

# NewsLetter

Biotech/Pharmaceutical

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## PROCESSING OF TOXIC OR POTENT APIs WITH ISOLATION TECHNOLOGY - PS&S Process Engineering Group

Isolation technology in processing of toxic or potent Active Pharmaceutical Ingredients (API) is gaining increasing consideration in the pharmaceutical industry. Whether used to prevent contamination during aseptic operation or to protect operating personnel from exposure, this technology is capable of accommodating production in a cGMP environment.

Pharmaceutical Actives are classified into five hazard categories of Performance-Based Occupational Exposure Limit (PB-OEL), see table below. Some of the design issues are:

- People and material flow design
- Means for raw material and product transfer in and out of isolator system
- Operator protection
- Cleaning and sterilization of equipment and isolators
- Environmental protection of the containment suite
- Ergonomics
- Waste disposal

PS&S has just completed a facility design for filling a liquid potent and sterile product with provision for future lyophilization. Important issues to deal with in any such project include:

**The Core Design Team** must be given full participation by the owner's project manager and operating personnel in the development of detail design scope. The owner's industrial hygiene and safety group should identify safeguards to incorporate in the detailed design phase. The design team should also conduct a validation review prior to ordering isolators and associated cleaning and sterilizing systems.

### Architectural

Programming of space should incorporate adequate circulation for process containment and separation from the existing facility. People, material and waste flow should be unidirectional and avoid cross contamination. Clean and exit corridors should isolate the processing space. Loading and unloading of the isolators must be considered in creating a layout. Airlocks for exits and degown should have misting stalls. The owner should prepare a User Requirement Specification (URS) document. The design should follow the URS very closely and specify vendor equipment to meet the needs of the owner's process.

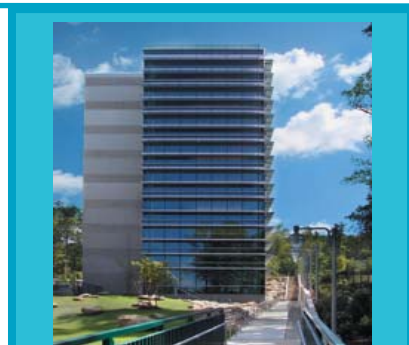
### Process

The process equipment is designed based on the PB-OEL level and the process solution solvent (aqueous or hydrocarbon). The design must specify the type of internal environment for the isolator. The isolators must be cleaned after each operation by an automatic Clean-in-Place (CIP) System. All items loaded into the isolator must be pre-sterilized; vaporized hydrogen peroxide is used to sterilize the isolators. Rapid Transfer Ports (RTP) are utilized for loading and unloading isolators.

### Mechanical

A dedicated single pass HVAC system may be required to eliminate the possibility of adjacent area contamination. This system utilizes 100% outside air, which is HEPA filtered on intake and again on exhaust to the outside. The need for a single pass system should be analyzed early in the project based on product criteria provided by the owner. The design must establish the requirements for pressure in the airlocks based on separation and cleanliness requirements.

*continued on page 3*



### PS&S... Not Just Biotech/Pharma

PS&S received an Award of Merit from New York Construction for the design of a new dormitory at Ramapo College of New Jersey.

The eight story, state of the art, \$20 million student living center was completed on budget and on schedule, in 18 months, on a very challenging site. This compact pre-cast concrete and glass student living center maximizes energy efficiency, minimizes environmental impacts, and takes full advantage of the natural topographic beauty of the surroundings.

The site layout, floor plate, height and orientation were designed in response to the constraints of a steeply sloping site dominated by wetlands. PS&S provided technical guidance in wetlands delineation.

Orienting the building perpendicular to the slope avoided wetlands, minimized the acoustic impact of an adjacent interstate highway, provided good views from all student spaces, and located one end of the building as close as possible to the center of campus.

Responding to its solar orientation, the building has two distinct expressions, architectural pre-cast concrete with punched windows on the north elevation and an aluminum and glass curtain wall with sunshades on the south.

PS&S provided full architectural\* and engineering services, including site evaluation, site engineering, structural, mechanical and electrical design, survey and geotechnical investigation.

\*Architectural services provided by PS&S Architecture, P.C. or PS&S Engineering, P.C.

### PB-OEL Categories\*

|                  | PB-OEL Category                             | 1         | 2                | 3 (3A)         | 4 (3B)          | 5 (4) |
|------------------|---|-----------|------------------|----------------|-----------------|-------|
|                  | Exposure level ( $\mu\text{g}/\text{m}^3$ ) | 1000-5000 | 100-1000         | 1-100          | <1              | Nil   |
| <b>1. Active</b> | Potency (mg/day)                            | >100      | 10-100           | .1-10          | <0.1            | <0.1  |
| <b>2. Hazard</b> | Toxicity                                    | Non-toxic | Almost non-toxic | Slightly toxic | Toxic           | Toxic |
| <b>3. Others</b> | Carcinogenicity                             |           |                  |                | Potentially yes | Yes   |
|                  | Sensitivity                                 | Low       | Low-middle       | Middle         | Middle-high     | High  |

\*American Industrial Hygiene Association Journal

^Local affiliates.

# A COMPARISON OF EU, ISO, AND FDA GUIDELINES FOR ASEPTIC PROCESSING ENVIRONMENTS - J. ROGERS<sup>‡</sup>

The following is a review of the EU, ISO and FDA definitions for clean spaces and recommendations for environmental conditions, noting differences in the new FDA Aseptic Guideline.

In 1987, the FDA issued the "Guideline on Sterile Drug Products Produced by Aseptic Processing" (FDA 1987). One section was devoted to recommendations for the room environment of aseptic processing areas. "Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice" (FDA 2004), revised several of the recommendations for establishing and monitoring of room environment found in FDA 1987.

Both FDA 1987 and FDA 2004 include definitions for room cleanliness requirements in terms of particulate and microbiological contamination. FDA 1987 references Federal Standard 209B, "Clean Room and Work Station Requirements, Controlled Environment", (Fed Std 209) a U.S. standard issued in 1973 and subsequently revised several times. FDA 2004 instead references ISO Standard 14644-1, "Cleanrooms and Associated Controlled Environments, Classification of Air Cleanliness", issued by the International Organization for Standardization (ISO).

The European Union's (EU) most recent cGMP guidelines for aseptic processing are "Rules and Guidance for Pharmaceutical Manufacturers and Distributors, 2002", Annex 1, "Manufacture of Sterile Medicinal Products" (EU 2002). The edition most used by English speakers is the one published by the British Medicines Control Agency (MCA), fondly called the Orange Guide due to its cover color.

Table 1 compares cleanliness requirements for different aseptic processing areas under dynamic conditions:

| Room type                  | FDA 2004      | FDA 1987      | EU      | ISO     |
|----------------------------|---------------|---------------|---------|---------|
| Critical (open processing) | Class 100     | Class 100     | Grade A | Class 5 |
| Adjacent areas             | Class 10,000  | Class 100,000 | Grade B | Class 7 |
| Prep areas                 | Class 100,000 | Class 100,000 | Grade C | Class 8 |
| Wash areas                 | N/A           | N/A           | Grade D | N/A     |

FDA 1987 defined a Critical Area as "...one in which the sterilized dosage form, containers, and closures are exposed to the environment." This definition is similar in FDA 2004: "Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations..." should be Class 100 (ISO 5).

EU 2002 defines four grades of clean areas. Grade A has a definition similar to the FDA's Critical Area: "The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections."

FDA 1987 defined a Controlled Area as, "...where components are compounded, and

where components, in-process materials, drug products and drug product contact surfaces of equipment, containers, and closures, after final rinse of such surfaces, are exposed to the plant environment." FDA 2004 replaces this with a more general description of "Supporting Clean Areas" which have various functions serving to "...minimize the level of particle contaminants in the final product and control the microbiological content (bioburden) of articles and components that are subsequently sterilized." FDA 2004 then provides an important distinction between areas immediately adjacent to the Critical Area and other Supporting Clean Areas, recommending that "...the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 (ISO 7) standards...". This is similar to Grade A/Grade B areas described in EU 2002. FDA 2004 then goes on to provide an example of other Supporting Clean Areas: "An area classified at a Class 100,000 (ISO 8) air cleanliness level is appropriate for less critical activities (e.g., equipment cleaning)."

EU 2002 defines Grade B as "...the background environment for grade A zone." Grades C and D are: "Clean areas for carrying out less critical stages in the manufacture of sterile products."

EU 2002 differs from FDA 2004 in recommendations for room cleanliness. Both FDA 1987 and FDA 2004 provide recommended cleanliness levels for dynamic conditions, or when actual processing activities are taking place. The EU in "Rules and Guidance for Pharmaceutical Manufacturers 1993" introduced the concept of at-rest conditions, described as, "The conditions... achieved throughout the background environment where unmanned, and recovered after a short 'clean up' period." In fact, room cleanliness requirements for Grades B through D were given for the at-rest condition only. This produced great anxiety for U.S. manufacturers developing facilities with production slated for the European market as they tried to correlate the clean room design for at-rest recommendations with the clean room design they were used to for dynamic conditions. The EU came to the rescue in 1997, and continued in EU 2002, providing clarification by including the recommended cleanliness levels for both dynamic and at-rest conditions.

EU 2002 recommends no difference between dynamic and at-rest conditions for Grade A. For Grades B, C and D, cleaner conditions are required in the at-rest condition, with Grade D requiring an ISO 8 equivalent condition for at-rest but no limits for dynamic condition. The at-rest conditions are to be achieved after activity in the room has ceased, personnel have left the room, and a short time period allowed for the HVAC system to flush the room. EU 2002 recommends 15 to 20 minutes

for this short "clean-up" time period.

Table 2 compares particulate and microbiological limits between the FDA and EU guidelines and the ISO standard. Limits shown are for dynamic conditions; the limits for at-rest conditions from EU 2002 are also shown for comparison.

Note that FDA calls for 0.5µm size monitoring, but does not mention 5.0µm. Also, the FDA offers no equivalent for the EU 2002 Grade D. "Controlled environment" areas are often used by U.S. manufacturers for areas similar to Grade D areas, and sometimes these areas are referred to as Grade D. The concern here is that these controlled environment areas were often defined with no particulate or microbial contamination limits, whereas the Grade D classification requires such limits.

ISO 14644-1 cleanliness classifications are defined only in terms of the quantity and size of airborne particulate. It does not address microbial contamination, and therefore does not define limits for colony forming units.

Table 3 compares design criteria for airflow, air change rates, and pressurization presented in the guidelines and offered by the author as commonly used in the industry.

The table provides the absolute numbers engineers (and some architects) all love. FDA 2004 and EU 2002 are much less emphatic concerning these numbers; the emphasis is rather on defining the particular situation and developing the design most appropriate to that situation.

In FDA 1987, laminar flow air at 90 fpm +/- 20% was the recommended design for Class 100 areas, "...although higher velocities may be needed...". In FDA 2004 a more general approach is taken; unidirectional airflow is recommended, with "...velocity parameters established for each processing line ... justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within the critical area...". The recommended air velocity is now relegated to a footnote, 0.45 m/s (90 fpm) +/- 20%. The footnote also states: "Higher velocities may be appropriate..."

EU 2002 calls for laminar air flow with "...a homogenous air speed of 0.45 m/s +/- 20% (guidance value) at the working position."

FDA 1987 called for at least 20 air changes per hour for Class 100,000 areas. FDA 2004 still calls for 20 AC/Hr as a minimum for Class 100,000, but states: "Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas."

EU 2002 offers no guidance for minimum air change rates in clean areas. Instead, it states: "...the number of air changes should be related to the size of the room and the equipment and personnel present in the room."

FDA 1987 called for a minimum positive pressure differential of 0.05" water gage (WG) relative to adjacent less clean areas. FDA 2004 modified that to a recommendation of 10 to 15 Pa (0.04" to 0.06" WG), with at least 12.5 Pa (0.05" WG) between an aseptic area and an adjacent unclassified area. EU 2002 also offers 10 to 15 Pa as guidance values.

**Table 2**

| Cleanliness Class        | 0.5 µm                   | 5.0 µm                | Cfu*                           |
|--------------------------|--------------------------|-----------------------|--------------------------------|
| Class 100 (FDA 1987)     | 100/ft <sup>3</sup>      | Not defined           | 1 per every 10ft <sup>3</sup>  |
| Class 100 (FDA 2004)     | 3520/m <sup>3</sup>      | Not defined           | 1/m <sup>3</sup> **            |
| Grade A (EU 2002)        | 3500/m <sup>3</sup>      | 0/m <sup>3</sup>      | <1/m <sup>3</sup>              |
| Grade A (at rest)        | 3500/m <sup>3</sup>      | 0/m <sup>3</sup>      | <1/m <sup>3</sup>              |
| Class 5 (ISO)            | 3520/m <sup>3</sup>      | 29/m <sup>3</sup>     | Not defined                    |
| Class 10,000 (FDA 1987)  | Not defined              | Not defined           | Not defined                    |
| Class 10,000 (FDA 2004)  | 352,000/m <sup>3</sup>   | Not defined           | 10/m <sup>3</sup>              |
| Grade B (EU 2002)        | 350,000/m <sup>3</sup>   | 2000/m <sup>3</sup>   | 10/m <sup>3</sup>              |
| Grade B (at rest)        | 3500/m <sup>3</sup>      | 0/m <sup>3</sup>      | Not defined                    |
| Class 7 (ISO)            | 352,000/m <sup>3</sup>   | 2930/m <sup>3</sup>   | Not defined                    |
| Class 100,000 (FDA 1987) | 100,000/ft <sup>3</sup>  | Not defined           | 25 per every 10ft <sup>3</sup> |
| Class 100,000 (FDA 2004) | 3,520,000/m <sup>3</sup> | Not defined           | 100/m <sup>3</sup>             |
| Grade C (EU 2002)        | 3,500,000/m <sup>3</sup> | 20,000/m <sup>3</sup> | 100/m <sup>3</sup>             |
| Grade C (at rest)        | 350,000/m <sup>3</sup>   | 2000/m <sup>3</sup>   | Not defined                    |
| Class 8 (ISO)            | 3,520,000/m <sup>3</sup> | 29,300/m <sup>3</sup> | Not defined                    |
| Grade D (EU 2002)        | Not defined              | Not defined           | 200/m <sup>3</sup>             |
| Grade D (at rest)        | 3,500,000/m <sup>3</sup> | 20,000/m <sup>3</sup> | Not defined                    |

\* Cfu: colony forming units. Limits shown are average values for air sampling.

\*\* FDA 2004: "Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants."

**Table 3**

| Class        | Velocity (m/s) |          |       | AC/Hr   |          |         | Diff Pressure (Pa)* |          |         |
|--------------|----------------|----------|-------|---------|----------|---------|---------------------|----------|---------|
|              | EU 2002        | FDA 2004 | Indus | EU 2002 | FDA 2004 | Indus   | EU 2002             | FDA 2004 | Indus   |
| 100 Gr.A     | 0.45           | 0.45     | 0.45  | N/D     | N/A      | N/A     | 10-15               | 12.5     | 12.5-15 |
| 10,000/Gr.B  | N/A            | N/A      | N/A   | N/D     | >20      | 40 - 60 | 10-15               | 10-15    | 12.5-15 |
| 100,000/Gr.C | N/A            | N/A      | N/A   | N/D     | >20      | 25 - 30 | 10-15               | 10-15    | 12.5-15 |
| Grade D      | N/A            | N/A      | N/A   | N/D     | N/A      | 10 - 20 | 10-15               | N/D      | 12.5-15 |

\* Positive pressure relative to adjacent less clean area

N/A: Not applicable; N/D: Not defined

The pressure differential between areas should be large enough for proper monitoring and alarm. FDA 2004 states, "For example, pressure differential specifications should enable prompt detection (i.e., alarms) of an emerging low pressure problem to preclude ingress of unclassified air into a classified room."

This comparison of the EU and FDA guidelines for the environment of areas containing aseptic processing provides a quick reference for some of the important design parameters and how they differ. It also illustrates how the guidelines are evolving toward a common understanding. ■

\*This article was written by Jonathan Rogers while at PS&S and before he joined Johnson & Johnson.

## PROCESSING OF TOXIC OR POTENT APIs WITH ISOLATION TECHNOLOGY

-continued from page 1

### Electrical

The design should consider emergency power for the entire facility. All conduits in the clean area should be sealed to avoid contamination to/from the outside.

### Equipment

Many different technologies can be used for isolation. The following are some common types of isolation:

- Laminar flow booth
- Glove box with bagging flanges
- Flexible wall isolator or disposable glove bag
- Rigid wall isolator with air lock/pass-through chamber
- Rigid wall isolator using glove ports and RTPs

### Safety Considerations

During the design of a toxic isolated process, it is necessary to perform hazard operability review (HAZOP/FMEA). Each P&ID drawing is reviewed in detail. Multiple "what if" scenarios are documented with respect to possible hazards and consequences. Existing safeguards are reviewed and recommendations are made to increase process safety.

Designing an API processing facility with isolators requires extensive teamwork between the owner, designer, and vendors to ensure project success. Proper interpretation of the PB-OEL category and the owner's URS should play an important role in selecting the appropriate vendor equipment for the project. Specific requirements and information must be developed early in the project to accomplish proper integration of the isolator systems. Validation review and inputs early in the design process can expedite the overall project execution. ■

With a staff of over 500 in 8 offices as well as resident project managers at several client locations, PS&S's services are so diverse that I occasionally need to stop some of our partners to learn what's new with their market segments. Although this newsletter is geared toward our pharmaceutical and biotech clients, I thought you might be interested in knowing the services we offer to clients in other industries.

**Energy** has been in the news more often than not in recent months due to the huge jump in oil prices. PS&S is considered a leader in the field and is working jointly with some of our major clients to reduce their energy spending through implementing varied innovative programs and applying the latest technologies. Many of our clients need rate and tariff analysis, forward energy pricing, and advice on available rebates and credits that are of value to any major energy user including big pharma. Emissions credits also play a big role in the energy area. PS&S has extensive and useful resources in the energy industry that allow us to approach energy and emissions issues with greater perspective than most firms.

**Sustainable Design** has also been talked about lately for partly the same reasons energy and the environment have been discussed. PS&S, a leader in the environmental and energy fields, is LEED™ accredited and I understand that PS&S Architecture, P.C. is the first New Jersey based architectural firm to become an ENERGY STAR partner. What this means is that we can design an aesthetically pleasing building with a deep appreciation for high performance and sustainability.

**Site Development** is also a center of excellence at PS&S. As one of the best in the region, we handle site massing, planning surveying, site engineering, and landscape architecture for our residential, commercial, institutional, hospitality, and industrial clients. We prepare the documentation and permit applications required to obtain government approvals. We have the skills required to navigate land use issues and at the same time maintain the right balance between the environment, development, and project budget.

Let us know if you would like more information on any of the topics in this newsletter. My partners love to talk about what they do.

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