Sterile Drug Production Practices: *USP* <797> vs. CGMPs

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Summary of Presentation

- Fundamentals
- Facility design and qualification
- Environmental and personnel monitoring
- Equipment, containers and closures
- Components
- Production and process controls
- Laboratory control
- Beyond-use/expiration dating
- Quality assurance

Drug Quality Attributes

- For injectables
  - **Sterility**
  - Endotoxin
  - Identity
  - Strength (a.k.a. Potency)
  - Purity
  - Other, for example:
    - Content uniformity
    - Anti-microbial effectiveness (if multiple dose container)

Drug Quality Assurance

- Drug quality is built into the drug by paying attention to facility design and production process.
- Drug quality cannot be tested into the product.
  - Vast majority of all drug analytical testing is destructive.
  - Quality of non-tested units is inferred by test results, but not confirmed.
  - The ability of the test to infer quality of the non-tested unit is also dependent upon the quality attribute under assessment.

Sterility Tests

- *USP* <71> - *Sterility Tests*
  - Most commonly used and best understood
  - Detection method is based upon microbial proliferation

"These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures." – from *USP <71>*

Sterility Test Hypothetical

- 100 mL stock solution of drug X is prepared to produce a batch of 100, 1-mL vials.
- There is a breach in aseptic processing during production and, unknowingly, 10 colony-forming units (CFUs) are introduced into stock solution before filling into vials.

Hypothetical

- If *USP* <71> sampling requirements are followed, 10 of 100 vials would undergo sterility tests.
- Statistically, even if you assume that the contamination is concentrated in the 10 vials tested at 1 CFU per vial, there's a 15% probability that the vials you pick will not be contaminated

Sterility Test Limitation

- Microbial contamination is highly unlikely to be equally distributed throughout the stock solution and actual distribution is unknown.
- In addition, no guarantees that all 10 CFUs will proliferate during sterility testing.
  - Some may be viable, but not cultivatable (VBNC).
- **Under actual testing conditions, probability of false negative is:**
  - **Higher than simple statistics would estimate and**
  - **Not calculable**.
- Ability of sterility test to detect contamination also decreases if:
  - Less than required (as per *USP* <71>) sample number is used
  - Drug formulation inherently inhibits microbial growth and no modification made in sample preparation to address

Sterility Test – Summary

- If contamination is identified, you have been alerted and can withhold lot. However:
- Ability of sterility tests to detect contamination is dependent upon:
  - Degree of microbial contamination (bioburden), which is unknown
  - Distribution of contamination through batch, which is unknown
  - Percentage of VBNC microbes, which is unknown
  - Number of samples taken from batch

Sterility Assurance

Potential sources of microbial contamination:

- Air
- Water
- Equipment and supplies
- Drug components
  - Drug substances
  - Excipients
  - Container & Closures
- Personnel

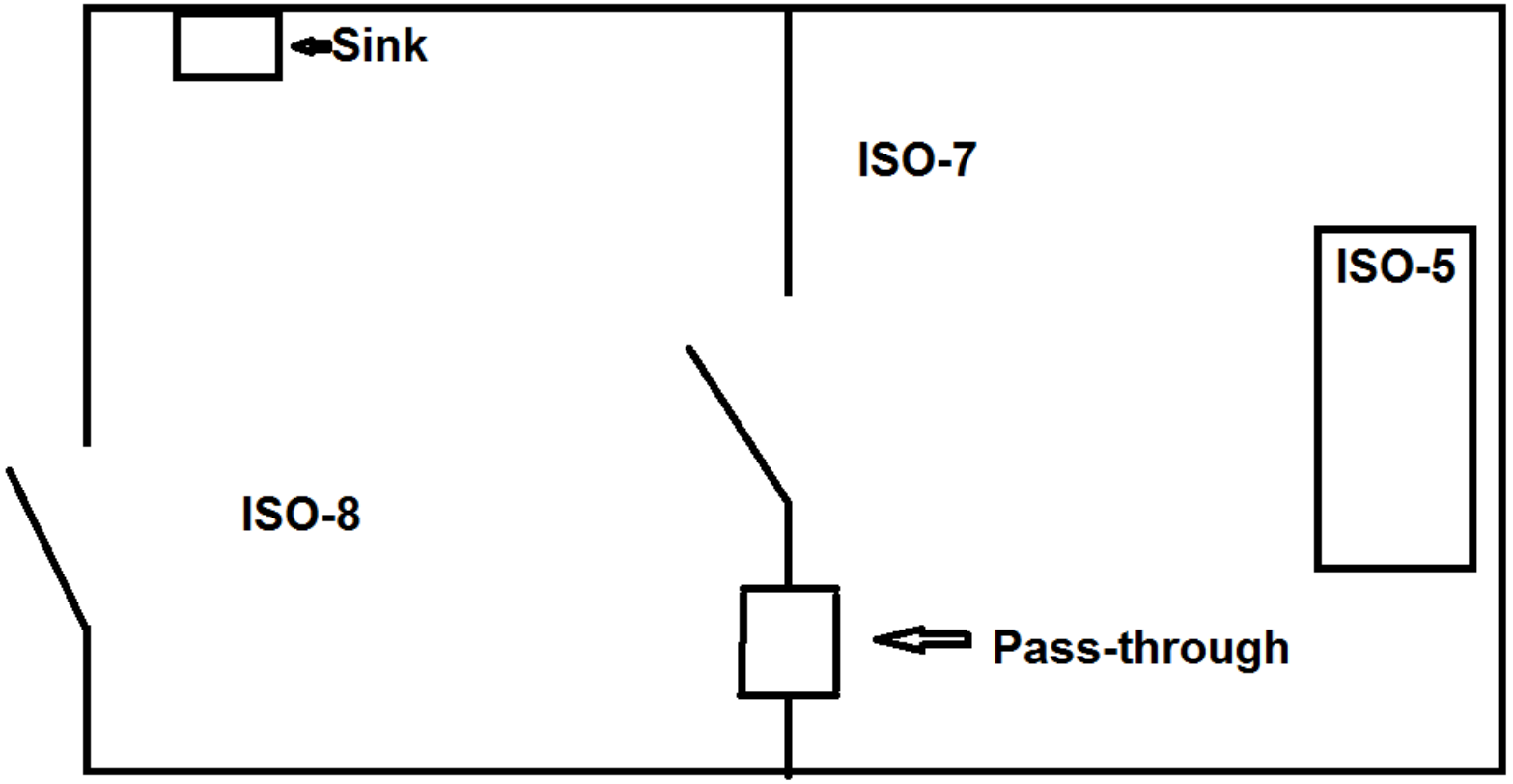
Facility Design

- “Normal” air contains numerous suspended particles.
- Suspended particles contain unknown numbers of microbes adhering to particle surfaces.
- Design of firm must include built-in features that remove and control number of air particles in aseptic processing areas.

Air Cleanliness

- International Organization for Standardization (ISO) air cleanliness standards:
  - ISO-5: 3,520 particles of 0.5 µm/m^3
  - ISO-7: 352,000 particles of 0.5 µm/m^3
  - ISO-8: 3,520,000 particles of 0.5 µm/m^3
- Air cleanliness within a defined space is brought about by “high-efficiency particulate arrestance” (HEPA) filters incorporated at key location within a firm’s “heating, ventilation, and air-conditioning” (HVAC) system.

Basic Facility Design – Pharmacy



Qualification of ISO-5

<797>	Proposed <797>	CGMP
Meet ISO-5 particle count		
Yes	Yes	Yes
Frequency of monitoring/test		
6 months	6 months	Continuously during production
Conditions of Test		
Dynamic	Dynamic	Dynamic

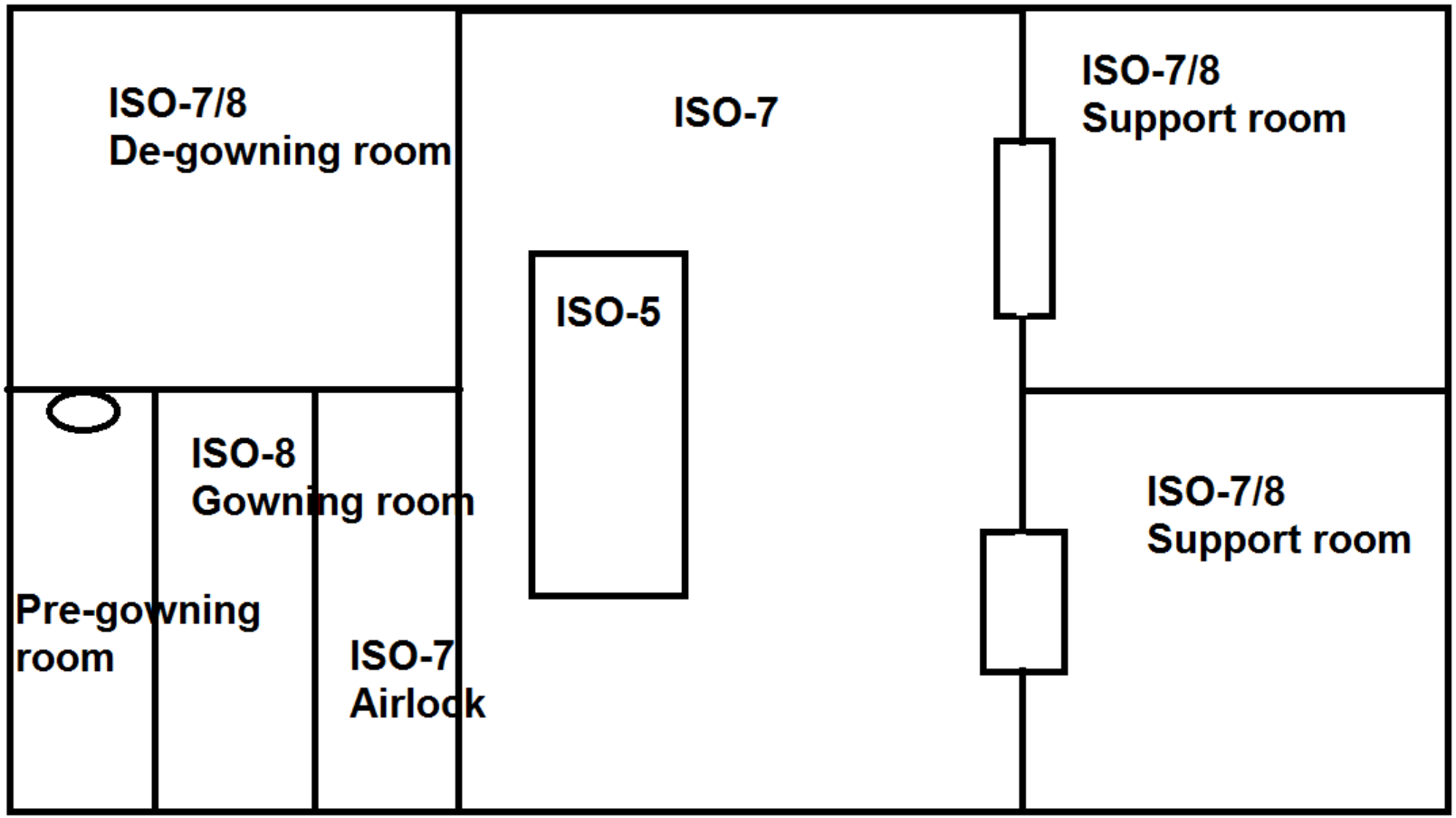
Qualification of ISO-5

<797>	Proposed <797>	CGMP
Demonstration of uni-directional air flow		
Yes	Yes	Yes
Conditions of test		
Dynamic	Dynamic	Dynamic

Qualification of ISO-7 & 8

<797>	Proposed <797>	CGMP
Meet ISO-7/8 particle count		
Yes	Yes	Yes
Frequency of monitoring/test		
6 months	6 months	Continuously during operations
Conditions of test		
Dynamic	Dynamic	Dynamic
Demonstration of air-flow through and out of rooms		
Not addressed	Not addressed	Recommended

Design – Conventional Manufacturer



Environmental Monitoring Frequency

<797>	Proposed <797>	CGMP
Particle count (a.k.a. "non-viable air")		
6 months	6 months	Continuously during operation
Viable air particle		
6 months	1 month	Continuously during operation
	Surfaces	
6 months	1 month	Multiple times during operation
Pressure differentials between rooms		
Daily before production	Daily before production	Continuously during operation

Personnel Monitoring

<797>	Proposed <797>	CGMP
Frequency		
6 months	3 months	Multiple times during operations
Area sampled		
Gloved fingertips only	Gloved fingertips only	Gloved fingertips plus other, select areas of gown.

Equipment, Containers and Closures

<797>	Proposed <797>	CGMP
Routine calibration of "measuring" equipment		
Implied	Implied	Explicitly required
Ability of container-closures to maintain sterility		
Assumed	Assumed	Required to be demonstrated

Components

<797>	Proposed <797>	CGMP
Acceptance of incoming drug components		
Review of COA	Review of COA	Review of COA plus confirmatory testing
Determination of bioburden/endotoxin of incoming non-sterile ingredients		
Not required	Not required	Required

Production and Process Controls - Gowning

<797>	Proposed <797>	CGMP
Required sterile gowning items		
Gloves, only	Gloves and sleeve covers, only	Gloves and all other gowning items
Exposed skin?		
Neck, checks, eyes, and forehead allowed. Wrist skin not allowed.	Neck, checks, eyes, and forehead allowed. Wrist skin not allowed.	None allowed
Reuse of gowning items?		
Gloves and mask, no. All others, yes, if gloves/mask stored in ISO-8 anteroom.	Gloves, sleeve and mask, no. If other items sterile when first donned, then no. If other items were non-sterile when donned, then yes if stored in ISO-8	No

Production and Process Control – Sterilization and Maintenance of Sterility

<797>	Proposed <797>	CGMP
Filter sterilization		
Acceptance of filter based upon certificate of suitability alone	Acceptance of filter based upon certificate of suitability alone	Need to confirm suitability of filter with actual product
Terminal sterilization		
Process verified (no qualification of equipment required)	Process verified (no qualification of equipment required)	Process validated and includes qualification of equipment
Aseptic media fill simulation		
"most challenging and stressful conditions" – no guidance given	"most difficult and challenging…conditions" – guidance given	Simulate actual process

Production and Process Control – Cleaning and Disinfecting

<797>	Proposed <797>	CGMP
Use of sterile cleaning and disinfecting agents/aids		
Isopropanol required to be sterile, silent on all other agents/aids	All agents/aids required to be sterile	All agents/aids required to be sterile
Routine use of sporicidal agents		
Recommended if EM data indicates presence of spore-forming microbes	Required (weekly)	Required (weekly recommended)
Disinfecting agent efficacy studies		
Not required	Not required	Required

Release/finished Product Testing

<797>	Proposed <797>	CGMP
Sterility Tests		
Not required, if default storage times (BUDs) are assigned	Not required, if default storage times (BUDs) are assigned	Required
Endotoxin Test		
Required only for CSPs made from non-sterile ingredient(s) and batch sizes of 26^{+} units	Required only for Category 2 CSPs made from non-sterile ingredient(s). Elimination of batch size requirement	Required
Strength (potency) and other quality attribute tests		
Not required	Not required	Required

Laboratory Controls

<797>	Proposed <797>	CGMP
<u>Sterility and Endotoxin Tests</u>		
Compliance with *USP* <71> and <85> *Bacterial Endotoxin Testing* implied	Compliance with *USP* <71> and <85> *Bacterial Endotoxin Testing* explicit	If <71> and <85> are used, then must comply with stated requirements. If alternative methods are used, methods must be fully validated.

Beyond-use/expiration Dating

<797>	Proposed <797>	CGMP
Performance of stability tests		
Not required, reliance on published literature	Required only for anti-microbial agent, if present. Otherwise, from published literature.	Required
BUD/Expiry limits		
Can be based solely upon published literature, no upper limits placed on BUDs	Upper limits placed on BUDs due to lesser sterility assurance compared to CGMP-compliant firms	Expiration date must be supported by comprehensive stability studies

Quality Assurance

<797>	Proposed <797>	CGMP
Sterility and other quality failures – investigations		
Recommended, not required. Silent regarding need to consider impact of failure on other products	Required. Investigation must be comprehensive and consider the impact of failure on other products	Required. Investigation must be comprehensive and consider the impact of failure on other products

Questions?

Inter-governmental Working Meeting on Drug Compounding and DSCSA

U.S. Food and Drug Administration
Silver Spring, Maryland

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