Letter to the Editor

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Sed Lex, EudraLex: A Near Future Possibility for a Real Time Release Testing in Aseptic Processing when the Practice of Sterility Testing is not Possible

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The use of isolator for any aseptic process allows to separate people and product, so with a proper use to get and keep the sterility of the process and the product. One of the definitions of isolator in use in the pharmaceutical industry is coming from PDA Technical Report 34 [1]:

> An isolator is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated. When closed, it uses only decontaminated (where necessary) interfaces or Rapid Transfer Ports (RTPs) for materials transfer. When open, it allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination. It can be used for aseptic processing activities, for containment of potent compounds, or simultaneously for both asepsis and containment.

This described isolator is not quite different from a Biosafety Cabinet Class III (BSC III) according to the 5th edition of "Biosafety in microbiological and biomedical laboratories" except that this last one is designed to work only in negative pressure and has no reproducible biodecontamination system.

Sterile compounding in hospital pharmacy accordingly to the country has to be made in accordance with cGMP rules [2] or/and with local rules as for instance USP<797> in USA [3], "PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments and guide to good manufacturing practice for medicinal products » [4] in Europe and "Bonnes Pratiques pour Préparations Hospitalières" in France [5].

Within US and French regulation the use of contained isolators like the Compounding Aseptic Containment Isolator (CACI) of USP <797> is recommended.

This type of isolator is similar to the ones routinely used by the pharmaceutical industry for aseptic process. Its design includes a leak-tight enclosure with a specific leak-rate which makes possible a reproducible chemical surface sterilization without any chemical risk for the surroundings, a class A HEPA filtered airflow as process environment, gloves or half-suit to handle inside the enclosure keeping the operator biologically outside and sterilizable lock-chambers or RTP transfer systems to get on time in a proper way components and products in and out.

These technical features can be measured, qualified and validated with mini and maxi values for any given protocol. These physical and chemical values can be real time measured during a production process and give a high quality assurance for the working environment. What is missing in this real time concept is the microbiological contamination as the results will be only known after a delay between 3 to 14 days according to the incubation times.

So when the sterile product from the aseptic process in isolator has to be administered to the patient the fastest after its production, there is not enough time for having a result regarding both the microbiological status of the product and its process environment thus bringing an eventual risk for the patient.

In such a case, a real time knowledge of the quality assurance of this process environment can come from the parameters of the isolators and a Process Analytical Technology (PAT) can be applied [6].

The CACI goes through qualification steps explained in the International Convention on Harmonization (ICH) documents from ICH 7 to ICH 9 [7]. ICH Q7A has been

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incorporated into the EU GMPs as Part II: Basic Requirements for Active Substances used as Starting Materials, which also includes specific references to qualification activities. In ICH Q 9, Quality Risk Management (QRM), includes an appendix of applications of quality risk management. Appendix II.4 describes how to use quality risk management for facilities, equipment, and utilities, including: "... to determine the scope and extent of qualification of facilities, buildings, and production equipment ...". ICH Q9 has been adopted by the EU as part of its Vol 4 GMPs as Annex 20.

In addition there is a specific step for the qualification of the sterilization of the isolator enclosures which is usually named "cycle development" and which requires the use as Biological Indicators (BI) of resistant spores at a concentration between 10^4 to 10^6 to validate the process.

After the qualification steps and the cycle development the knowledge of the parameters of the CACI regards:

- Leak rate of enclosures
- HEPA filter performances
- Leak rate of gloves
- Leak rate of RTPs
- Particulate counting
- Airborne and surface viable particulate counting
- Pressure differentials
- Air change and air speed
- Values of the cycle developments for sterilization

Pressure differentials, air speed and particulate counting can be measured on a continuous basis, the frequency of the measurements of the other values are defined through the QRM of the production unit.

This Eudralex document to come in 2016 [1] emphasizes this idea, when sterility testing cannot be practiced or when it is economically absurd about a Real Time Release Testing (RTRT): "The previous guideline only focused on the application of Parametric Release for the routine release of terminally sterilized products waiving the performance of a test for sterility on the basis of successful demonstration that predetermined and validated sterilizing conditions have been achieved. Moreover, advances in the application of process analytical technology (PAT), quality by design (QbD) and quality risk management (QRM) principles to pharmaceutical development and manufacturing have shown that appropriate combination of process controls together with timely monitoring and verification of pre-established material attributes provides greater assurance of product quality than finished product testing (conventionally regarded as the end-product testing) alone".

Moreover injectable compounding in hospital pharmacy, this could be applied to other injectable process for instance to Cell and Gene Therapy (Advanced Therapy Medicinal Product) where the production is unique for a specified patient, to orphan drug production where the quantities are small and the price is high, to phase III biotechnology clinical batches, etc...

In the high throughput industrial injectable production with isolators as for insulin or vaccines, when the duration for a batch lasts 2 or 3 weeks on a 24/7 basis, the RTRT allows making a real time follow-up of the Quality Assurance (QA) through qualified defined parameters.

Again what is missing is a real time microbiological Environmental Monitoring (EM) as described in USP <1116> [8]. Some cautions have to be taken in the isolator beyond its known physical and chemical parameters like avoiding to introduce culture media or if so to have a stringent protocol of cleaning. Any increase in the real time 5 microns airborne particulate monitoring can be an indication of a risk of microbiological contamination.

New equipment as for instance Biovigilant® [9] is intended to give a real time microbiological airborne contamination. Its performance has to be proven but a direction is given.

What we can say to-day and for the future, thanks to CACI isolators and to the application of RTRT, is that we assure in injectable aseptic process the highest quality assurance for the administration to the patient when sterility testing is either not applicable or when its result is only available after the administration.

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Didier Meyer holds a Bsc in Biochemistry.
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