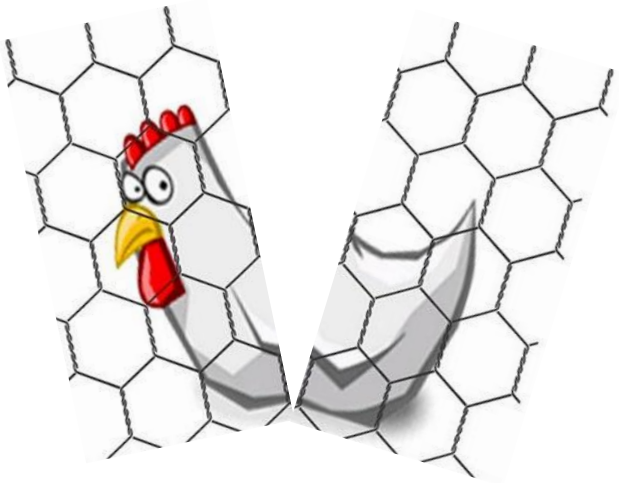
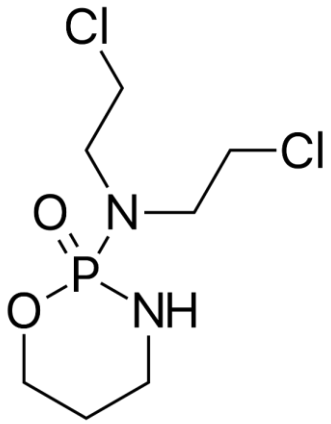
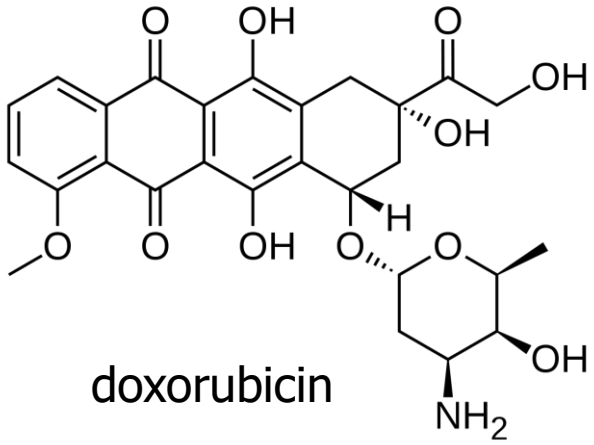
Chicken Wire?

Many drug structures look like chicken wire to me…

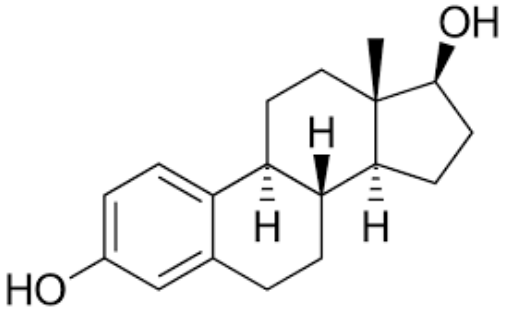




cyclophosphamide



doxorubicin



estradiol

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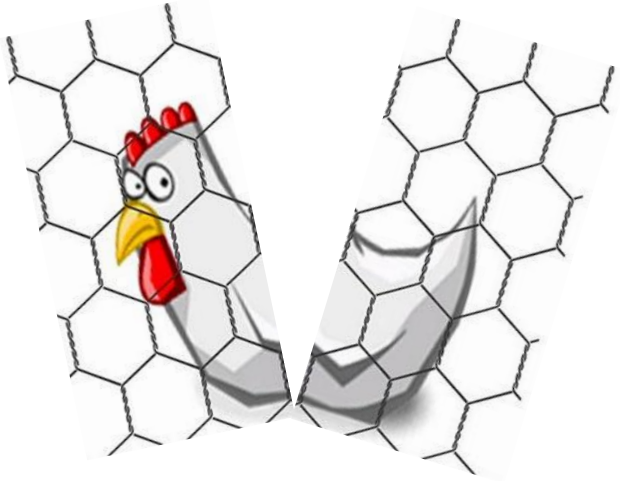
Deactivation



- “Deactivation is the treatment of a hazardous drug to create a less hazardous agent, for example, by chemical deactivation.”
- “The material safety data sheets for some hazardous drugs recommend sodium hypochlorite for this purpose, usually as a 2% solution.”

Deactivation: Safety Data Sheets?

Review of SDSs for all 239 HDs on 2019 NIOSH List

Analysis of SDSs for NIOSH Hazard Drugs (2019 List)				
NIOSH Group	Total Number of Drugs in Group	Number of SDS that state "Oxidizer"	Number of SDS that State "Oxidizer & Acid"	Number of SDS with a Chemical Agent in Section 6
1	126	97	26	• Alcohol = 17 • Ethanol = 1 • Bleach = 6 • Caustic Ethanol Sol. = 1 • 10% Caustic Sol. = 1
2	57	49	6	• Alcohol = 2 • Bleach = 1
3	56	44	8	• 10% Caustic Sol. = 1 • Alcohol = 3

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Gloves, Gown

HD Permeation Methods

- Gloves
  - "Both pairs of gloves **must** be discarded and replaced at the earliest of the manufacturer's limit for permeation of the gloves, every 30 minutes or immediately if a tear, puncture, or contamination has occurred or is suspected."

ASTM-D6978

- Gown
  - "The gown **must** have been tested by the manufacturer for resistance to permeability by hazardous drugs."
  - The gown **must** be discarded and replaced at the earliest of the manufacturer's time limit for permeation of the gown or after 2–3 hours of continuous compounding work or after each removal, or after a contamination has occurred or is suspected."

New! **ASTM-F3267**

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Masks, Beard Coves, "Prep" Mats

- Masks, Beard Covers
  - "…**must** be changed at the earliest of the following: after 3.5 hours of continuous compounding work, after each removal or if contamination has occurred or is suspected."

ASSTSAS
Joint Sector-based Association for Health and Occupational Safety for the Social Sector

- Mats
  - "It should be changed after 3.5 hours of continuous work or for a new batch of preparations (e.g. a set of vials of a given drug) or in the event of a spill or contamination."

Decontamination of HD Residues on IV Bags

- ASSTASS: Decontaminate IV bags, pumps and syringes containing HDs
- A recent study examined the risk of a PAA/HP disinfectant migrating through IV bags and decontamination HD residues


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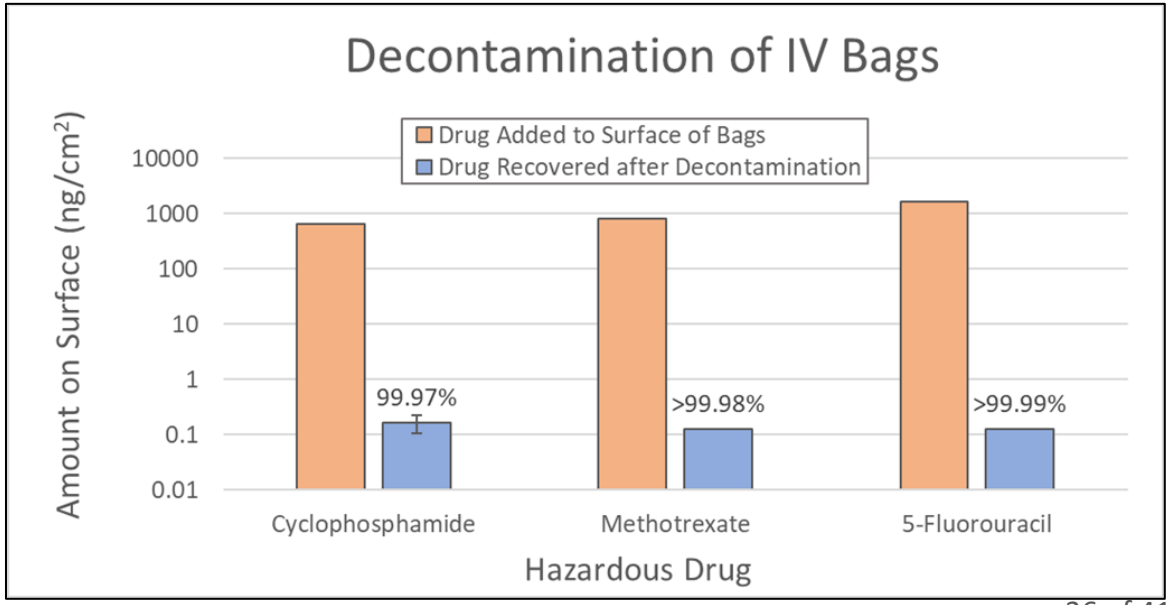
An Investigational Study on the Use of a Sporicidal Disinfectant to Decontaminate Hazardous Drug Residues on IV Bags



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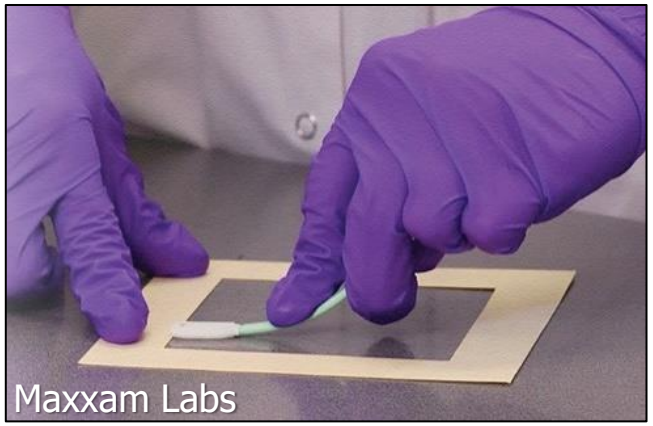
Sampling for HDs per NAPRA, ASSTASS



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Sampling for HD Residues per NAPRA, ASSTASS

- The level of HD contamination should be measured at least every 6 months…
- …should sample…sites…most likely to be contaminated
- A baseline assessment should precede any preventive measure (as described in the ASSTSAS guide), and monitoring should be repeated after implementation of such measures, to determine their effectiveness.
- Surface contamination by hazardous antineoplastic drugs, as determined by environmental monitoring, **must** be recorded in the general maintenance log.

USP <800>: What is a “Safe” Level of HD Residue?

- There is currently no standard for acceptable limits for HD surface contamination.
- An example of measurable contamination would be cyclophosphamide levels >1.00 ng/cm^2, which were shown in some studies to result in uptake of the drug in exposed workers.
- If any measurable contamination is found…must identify, document, and contain the cause of contamination.

What is a “Safe” Level of HD Residue?

Practical Considerations

- Instead of stressing if <u>any</u> drug is detected, consider “ALARA”
  - ALARA = <u>A</u>s <u>L</u>ow <u>A</u>s <u>R</u>easonably <u>A</u>chievable

(CP) in The Netherlands (CP) = Cyclophosphamide				
	Strive risk level			Prohibitory risk level
Urine CP (µg/24 h)	< 0.02	0.02–0.2	0.02–2	> 2
Contamination CP (ng/cm^2)	< 0.1	0.1–1	1.0–10	> 10
Actions	Monitoring once a year Evaluate after 4 years	Risk estimate Monitoring within 3–6 months Eventually followed by measures		Take measures Check by monitoring

Sessink, P. J. (2011). Safety Considerations in Oncology Pharmacy. Special Edition


The End


4


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