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Chairman, US TAG to ISO/TC 209
Clean Room Management Associates, Inc.
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Re: ISO/DIS 14644-7 Cleanrooms and Associated Controlled Environments – Part 7: Separative enclosures (clean air hoods, gloveboxes, isolators and minienvironments) Date 2001-02-22

Dear Ms. Dixon:

PDA is pleased to have the opportunity to comment on the subject draft guidance on separative enclosures which has substantial implications for the implementation of this and related technologies. PDA attempts to assess the validity of regulatory issues primarily on their scientific and technical merits. We trust our comments will assist ISO in moving ahead with the guide.

We appreciate the fact that the document is intended to address an overview of a wide range of technical solutions to processing environments and this has made the task extremely complex. We believe that caution is always in order in the manufacture and testing of pharmaceutical products and that safety and care can best be encouraged from a strong base of sound engineering and scientific judgment.

One of our primary concerns is that many of the issues raised in this guidance document are intended to apply solely to classified environments. It is PDA's experience that the situation within our industry is not that simplistic. The majority of isolators used within our industry are not located in classified environments, and in addition many of them are not subject to internal classification either. This severely limits the applicability of the ISO document within the global healthcare industry. We recommend that ISO either consider substantial revision to the document, or moving it outside the scope of the ISO 14644 series.

To help you better understand our concerns we have provided detailed comments to the ISO document, and in addition we have provided a copy of our own soon to be published guidance on isolation technology entitled "Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products." We believe that in combination it will help ISO to better address the needs of the global healthcare industry with regard to the application of these novel technologies.

PDA would appreciate the opportunity to discuss isolation technology with the ISO task group, and we encourage such a dialogue. We believe that an exchange of ideas would benefit the industry, the regulatory community and the end users of health care products.

Thank you for considering our comments.

Sincerely,

Edmund M. Fry
President

General Comments

The ISO/DIS 14644-7 Cleanrooms and Associated Controlled Environments – Part 7: Separative enclosures (clean air hoods, gloveboxes, isolators and minienvironments) draft document does not specifically define what an isolator is, therefore a PDA guidance document is still needed to reflect the narrower application of the term within the global healthcare industry. This is not a criticism, but a statement of fact. This duality will force both firms and regulators to review multiple documents, to determine what an isolator is and what must be done to make it ISO compliant.

The ISO document states that the air cleanliness definitions in ISO 14644-1, -2 and -3 generally apply to separative enclosures, internally as well as externally. This is most likely a result of the placement of this document under the ISO 14644 series. In the global healthcare industry, this requirement is substantially overstated. There are numerous successful installations within the industry in which neither the isolated nor surrounding environments are classified. There are also many installations in which only one of the environments (internal or external) is classified. This makes the separative enclosure document substantially more restrictive with regard to their application than is common for isolators in the healthcare industry. We suspect that this situation may also prevail in other industries. The guidance on separative enclosures should not be so restrictive as to mandate classification of either or both the internal and external environments. Consideration should be to removing this guidance document from the ISO 14644 series where the focus is cleanrooms and classified environments. For those separative enclosures where classified environments are present (internally, externally or both), then some adaptation of the ISO 14644 series requirements may be appropriate. The experience with many of these technologies is insufficient to establish the broad applicability of cleanroom standards to separative enclosures at this time.

Specific Comments

Introduction
No clear definition of a “separative enclosure” is provided. The definition provided in 3.22 (and stated in the introduction as well) loses its meaning in the context of what this document purports to embrace (see below). For example, a cardboard box could be interpreted to be a “separative enclosure” by the proposed definition.

2. Normative references
Classes (not classification) of separative enclosures are to be established per ISO 10648-2, which defines what fits in what class (via the leak rate), but provides no guidance on what the classes

mean in any other way other than continued containment operation with either an inert gas or a permanently hazardous atmosphere. These same classes are repeated elsewhere (Annex A) in this document with no interpretation. What use a particular class enclosure can be put to is not defined in either document (ISO10648-2 or 14644-7) where atmospheric conditions prevail inside the enclosure or where the enclosure is used for a non-containment application. This is a common situation in the healthcare industry, but the class guidance is not applicable. Reference to classes for separative enclosures should be clarified across either the full range of applications in all industries or it should be deleted. Considering that many separative enclosures have no ready means to establish their class according to ISO 10648-2 we suggest that this reference be dropped.

3.18 leak (of separative enclosures)
In the context of separative enclosures where air sealed systems are a part of the continuum, a leak is not specifically a defect unless it is of a size which alters either the undefined class or, in a real sense, the functional performance of the system. Thus a leak is not always a defect, especially in the context of separative enclosures which are air sealed as provided for within the continuum on page 10.

3.21 separation descriptor, $[A_a : B_b]$
The definition is clear, but the application of it is unclear. Are there limits to the difference between the internal and external classification? If not used for that purpose, then for what purpose is this term introduced? There are numerous applications of isolators for containment and asepsis in the pharmaceutical industry where no classification of the interior and exterior is required. There is no indication how this term might be used if the separative enclosure might be exposed to multiple surrounding environments (some classified and others unclassified). There is also no indication how this term is to be used if a large separative enclosure has multiple internal classifications. Given that this term is not clear and has no specific purpose in the guidance, it should be removed from the document entirely.

3.22 separative enclosure
This definition encompasses all sorts of designs and gives no clear understanding of what makes a separative enclosure as something unique from a box or plastic bag. This is clearly inconsistent with the implied requirements that all separative enclosures be classified and be located in classified environments. As stated earlier, classification of these systems should not be a universal operational requirement. Therefore, this definition is inconsistent with the defined scope of this document. In our opinion, this definition is a good one, but it is best interpreted along with the elimination of a classification requirement throughout the document. If this guidance is kept within the ISO 14644 series then a new and substantially narrower definition is

warranted.

4.3
Add the following to the sentence (underlined text added)
. . . such as material compatibility, cleanability, environmental requirements, residues and effluents.

Section 4.5 speaks to the cleanliness of the enclosure and is appropriate in the context used. Section 4.3 speaks to cleanability of the contents of the enclosure, which is an important design consideration. The environmental requirements of the enclosure contents also dictate its design, i.e., type of chemical, temperature, etc. used in the preparation for use or even during use depending upon design expectations.

4.5
As mentioned previously, many separative enclosures do not require classification of either environment. This sentence should begin as:
Where appropriate, . . .

4.7
Reference is made to annex F, but that annex makes no mention of how a separation descriptor is to be used. The term is thus functionally useless in this document. Given the earlier difficulty with this as a general requirement for all enclosures, it should be eliminated from the document.

4.12
Requiring defined methods for entry/exit during installing and commissioning is an outgrowth of the "clean build" concept for microelectronic cleanrooms. That should not be a requirement for enclosures in general. The "clean build" concept is not a universal practice, nor should it be, thus this requirement is overstated. As many separative enclosures are manufactured elsewhere rather than in-situ, this requirement should be limited to those systems which are fabricated in-situ. Pharmaceutical isolators do not need to follow a clean build protocol.

5.17
The gasket materials and frame associated with the viewing panels should also be considered in this section.

6.2.1.3
Add a section:
i) hygiene of the operators when several are involved

6.2.2 Remote manipulation
These systems also have to provide for protection of the mechanics and others by allowing maintenance and adjustment externally wherever possible.

6.3 Robotic handling
This should be restated and expanded to include automated handling. In the healthcare industry machines rather than robots within the enclosure are often used. Robotics implies a narrower scope than is commonly seen.

8.2
d) toxicity of products
Suggest change to: d) toxicity of products and/or process chemicals

This could be perhaps implied by 8.2 e), but the proposed revision makes it clearer. 8.2 e) would still remain to reflect other process hazards, which include many other issues.

8.2
Add a section:
j) design of transfer devices

9.2 Glove breach test
The utility of this test as a general requirement for all separative enclosures is unproven and it should be restricted to containment applications only. The need for glove breach tests should be defined by the user in terms of relevant, specific technical requirements. Tests with the glove port open are not typically done in the pharmaceutical industry. In any case, a reference should be provided for the guidance value of NLT 0.7 m/s.

9.3.2
Add the following sentence:
Documentation of the differential pressure monitoring may be required based upon local regulatory requirements.

9.4 Leak testing, Note 2
This section provides no guidance as to when an induction leak must be considered. This "requirement" should be clarified or removed.

9.5.3 Recommendations for testing frequency:
The routine testing frequency should vary with the degree of criticality associated with the

application/usage of the enclosure. If there is a continuum with regard to leak testing limits, there should be a continuum with regard to the testing of all elements of the enclosure. Mandating the same frequency for all applications is certainly excessive for some installations, and belies the importance of the testing for others. This is applicable to all of the tests in this section. The user should be required to defend their specific rationale for routine testing of the enclosure and no more.

If this section remains unchanged we suggest that the following be added to sections 9.5.3 a) and 9.5.3 b):
4) before any sanitizing procedure

Annex A
A.1.1
The paragraph uses the term "degree of rigidity" as a way of segregating the continuum along aerodynamic or physical separation. This terminology suggests that flexible walled systems are inherently inferior to rigid walled systems. At some extreme level that may certainly be the case, however for many applications flexible wall systems have been shown to have lower leak rates than similar rigid wall systems used for the same purpose. For this reason, we suggest that the word "rigidity" be replaced with "integrity," which speaks to leak rate rather than physical construction as the real divider among equipment designs.

The class system (ISO 10648-2) is mentioned again, without any linkage to the continuum description either in the diagram or the table. Applying the class system to either of these would demonstrate how limited it is in the general context of separative enclosures.

A separative enclosure may change its mode of operation during ordinary use. For example, a cytotoxic aseptic processing enclosure normally operated under positive pressure may contain a sanitizing gas under positive pressure, then be used for aseptic processing under positive pressure, and then be operated under negative pressure during the post use cleaning of the enclosure. Similarly, an isolator may be treated with a potent gas prior to use, and during use be opened to allow for the high speed ingress/egress of materials. This type of enclosure uses different separation means at different times during routine usage. The guidance should reflect these types of changing usage (and others) as wholly acceptable for separative enclosures provided they are properly managed.

Table A.1–Separation continuum
There is an implication that flexible film systems are more prone to leakage than rigid wall systems. This belies the current experience in the healthcare industry, where flexible wall

systems have consistently demonstrated lower leak rates than similar size rigid wall units intended for the same application. These flexible walled systems are capable of meeting class 2 of ISO 10648-2.

A.1.2

The operation of dual mode devices is briefly described, but no definition of a dual mode device has been provided in the document or glossary. This section is thus completely unclear to the reader.

Annex B
B.1.2 a), B.1.2 d), B.1.2 e), and B.1.2 g)
This section implies the need for integrity testing of filters, air cleanliness, etc., which, while useful, should not be mandatory as un-classed environments may be found on either or both sides of the enclosure. These subsections should all begin as follows:
If necessary, . . .

B.1.2 h)
Separative enclosures can operate in either negative or positive modes. Therefore, this requirement needs generalization to cover both.

B.2.3 Single pass gas system, Note 2
Add the following at the end of the second sentence:
. . . exhaust gas system to be installed after the outlet filter on an enclosure operating under positive pressure.

Annex C
C.3.5
This section describes the use of a pre-glove for radiation protection of a gloved hand. Logically, this could be extended to pre-gloves as a general protective measure for any containment application. Similarly, no mention is made of over gloving as a means of enhancing protection to the gloved hand in a containment setting or as an additional means of protection in an aseptic setting.

C.4.2 Length of glove or sleeving
The length of the typical human arm allows reach to only 650 mm. When extra length sleeves are mandated, the folds can get in the way of equipment and make cleaning /sanitizing more difficult. We suggest the second sentence be deleted as an unnecessary detail. The point is made

adequately in the text without the need for a dimension.

C.5
This section (and the entire document) is silent relative to test methods and/or specifications to be used for gloves. The earlier section (C.3) outlined glove quality primarily from a chemical resistance perspective, which appears inadequate to address physical defects in gloves. Given the extremely tight leak rates provided for in this document, some specifics on glove specifications and test methods should be provided.

C.7 and C.8
The same issues which relate to gloves regarding chemical resistance, permeability and fault checking apply to sleeves and half-suits as well.

C.7.2
The changing of gloves as described in this section should be restricted to positive pressure isolators. Changing the gloves in an isolator used for containment applications is not desirable during use.

Annex D
General Commentary
The discussion of transfer devices without some indication of which transfer devices are associated with which general class of separative enclosure is largely meaningless. Some of these systems cannot be used in critical applications and yet there is no guidance provided which can help the reader to understand where and how they are to be applied.

Annex E
E.1.1 Procedures
No quantitative limits are provided for induction leak testing, so this section only serves notice that the subject is somehow important without providing any meaningful guidance on how a firm is to address it or apply the guidance. “Significant penetration” as a criterion is overly vague. As written it suggests that it is equally important for all types of enclosures. Considering the detail to which this document provides regarding other types of leak testing, these types of leaks (which are presumably larger by several orders of magnitude) can hardly be ignored.

E.1.3 Method
The Ljungqvist-Reinmüller method should be cited as a means of evaluating this aspect of enclosure performance.

E.2.2
The la Calhène ammonia detection cloth should be cited in this section. None of the described tests seems to fit that widely used test method. The sensitivity of that test should be readily definable by la Calhène.

E.3 Quantitative leak testing

Throughout this section there is guidance about particular methods as appropriate for particular designs. That type of guidance is not substantive; users should be free to chose the leak method most appropriate for their application. There is no reason to believe that the suggestions provided in the document are universal for all designs and applications. This section should be entitled "Examples of Quantitative Leak Testing" to allow for additional methods not specifically identified.

E.3.1.1
The use of test pressures as high as 1,000 Pa is excessive for equipment intended to operate at 25 Pa. This pressure is appropriate for nuclear industry but not as a general requirement for all enclosures. The choice of a test pressure should be left to the user. Mandating all testing at high pressures is inappropriate and may damage equipment and be hazardous to personnel. True the use of a higher pressure can highlight leaks, but it represents undue stress on the equipment.

Mandating testing in both directions is an excessive requirement for some systems. It may be justifiable for the tightest classes of separative enclosures, but should not be a general requirement for all systems. Note also that testing of entire isolators under negative pressure is only possible using a pressure change method. None of the other leak detection methods lend themselves directly to application in a negative operational mode.

E.3.1.2
This section (paragraph 2) shows the enlightenment missing from the prior section regarding the hazards of testing at extreme pressure or vacuum levels. This type of thinking should be adopted in the previous section.

Many of the precautions given in this section could be alleviated somewhat if the testing is performed under conditions more closely approximating actual usage.

E.3.1.3
This section suggests that all enclosures are small, and movable units. Many enclosures are of substantial size and the idea that they can be placed into a room is spurious. Some enclosures are

room size or even larger. The methods cited should consider the diversity of design and be less prescriptive, considering the method, limits and other assumptions regarding enclosures.

E.3.1.4
The pressures cited throughout this section are excessive for many enclosure designs.

E.3.1.4, Note 2 after (E.4)

It is unclear how this note is meaningful. Leakage should always be in direction away from clean toward dirty, so the disturbance of the less clean environment by leakage from the cleaner one is an unfortunate circumstance, but one that is hardly significant to the needed protection. To maintain the higher quality of the clean environment, disturbing the other environment must be permissible at times. This problem could only manifest itself where the pressure differential between the environments is misapplied and allows for the cleaner environment to have leakage from the dirtier one, a clear design error which should be avoided wherever possible. In the context of classified environments internally and externally, this issue takes on greater importance, but it appears overstated for all applications.

E.3.1.5
Closing off the gloves and half-suits (as designated earlier Annex C "Gloves tend to form the weakest link to the integrity of a separative enclosure") makes this entire section largely moot. If gloves are so important, then systems should be tested with them in place and as part of the system. Remember also that the gloves were not tested independently for leakage as part of their acceptance for use on a system. The approach described suggests that an enclosure can be considered leak tight if it leaks without the gloves, sleeves and half-suits being evaluated. The enclosure must be considered as a total system, there is no merit to excessive concern over one element of leakage if another is not considered equally.

E.3.1.5, Note 1
If the test is performed over a relatively short period of time, there is no difficulty whatsoever to applying this method to flexible walled systems.

E.3.1.6
We believe the hourly leak rate for medium pressure integrity enclosures given in Table E.1 is too strict. In our view a specification of not more than 0,5 % of the enclosure (isolator) volume per hour is a suitable leak rate (see American Glove Box Society, Guideline for Gloveboxes, AGS-G001-1994, p. 118).

Table E.1
No definition or description is provided which can convert the listed classes to the continuum or any other designation within this document. Their designation herein is thus wholly unclear. Handling toxic or inert gases in the enclosure is of no use whatsoever in designating an enclosure that is used for neither. Clarification is needed to indicate how these classes can be used in other applications. The "integrity" designations are not useful in this context, as they are undefined except in terms of containment applications. There is also no direct link between the column on test methods and the test methods described in the document.

Each test method mentioned in the document should be linked to a particular class (or classes if appropriate). This assumes that the classes have meaning outside the context of containment for which they were developed.

Leaks are an integral part of the design of ordinary cleanrooms where the overpressure is deliberate to ensure the protection of the more clean environment from surrounding less clean environments. These leaks are substantial in size and several orders of magnitude greater than anything in the table. Leaks discussed in this document are raised to a level of importance that is unrealistic in the broader context of the application. We protected materials and personnel with air differentials for generations, and to suggest that minute leaks as associated with separative enclosures can have real meaning is spurious. Properly managed leaks are of substantially less significance than many would believe.

E.3.2
The description of the Parjo method uses a jargon of terms and apparatus that is not clearly defined, with the expectation that others can follow the method. It should be restated in more generic terms so that others can follow what is intended.

E.4.2, Note 2
The pressure at which the leak test is performed is approximately 5-10 times higher than the normal operating pressure for these systems. The appropriateness of these extreme pressures for leak testing should be reconsidered.

E.5 Example glove leak tests
The test methods described for gloves are restricted to specific installation designs, and appear not to be broadly applicable to other applications. One is for those that operate at -170 Pa, while the other requires testing at +1000 Pa. This subject would be better served if it was addressed in a means similar to the enclosure leak testing. A brief overview of available leak testing methods should be substituted, there are many others which are not listed.

E.5.2.1
As mentioned previously testing of gloves (or any part of the system) is not truly meaningful. Enclosures need to be treated in a systemic approach, not piece meal. The cited limit of -170 Pa is appropriate for nuclear applications only.

E.5.2.3.2 Fail
Operator safety must be a consideration of any failed glove used for a containment application.

E.5.3.1
An in-process test in precisely this fashion has merit for enclosures operated over an extended period of time without the opportunity for change.

E.6 Example half-suit leak tests

The methods and issues cited above for gloves and sleeves apply equally well to half-suits.

Annex F
F.2.2
Much of what is described in this section has wider applicability than is first apparent. The pods described appear similar to RTP containers used in the healthcare industry. This section should be revised to be more inclusive of other enclosure related separative technologies than it presently addresses.

Annex G
G.2
This section addresses the subject as if both the internal and external environments are classified. As discussed earlier in this review, this is not a universal situation so many of the concerns addressed in this Annex are certainly overstated.