Advanced USP <800> Topics

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Disclaimer

This presentation is not affiliated nor endorsed by the United States Pharmacopeia (USP).

Patient Case

Patient Case

A 55-year-old female pharmacist presented to the Emergency Department with chief complaints of **visual disturbances, dizziness & right upper extremity paresthesia for approximately 3-hours**. Patient states she was at work around 1500 when she noted that her vision in both eyes looked like “when you look at the sun”. She said it was spotted. She stated while driving home she developed **nausea, intermittent paresthesia & a racing heartbeat that would last several minutes and resolve.**

Patient Case

Patient was brought to the hospital by a family member when she **exhibited confusion, delirium, anxiety, agitation, aphasia and disoriented to current events.** Patient appeared to be exhibiting *stroke-like symptoms* without slurred speech, facial droop or muscular weakness.

Vitals:

BP: 153/89

Pulse: 96

Patient Case

Over the Next Several Hours

The patient's symptoms resolved but a moderate-severe headache was reported. All medical surveillance to rule out stroke were reported negative. Patient was discharged home to follow-up with PCP.

Next Day

Upon arriving back in the pharmacy, the pharmacist was immediately questioned by her technician (22 y/o female) regarding "feeling awful last night". She reported **nausea, blurred vision, possible hallucinations (according to her boyfriend), irritability and "migraine-like" headache.**

Patient Case

Investigation

Pharmacist and technician recalled cleaning medication storage shelves after lunch. They remembered **"spraying, wiping and cleaning a substantial (approximately 6") of a liquid medication spill"** that had dried and was sticky.

Conclusion

Based on the relatively similar symptoms that resolved, although the pharmacist experienced more severe symptoms, it is **likely that both individuals experienced a medication toxicity/adverse drug reaction.** The route of administration could have been through inhalation via aerosolization of the dried medication residue and/or dermal absorption through their hands and forearms.

Patient Case

Amantadine Side Effects

- Dry mouth
- Constipation
- **Nausea**
- Vomiting
- Decreased appetite
- Difficulty sleeping
- Abnormal dreams
- **Headache**
- **Confusion**
- Tightening of muscles

Amantadine Toxicity

- **Altered mental status**
- **Tachycardia or arrythmia**
- **Hypertension**
- Ataxia
- Delirium
- Hallucinations
- Distrust
- Depression
- **Anxiety**
- Suicidal ideation

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https://medlineplus.gov/druginfo/meds/a682064.html

https://go.drugbank.com/drugs/DB00915

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Priming for Dynamic Assessments of Hazardous Medications

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NIOSH Definition of a Hazardous Drug

NIOSH defines a hazardous drug as one that is:

1. Approved for use in humans by the FDA Center for Drug Evaluation and Research (CDER),
2. Not otherwise regulated by the US Nuclear Regulatory Commission and
3. Either
    a. Includes **Manufacturer's Special Handling Information (MSHI)** in the package insert,

    or

    b. Is identified as containing one or more of the following hazards:
        - Carcinogenic
        - Developmental toxicity (including teratogenicity)
        - Reproductive toxicity
        - Genotoxicity
        - Organ toxicity at low doses
        - Structure and toxicity profile that mimics existing drugs determined hazardous

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NIOSH [2024]. NIOSH list of hazardous drugs in healthcare settings, 2024. By Ovesen JL, Sammons D, Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP, Whittaker C. Cincinnati, OH: U.S. Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2025-103 (Supersedes 2016-161), https://doi.org/10.26616/NIOSHPUB2025103

NIOSH 2024 Hazardous Drug List Changes

- Table 1 now includes drugs that have MSHI in the package insert and/or meet the NIOSH definition of a hazardous drug and one or more of these criteria:
  - Are classified by the National Toxicology Program (NTP) as "known to be a human carcinogen"
  - Are classified by the International Agency for Research on Cancer (IARC) as Group 1 "carcinogenic to humans" or Group 2A "probably carcinogenic to humans"
- Table 2 now contains drugs that meet one or more of the criteria in the NIOSH definition of a hazardous drug and
  - Do not have MSHI
  - Are not classified by the NTP as "known to be a human carcinogen"
  - Are not classified by the IARC as Group 1 "carcinogenic to humans" or Group 2A"probably carcinogenic to humans"

DAILYMED

NIH NATIONAL LIBRARY OF MEDICINE

The DailyMed database contains 154949 labeling submitted to the Food and Drug Administration (FDA) by companies.

https://dailymed.nlm.nih.gov/dailymed/

National Toxicology Program
U.S. Department of Health and Human Services

The Report on Carcinogens (RoC) is a congressionally mandated, science-based public health document that lists substances that are known or reasonably anticipated to cause cancer in humans.

https://ntp.niehs.nih.gov/research/assessments/cancer/roc

International Agency for Research on Cancer

World Health Organization

Evaluates scientific evidence on whether a substance can cause cancer and classifies them into Groups:

- Group 1: **Carcinogenic** to humans
- Group 2A: Probably carcinogenic to humans
- Group 2B: Possibly carcinogenic to humans
- Group3: *Not classifiable* as to its carcinogenicity

https://monographs.iarc.who.int/list-of-classifications

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Hazardous Drug Decision Process

NIOSH defines a hazardous drug as one that is:

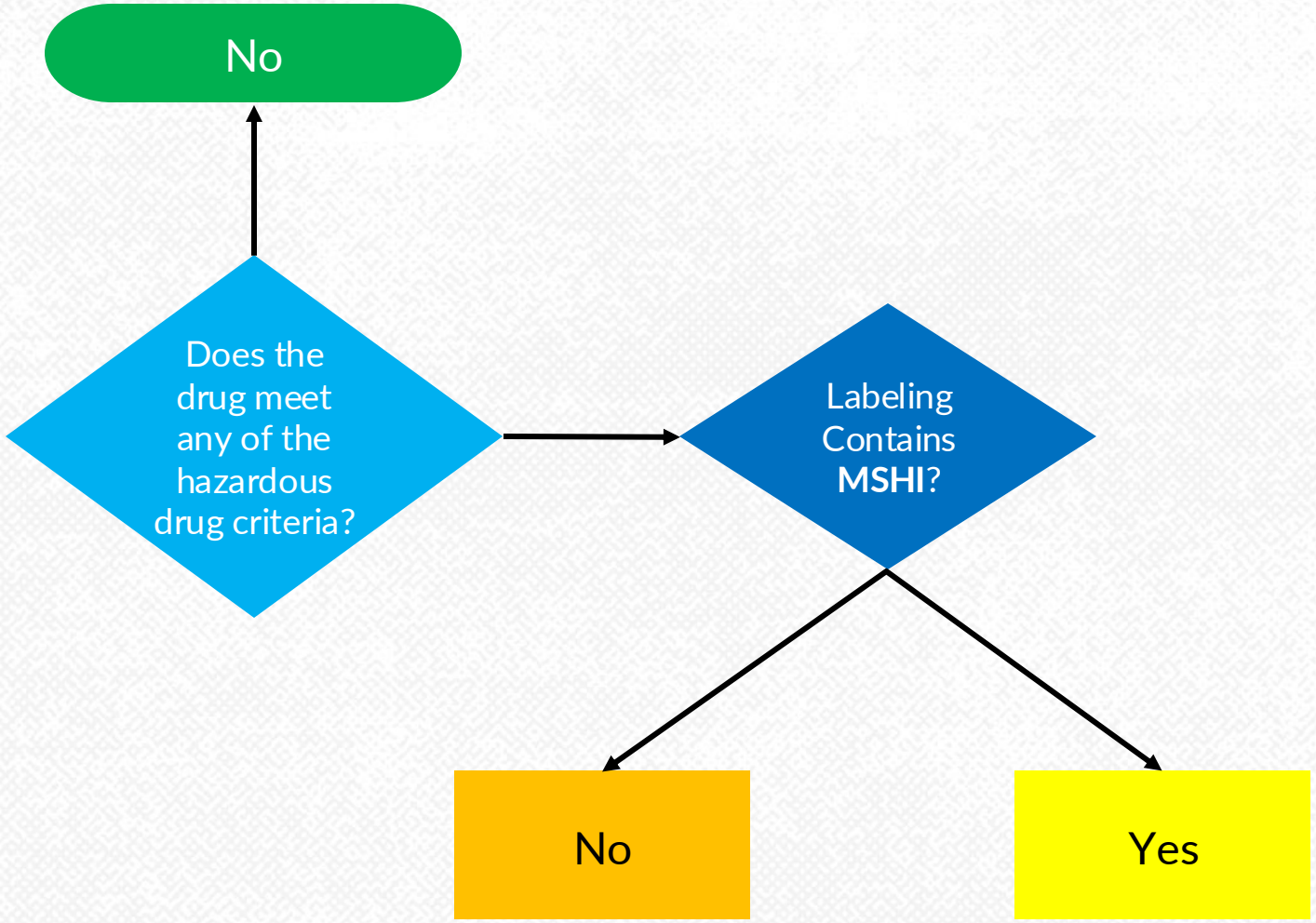
- ❑ Approved for use in humans by FDA CDER
- ❑ Not otherwise regulated by the U.S. Nuclear Regulatory Commission

EITHER

- ❑ Contains **Manufacturer's Special Handling Information (MSHI)** in the approved labeling (e.g., package insert, prescribing information)

OR … identified as containing at least one of the hazards:

- ❑ Carcinogenicity
- ❑ Developmental toxicity (including teratogenicity)
- ❑ Reproductive toxicity
- ❑ Genotoxicity
- ❑ Organ toxicity at low doses
- ❑ Structure and toxicity profile that mimics existing drugs determined hazardous



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https://www.cdc.gov/niosh/docs/2025-103/pdfs/2025-103.pdf?id=10.26616/NIOSHPUB2025103&id=10.26616/NIOSHPUB2025103

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Artificial Intelligence (AI) in Toxicity Prediction

- In drug toxicity prediction, **AI can quickly analyze massive data of drug structure, activity, toxicity, etc., and mine the hidden rules and associations** so as to establish a high-precision prediction model.
- AI is already enhancing prediction via big data, identifying at-risk individuals, and informing interventions. Other expected innovations include:
  - AI-Enhanced Toxicity Understanding: AI will better elucidate chemical toxicity by finding patterns in large datasets and epidemiological data to develop new safety regulations and safer chemical design.
  - Improved Risk Prediction: AI will increasingly forecast chemical exposure toxicity risks for individuals. This facilitates interventions to reduce high-risk individuals' exposures.
  - Novel Treatment Development: AI can identify new poison treatments and diagnostics and optimize care delivery to poisoned patients. It may also enable personalized toxicology via genetic/epigenetic data.
- **Quantitative Structure-Activity Relationships (QSAR)** models can analyze the relationship between several predictors (e.g., molecular properties) and a response (e.g., biological activities such as binding affinity). Good models will be highly predictive and fairly easy to interpret. There are several types of machine learning approaches that have been used for QSAR modeling.

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Zhang R, Wen H, Lin Z, Li B, Zhou X. Artificial Intelligence-Driven Drug Toxicity Prediction: Advances, Challenges, and Future Directions. *Toxics*. 2025;13(7):525

Hartung T. Artificial intelligence as the new frontier in chemical risk assessment. *Front Artif Intell*. 2023;6:1269932.

Basile AO, Yahi A, Tatonetti NP. Artificial Intelligence for Drug Toxicity and Safety. *Trends Pharmacol Sci*. 2019;40(9):624-635.

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Examples of Toxicological Databases

- **Toxicology Resources for Intelligent Computation (TOXRIC)**
  - Comprehensive toxicity database, containing a large number of toxicity data of compounds, which are derived from a variety of experiments and literature. Its data cover acute toxicity, chronic toxicity, carcinogenicity, and other types of toxicity, and the species involved include humans, animals, and aquatic organisms
- **PubChem**
  - World-renowned database of chemical substances, which contains massive data on the structure, activity, and toxicity of chemical substances . It integrates information from scientific research literature, experimental reports, and other databases, and has the characteristics of a large amount of data and timely updates.
- **DrugBank**
  - Comprehensive and freely accessible online database, which provides detailed information on drugs and their targets, including basic data, chemical structure, pharmacological data on drugs, and the sequence, structure, and pathway information of targets

Zhang R, Wen H, Lin Z, Li B, Zhou X. Artificial Intelligence-Driven Drug Toxicity Prediction: Advances, Challenges, and Future Directions. Toxics. 2025;13(7):525. Published 2025 Jun 23. doi:10.3390/toxics13070525

Environmental Protection Agency (EPA) Models

OncoLogic™ - An Expert System to Evaluate the Carcinogenic Potential of Chemicals

The OncoLogic™ model is an expert system that mimics the judgment of human experts by following sets of knowledge rules based on studies of how chemicals cause cancer in animals and humans. OncoLogic™ asks for chemical and use information from the user, and following knowledge rules incorporated into the system, uses the responses to construct an estimation of the potential of chemicals to cause cancer.

https://www.epa.gov/tsca-screening-tools/oncologictm-expert-system-evaluate-carcinogenic-potential-chemicals

Ecological Structure Activity Relationships (ECOSAR) Predictive Model

The Ecological Structure Activity Relationships (ECOSAR) Class Program is a computerized predictive system that estimates aquatic toxicity. The program estimates a chemical's acute (short-term) toxicity and chronic (long-term or delayed) toxicity to aquatic organisms, such as fish, aquatic invertebrates, and aquatic plants, by using computerized Structure Activity Relationships (SARs).

https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model

Tying it all Together

Integrating Hazardous Drug Categorization, Safety and AI Advances

- NIOSH defines hazardous drugs based on toxicity and handling information
- 2024 updates refine hazardous drug classifications by carcinogenicity and handling requirements
- Decision processes guide safe management of hazardous drugs in healthcare settings
- AI enhances toxicity prediction through data analysis and sophisticated modeling
- Toxicological databases provide critical data for AI-driven safety assessments
- EPA models evaluate chemical carcinogenic potential and ecological toxicity risks

Advanced Sterile Compounding Room Design & Engineering Controls

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USP <797> & USP <800> Secondary Engineering Controls (SEC)

Minimum Sterile Compounding C-SEC Standards

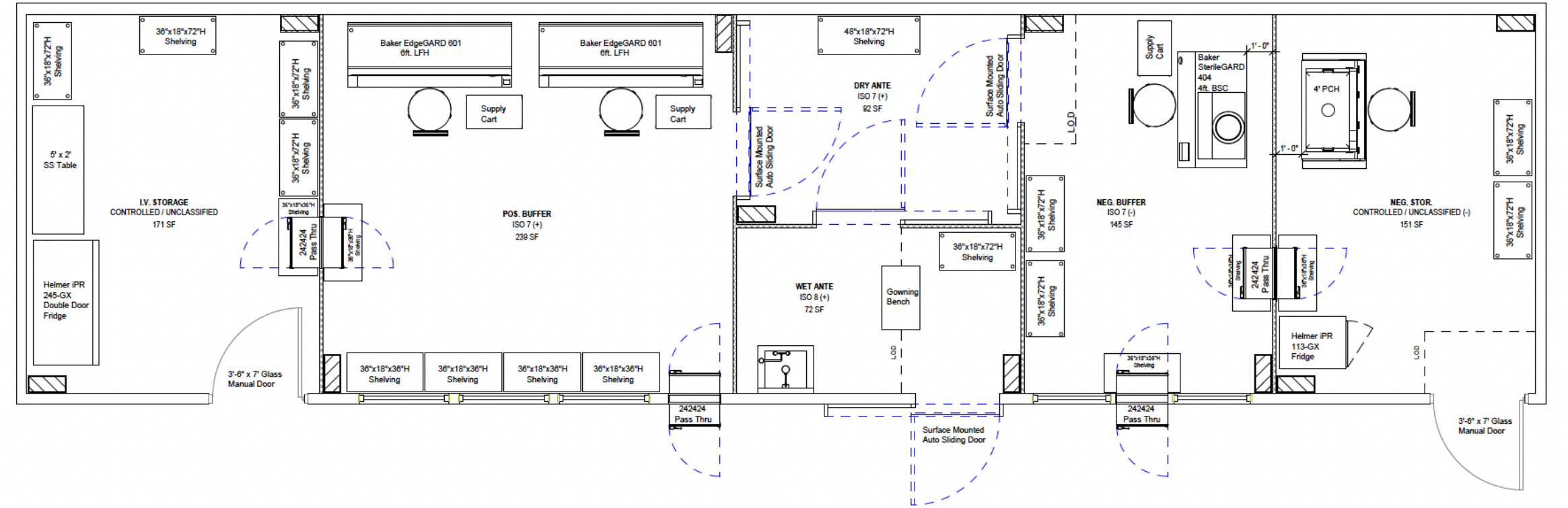
Room	ISO Class	Pressure	DP (in. WC)	ACPH
Ante	7	Positive	> 0.02	30
Buffer	7	Negative	(-) 0.01 – 0.03	30
Storage	NC	Negative	(-) > 0.01	12
Receiving	NC	Neutral/Negative	N/A	N/A

USP <797> & USP <800> Secondary Engineering Controls (SEC)

Advanced Sterile Compounding C-SEC Concepts

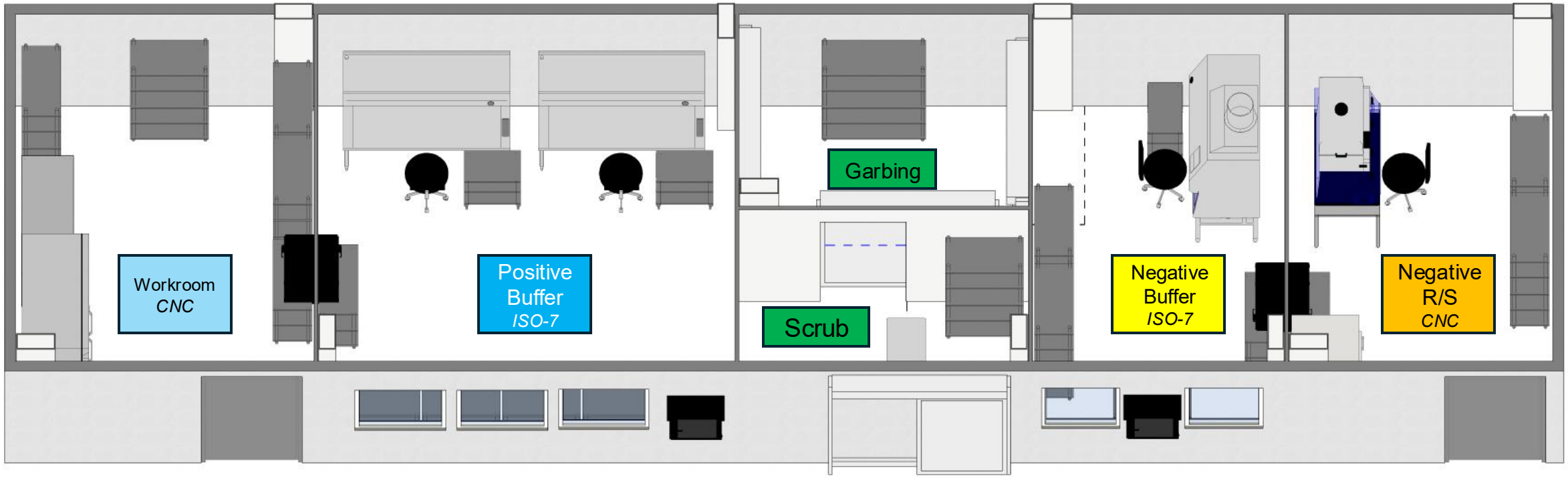
Room	ISO Class	Pressure	DP (in. WC)	ACPH
Ante: Scrub/Wet	8	Positive	> 0.02	20
Ante: Garbing/Dry	7	Positive	> 0.02	30
Buffer (-): Hazardous	7	Negative	(-) 0.01 – 0.03	30
Buffer (+): Non-Hazardous	7	Positive	> 0.02	30
Doffing: Hazardous	7	Negative	(-) 0.01 – 0.03	30
Doffing: Non-Hazardous	7	Positive	> 0.02	30
Exit: Hazardous	7 or 8	Positive	> 0.02	20 or 30
Storage: Hazardous	NC	Negative	(-) > 0.01	12
Receiving: Hazardous	NC	Neutral/Negative	N/A	N/A
Receiving/Storage: Hazardous	NC/CNC	Negative	(-) > 0.01	12

Current Cleanroom Template



Current Cleanroom Template

ProPharma CLEANROOMS



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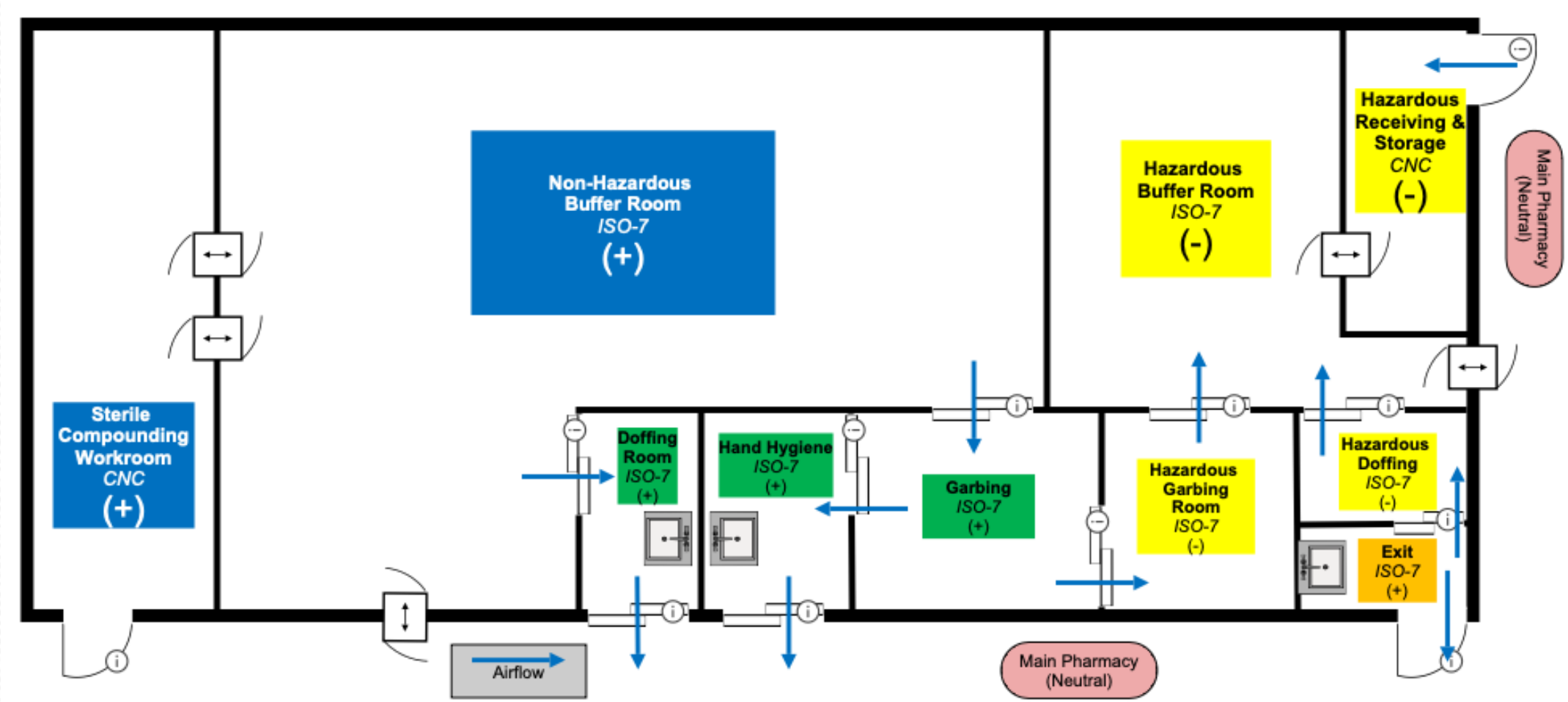
Advanced Hospital Cleanroom Design



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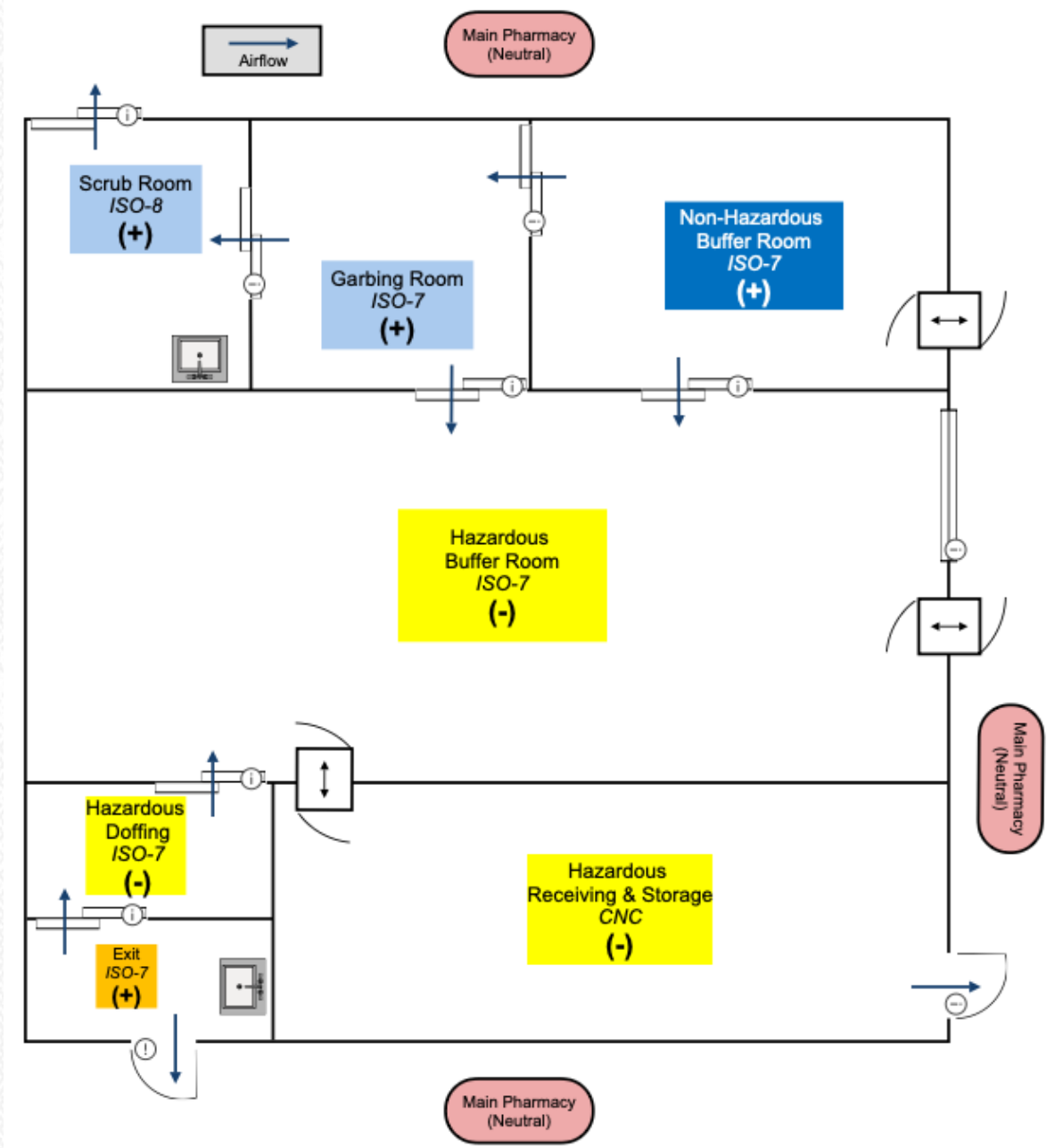
Advanced Hazardous Cleanroom Design



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Thinking Beyond the Standard

- 2-Level Ante Room
  - Hand-Hygiene/Scrub Room/Wet Room
  - Garbing/Garbing Room
- Cascading Pressure Gradients
  - Environmental Monitoring & Cleanliness
- Advanced PPE Containment
  - Doffing Room

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Closed-System Transfer Device (CSTD) Process Validation

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Validation of CSTDs

Validation is the **collection and evaluation** of data which establishes scientific evidence that a process is capable of **consistently delivering** quality product *throughout* the product lifecycle.

Validation/Qualification Over-Simplified

Performance Comparisons

The alternative method is tested against the standard method to prove it is noninferior in producing the desired outcome.

Repeatability & Reproducibility

The alternative should consistently deliver similar results under the same conditions (repeatability) and under different conditions (reproducibility).

Accuracy & Precision

The alternative method should provide results that are both accurate and precise, meaning they closely match the true value and yield minimal variation over repeated tests.

Specificity & Sensitivity

The method must accurately identify positives (specificity) and negatives (sensitivity).

Recent CSTD Literature

- The **proper implementation** of CSTD syringe adaptors was beneficial for reducing cytotoxic drug exposure to nurses administering intravenous syringes.
- When **appropriately designed and used**, CSTDs offer enhanced protection against potentially hazardous exposures to healthcare workers during the compounding and administration of hazardous drugs.
- Our teams were **trained to operate this novel device correctly** during the compounding process to avoid technical problems caused by human factors. The safety of CSTDs helped pharmacists to modify perception, which not only increased the degree of satisfaction but also improved the effectiveness of the operation.

CSTDs Validation

Performance Comparisons (CSTDs)

Closed-system transfer devices are tested against traditional needle compounding to show it is noninferior or superior in reducing HD residue.

Repeatability & Reproducibility (CSTDs)

Closed-system transfer devices should consistently deliver similar results under the same conditions (repeatability) and under different conditions (reproducibility–different vial sizes, for example).

Accuracy & Precision (CSTDs & HD Residue Sampling)

Closed-system transfer devices should provide results that are both accurate and precise, meaning they closely match the true value (accuracy – relative concentration of residue) and yield minimal variation (range is within acceptance) over repeated tests.

Specificity & Sensitivity (CSTDs & HD Residue Sampling)

HD wipe residue capture while using CSTDs must accurately identify positives (specificity – appropriate samples are accepted) and negatives (sensitivity – inappropriate samples are rejected).

But What about CSTDs Extending USP <797> BUDs?

European Journal of ONCOLOGY PHARMACY

USP <797> FAQ

43. Is the use of dispensing pins allowed per <797>?

The **chapter does not address the use of specific disposable supply items** other than to say supplies in direct contact with the CSP must be sterile and depyrogenated. It is the **responsibility of the facility to determine the appropriateness of specific items**, including dispensing pins.

"Evaluation of long-term prevention of microbiological contamination of sterile preparations in a controlled ISO class 5 environment and an uncontrolled environment using a closed-system drug transfer device"

This study showed that the **tested CSTD** safeguards the microbiological sterility of drug preparations for up to 4 weeks, even if manipulations are performed under conditions of high bioburden, as long as **a state-of-the-art preparation technique** and the device's operating instructions are **strictly observed.**

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Terkola, Robert MSc, PhD, aHPh; Pietrzak, Chiara N. J. Nebel, Alexander S. BSc Evaluation of long-term prevention of microbiological contamination of sterile preparations in a controlled ISO class 5 environment and an uncontrolled environment using a closed-system drug transfer device. The European Journal of Oncology Pharmacy 8(1):e00059, January-March 2025.

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But What about CSTDs Extending USP <797> BUDs?

The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited as long as they are **noninferior** to those described herein and ***validated*** for the intended purpose (e.g., *Validation of Alternative Microbiological Methods <1223> and Validation of Compendial Procedures <1225>).*

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United States Pharmacopeia (2024). *General Chapter, ⟨797⟩ Pharmaceutical Compounding—Sterile Preparations*. USP-NF. Rockville, MD: United States Pharmacopeia.

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Thoughts on what it may take …

Environmental Controls & Monitoring

- Proper disinfecting and transfer of materials into the SEC and PEC are imperative
- Robust air and surface viable particle sampling program

Compounding Process Qualification

- Manual Compounding Qualification (Media Fill Simulations)
- Continual process of removing aliquots for incubation

Garbing Qualification

- Choice of garbing style and/or material
- Enhanced garbing competency sampling program

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The Hard Pill to Swallow?

Process Validation at its core is **not just a snapshot in time, but an ongoing method to facilitate continual improvement.** For compounders that do not have any experience with process validation, consider reviewing *USP <1223> "Validation of Alternative Microbiological Methods"* to see the rigor of such processes.

It is unlikely that most compounders have the experience or knowledge to perform these tasks independently and should consider utilizing appropriate subject matter experts that can also independently verify the validation plan.

Key Takeaways

- Developing and maintaining dynamic Assessments of Risk for HDs is a pain point that could be possibly eased with AI using available databases and language models
- Cleanroom design for compounding HDs should focus on processes that increase personnel efficiencies, decrease particulate generation, enhance workflow/product movement and improve containment of trace contamination of PPE with advanced engineering controls
- Process validation of CSTDs for decreasing residue generation and/or extending BUDs is an emerging area of focus but is very complex and likely beyond the expertise of most compounders

Thank you for joining us for Cleanovators!

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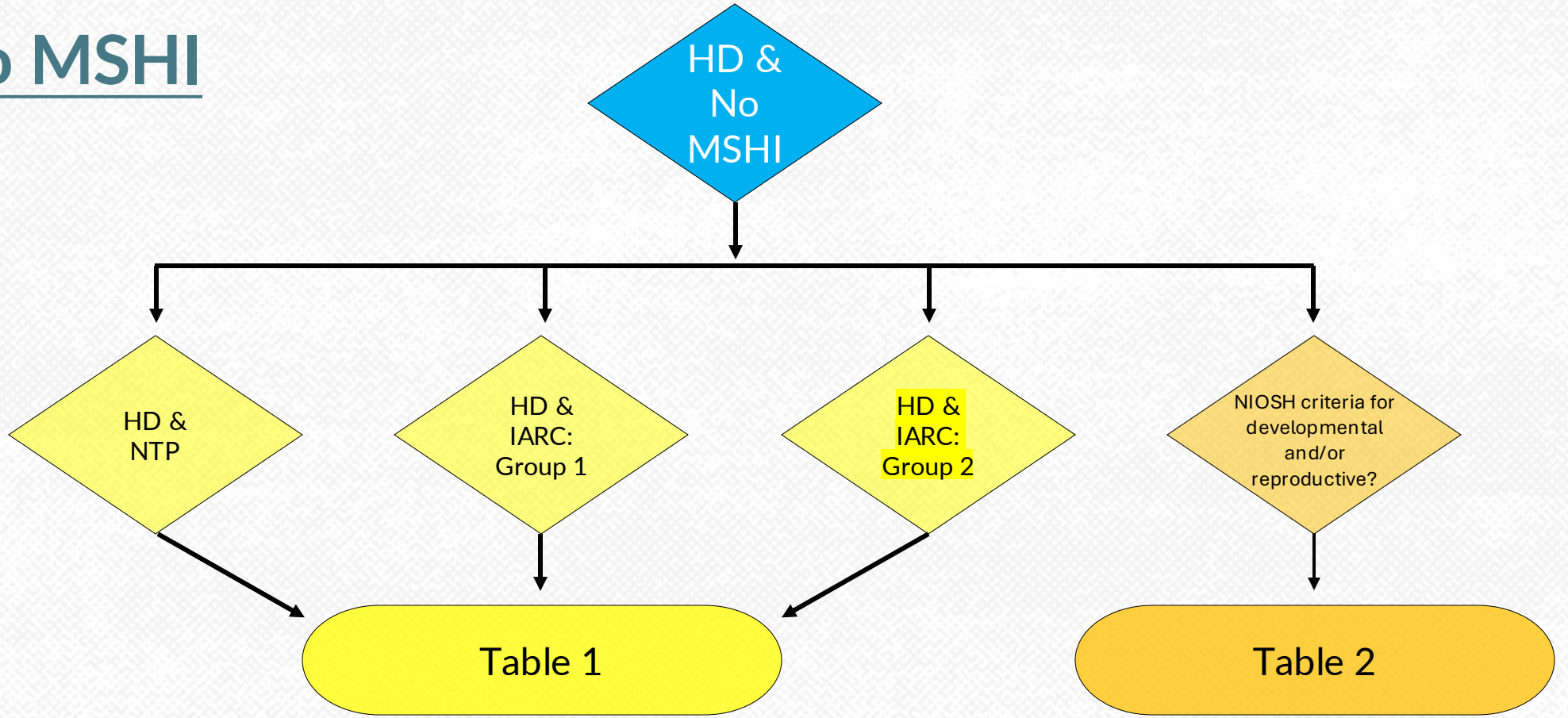
No MSHI



NIOSH Table 1 HD (No MSHI)

Drugs that meet the NIOSH definition of a hazardous drug and do not contain MSHI in their approved labeling but meet one or more of the following criteria: classified by NTP as a "known to be a human carcinogen" or classified by IARC: Group1, "carcinogenic to humans" or IARC: Group 2, "probably carcinogenic to humans"

NIOSH Table 2 HD (No MSHI)

Drugs that meet the NIOSH definition of a hazardous drug and do **not** contain MSHI in their approved labeling, **not** classified by NTP as a "known to be a human carcinogen" **nor** classified by IARC: Group1, "carcinogenic to humans" **nor** IARC: Group 2, "probably carcinogenic to humans"

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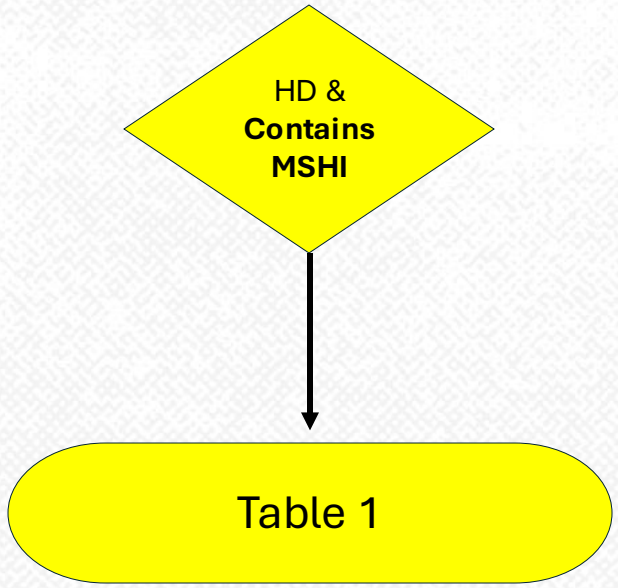
Contains MSHI



NIOSH Table 1 HD (No MSHI)

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