INTERNATIONAL
IV NUTRITIONAL THERAPY
GLOBAL PHYSICIAN EDUCATION

Compounding and USP/FDA 2018 Updates

Virginia Osborne ND, Paul Anderson, ND and Brenden Cochran ND

2018– Advanced IV Therapies

FDA and USP Rules Updates for Clinicians

An extensively referenced and edited PDF containing all the detail is too large to include in this presentation

It is available in the handout section of the notes.

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm606881.htm

Frequently Asked Questions:

- **Can I use anything for “office use” anymore?**
- Any non-compounded medication (currently) can be used, and in *some states the patient specific rule is not currently enforced by the Board of Pharmacy or Department of health.

* Check with your state pharmacy board

Frequently Asked Questions:

- **What is the "patient specific" rule and does it apply to all prescription products now?**
- It essentially states that a pharmacy can still offer a compounded prescription on physician order if it is specific to a patient and then the compounding pharmacy will not be considered a manufacturer for regulatory purposes. It renders that prescription specific to the patient it was compounded for.

Patient Specific Prescriptions

- Some States currently require patient specific prescriptions for all compounded medications. Some do not, but will soon. The following is a statement amalgamated from three pharmacy experts who all agreed to give input to the genesis of this rule (and the variations of it we see):
- 'The FDA decided that if compounding pharmacies process all orders as “patient specific” prescriptions the FDA will chose not to evaluate compounding pharmacies as manufacturers. Office Use is still on the books in California and some other states, but even the Board of Pharmacy supports the patient specific requirement.'

Frequently Asked Questions:

- **What are the rules for single and multi-dose sterile vials?**
- These have not changed:
  - 28 day use for multi-dose
  - Single use for single-dose product – with some qualifications noted in the main PDF document.

Frequently Asked Questions:

- **What rules apply to me as a clinician and to my clinic as a facility?**
- Many apply. The attached document spells out as succinctly as possible the intersecting rules relating to clinical practice that are involved in compounded and manufactured prescription use, injections and other forms of medications and guidelines influenced by multiple Federal agencies.

An excellent question is "I am not a pharmacist or pharmacy, how can an FDA Pharmacy "Act" be applied to me as a Physician?"
USP Section 503A

The IACP* (see reference at the end of this quote) have reviewed the Act and rules and state: "503A applies to "Traditional Compounders" and extends to Pharmacist as well as Physician:

"If a "traditional compounder", defined as a licensed pharmacist or licensed physician, meets ALL conditions within Section 503A, the compounder is exempt from THREE sections within the Food, Drug, and Cosmetic Act;

(1) Section 501(a)(2) (concerning current good manufacturing practices); (2) Section 502(f)(1) (concerning labeling or drugs with adequate directions for use); and (3) Section 505 (concerning the approval of drugs under new drug applications or abbreviated new drug applications)."

*Independent Academy of Compounding Pharmacists

Frequently Asked Questions:

- **I went to a presentation a few years ago and they said my IV bags fit the "immediate use exemption" and therefore I did not need a hood?**
- Most of the immediate use exemption is no longer valid. A few items meet this, but not very many. In the main document a great deal of detail is given to this rule.

Frequently Asked Questions:

- **I have heard I need a clean room to make my syringes and IV bags. Is that true?**
- Possibly. The rules depend upon the “risk level” of what you are making. Simple compounds may not require this and many commonly compounded injections and IV’s will. This is a bit complex but a great deal of information in regard to this is contained in the main document.

Frequently Asked Questions:

- **I have a “fume hood” already, can I use that?**
- If it is really a fume hood then no. Those hoods are used to prepare or manipulate dangerous products and exhaust the workspace air out of the building. The laminar flow hoods for compounding move purified air through the workspace and out of the hood, increasing sterility in the workspace.

What are the rules for use of the hood and the room it is in?

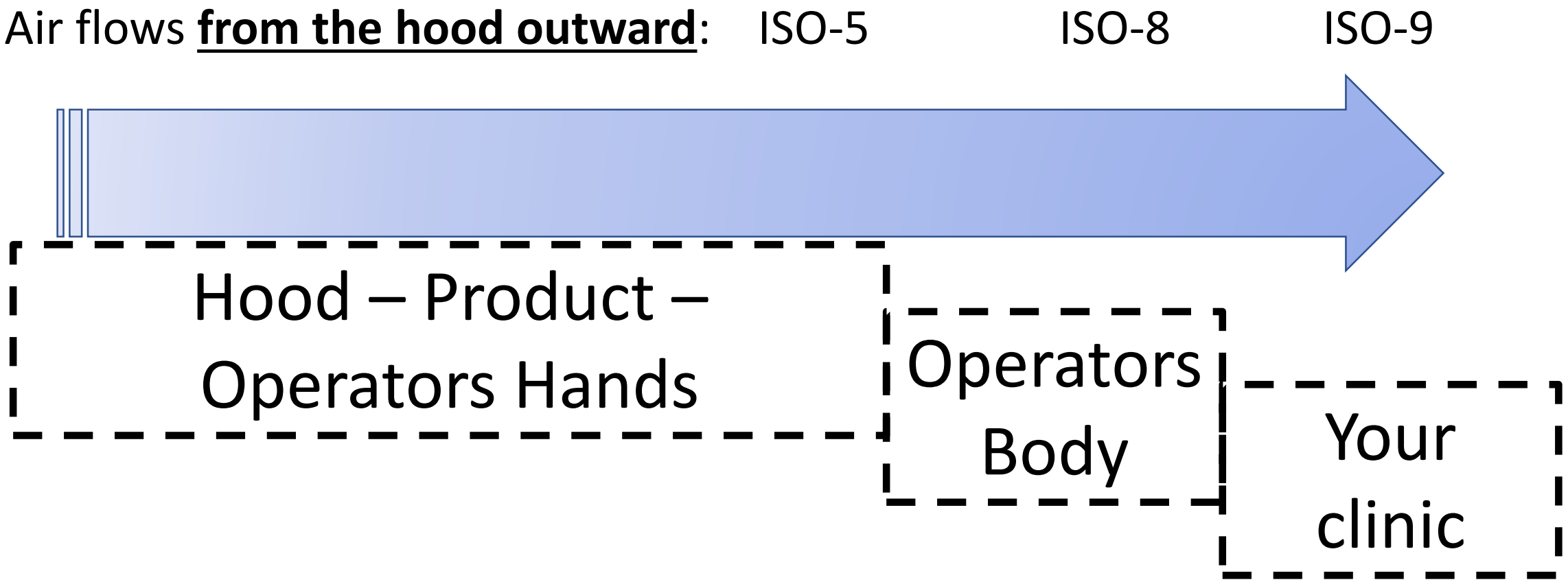
First, the environment created in order to maintain a cleanroom environment is based on positive pressure.

Cleanrooms are designed to maintain positive pressure, preventing "unclean" (contaminated) air from flowing inside and less-clean air from flowing into clean areas. The idea is to ensure that filtered air always flows from cleanest to less-clean spaces.

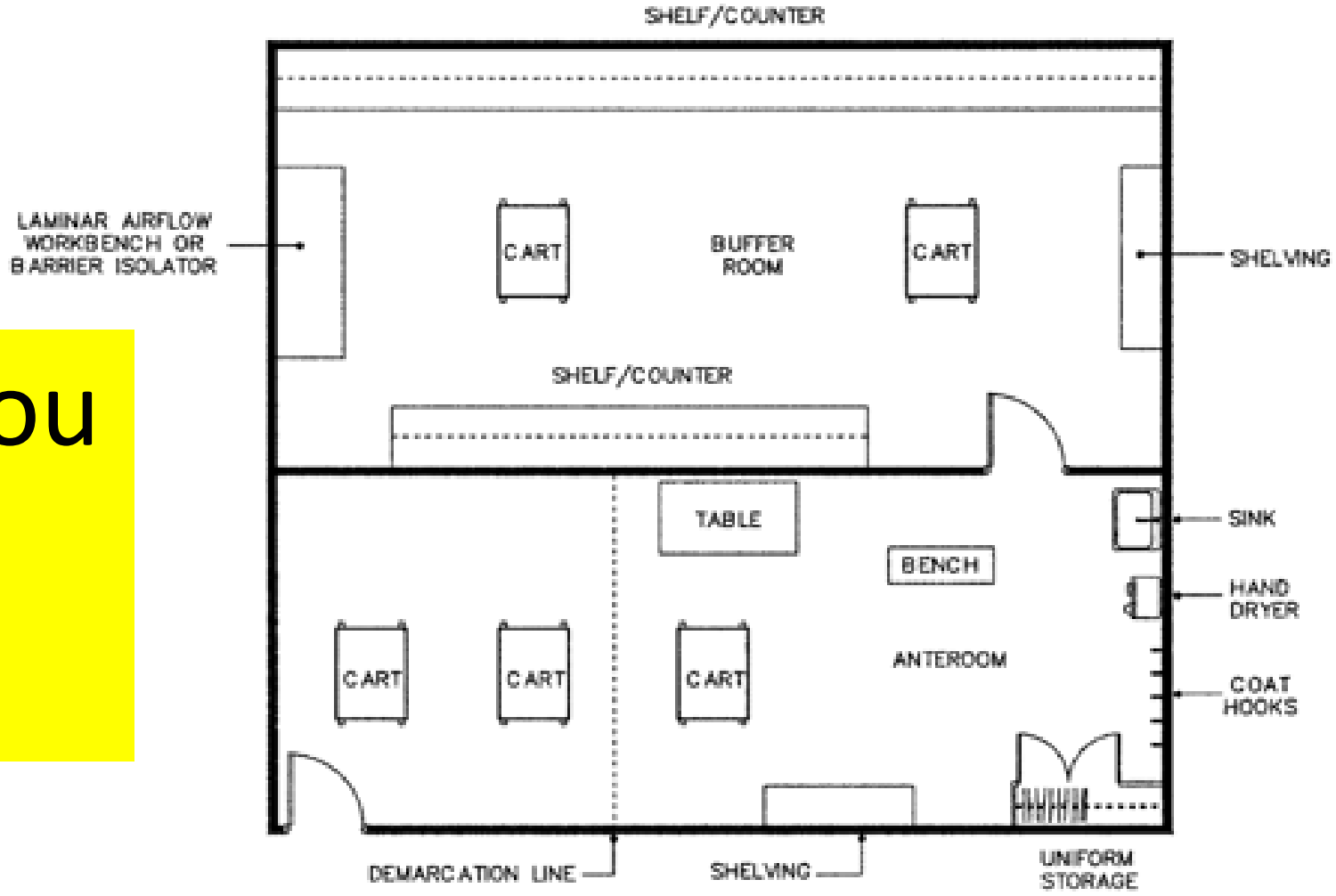
In a multi-chambered cleanroom, for instance, the cleanest room is kept at the highest pressure. Pressure levels are set so that the cleanest air flows into spaces with less-clean air. Thus, multiple pressure levels may need to be maintained.

*Practically speaking this is generated from the hood outward to the ante or buffer area. In the Low and Medium risk environment this can be the hood in an appropriate room with the hood pressure being highest, the room that houses the hood being next highest pressure and the remainder of the clinic being at lower pressure.

The Low to Medium Risk Product Compounding area has three environments to meet current criteria; ISO Class-5 (the hood), ISO Class-8 (the buffer or ante area) and ISO Class-9 “room air” (the rest of the lab or clinic)

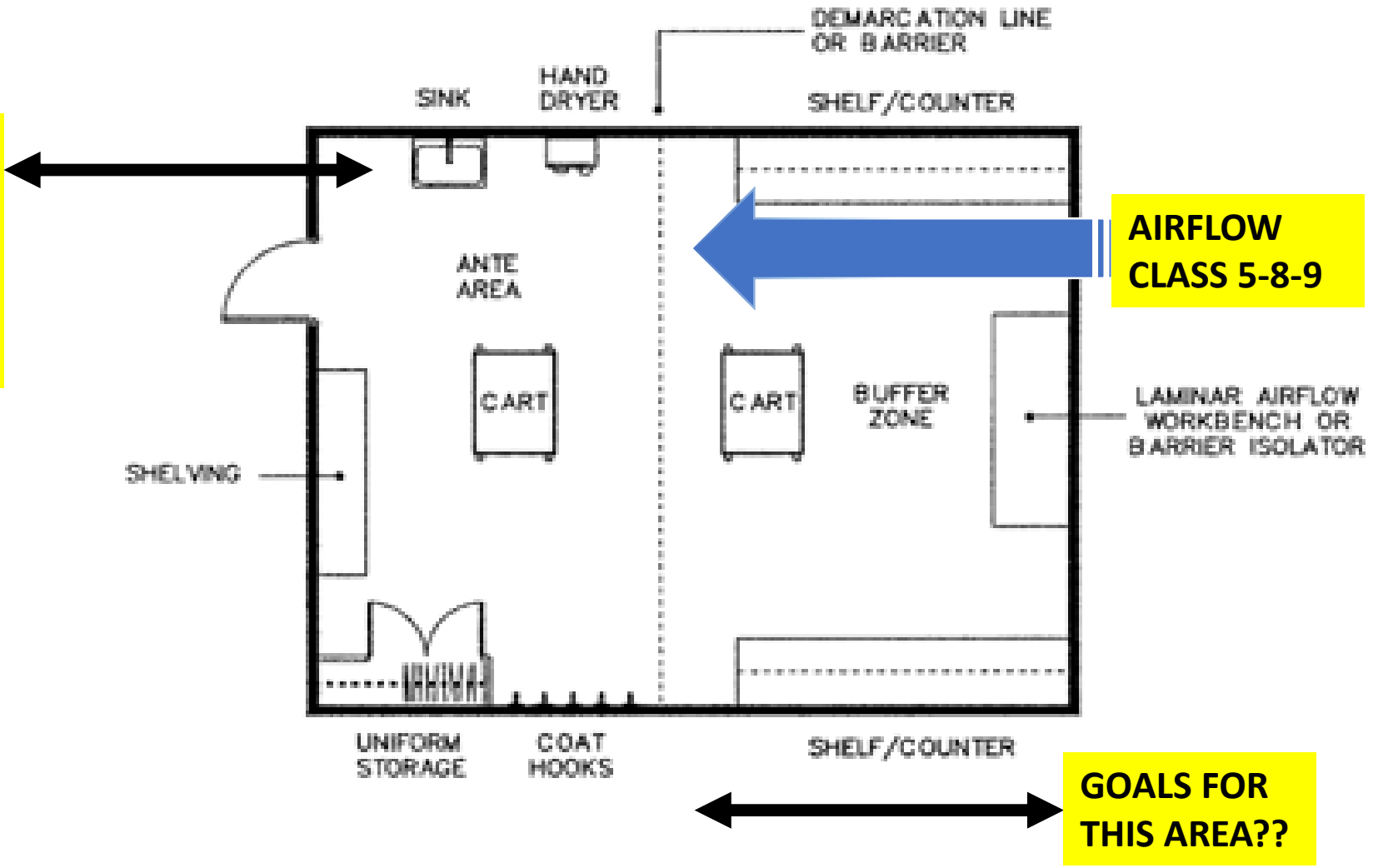


EXAMPLE OF CLEAN ROOM FLOOR PLAN SUITABLE FOR HIGH RISK-LEVEL CSPs



Do you need this?

EXAMPLE OF CLEAN ROOM FLOOR PLAN SUITABLE FOR LOW AND MEDIUM RISK-LEVEL CSPs



Why are these things out here?

AIRFLOW CLASS 5-8-9

GOALS FOR THIS AREA??

Do I need to perform batch sterility testing on the products I compound?

- Not unless you intend to store them longer than the above referenced “BUD”:

“Facilities that wish to store CSPs for periods longer than those described above must complete sterility testing for each batch to determine the extended BUD. Each batch of any risk-level CSP intended for storage outside the limits described above must be tested for sterility, according to the requirements of USP chapter 71, Sterility Tests.”

What are the rules that keep you in compliance with 503A as to the use of the hood?

These are the areas you need to attend to in order to comply.

<u>They are spelled out and referenced in the official document PDF:</u>

- Hood maintenance and inspection:
- Quality Assurance Program - Must have formal audit program which:
- USP 797 Guidelines - Minimum Requirements for Validation - Low to Medium Risk:
- Some things that should routinely be done as you are preparing CSPs:

Frequently Asked Questions:

- **Why did my pharmacy say the IV bag had a “9 day beyond use date” and in my recent IV class they told us to use the IV the same day it was made?**
- This is mixing the technical “use by date” the FDA and USP give a particular product with the pharmacologic stability of the compound. A great deal of information is given in the main document outlining this confusing issue.

How long can I keep a syringe or IV bag after making it?

This answer has two very important parts which will be outlined below:

1: BUD requirements for sterile compounds

2: Pharmacological stability of the constituents in the syringe or IV bag

- The problem with a specific answer is that it cannot exclude one or the other of these factors, and many times the advice given does just that. The maximum time is defined by the level of risk the compound carries but that time may be shortened by chemical and pharmacologic stability factors.

Beyond-use dating for CSPs according to Risk-Level

Risk Level	BUD at Room Temperature (20to 25° C)	BUD under Refrigeration (2° to 8° C)	BUD with Frozen Storage (-25 to -10° C)
Immediate Use	1 hour	N/A	N/A
Low Risk with 12h BUD	12 hours	12 hours	N/A
Low Risk	48 hours	14 days	45 days
Medium Risk	30 hours	9 days	45 days
High Risk	24 hours	3 days	45 days

1A. Immediate use:

- Unlike the other risk levels of CSPs, an ISO Class 5 environment is NOT required for immediate-use preparations. Immediate-use preparations are for emergency use or immediate patient administration (i.e., cardiac or respiratory arrest situation, emergency room or operating room treatments, or any time where waiting for a low-risk prep would put the patient at risk of harm because of delays in treatment). Administration of immediate-use preps must commence within one hour or less from the start of preparation. (Otherwise, they should be discarded.) Only preparations that would otherwise be low-risk can be considered immediate use. [EXAMPLES ARE - No more than three packages of sterile product can be used, and not more than two entries into any one of the sterile containers or packages can be made.]

* Medium-risk and high-risk preps cannot be prepared as immediate use. Hazardous drugs may not be prepped as immediate use.

*A syringe or IV bag prepared with a total of three or less sterile products (which includes the IV Bag or Syringe) would fit this rule.

1B: Low-Risk CSPs for Use Within 12 Hours

- Under limited circumstances, sterile compounding may occur in a segregated compounding area (such as a satellite pharmacy or dedicated sterile compounding space) in which the ISO Class 5 PEC is not located within an ISO Class 7 or 8 buffer area. A segregated compounding area is a designated space, either a demarcated area or room, in which compounding is restricted to preparing low-risk, nonhazardous CSPs with a beyond-use time of no more than 12 hours from the time of preparation. All other requirements for low-risk CSPs must be followed, with the exception that the ISO Class 5 PEC is not required to be located within an ISO Class 7 buffer area. The PEC must be separate from other operations, including sinks and other water sources or drains, and away from unsealed windows or doors that connect to high traffic areas, construction, warehouses, or food preparation areas. Distinct labeling for conveying short BUDs should be considered.

* Only syringes or IV bags prepared with a total of three or less sterile products would fit this rule.

1C: Low-risk CSPs

Low-risk CSPs must be compounded in an ISO Class 5 air quality environment or better, from sterile ingredients, products, components, and devices. No more than three packages of sterile product can be used, and not more than two entries into any one of the sterile containers or packages can be made.

* Only syringes or IV bags prepared with a total of three or less sterile products would fit this rule.

FOR LOW RISK USE (1 "A, B & C" ABOVE) COMMON EXAMPLES INCLUDE:

- *A syringe with one or two injection products added (The syringe counts as one sterile product)*
- *An IV bag with one or two injection products added (The IV bag, filled or not, counts as one sterile product.)*

1D: Medium-risk preparations

Medium-risk preparations are compounded under the same conditions as low-risk preps, with any one or more of the following conditions:

- Multiple individual or small doses of sterile products are combined or pooled to make a prep that will be administered to multiple patients or to one patient on multiple occasions
- Manipulations other than a single volume transfer are involved
- Unusually long duration of compounding process is involved

MEDIUM RISK EXAMPLES INCLUDE:

- *A syringe with three or more added injection products*
- *Any IV bag with three or more additives*

1E: High risk

High risk: A high-risk sterile preparation is one where a non-sterile product is included, so that the prep has to be sterilized. Sterilization usually involves the use of filtering with a 0.2 or 0.22 micron filter within an ISO Class 5 environment. Filters of this size can remove very small particles, like bacteria. Steam and dry heat are other mechanisms of sterilization.

MOST all clinical compounding does NOT fall under High Risk.

Do I need to comply with 503B, and what is it? A 503B Facility is an Outsourcing Facility

"The new law allows an entity that compounds sterile drugs to register as an outsourcing facility. Once registered, an outsourcing facility must meet certain conditions in order to be exempt from the FDCA's approval requirements and the requirement to label products with adequate directions for use. Under the new law, the drugs must be compounded in compliance with CGMP by or under the direct supervision of a licensed pharmacist in a registered facility (section 503B(a)). The outsourcing facility must also report specific information about the products that it compounds, including a list of all of the products it compounded during the previous six months, and information about the compounded products, such as the source of the ingredients used to compound (section 503B(3)). In addition, the outsourcing facility must meet other conditions described in the new law, including reporting adverse events and labeling its compounded products with certain information (section 503B(b)(5) and section 503B(a)(10))."

Compounding > Information for Outsourcing Facilities - FDA

https://www.fda.gov/drugs/.../pharmacycompounding/ucm393571.htm

Frequently Asked Questions:

- **Can I just ignore all these rule changes? What would happen anyway?**
- It would be best to learn the rules and comply the best way you can. Should an inspection happen or an adverse event occur the burden of compliance would be immediately on the practitioner and clinic.

Thanks