

## Conference notes – KEVIN SMYTH 16 Nov 2022

The updated Annex 1 was issued on 22 August 2022.

As draft versions of Annex 1 have been readily available over the past several years, there were few surprises in the FINAL VERSION of the updated Annex 1.

As stated by one of our expert presenters, Patrick Nieuwenhuizen, Director Senior Consultant, PharmaLex PDA Letter, Nov 9, 2022, (feedback from the 2022 PDA Annex 1 Workshop, Amsterdam, 22–23 September).

*“As regulatory representatives indicated during the previous PDA Annex 1 workshops, the final text was not expected to deviate much from the Draft Revision 12 version published in February 2020. When comparing the final published version with Draft Revision 12, it can indeed be concluded that the body of the text remained essentially unchanged with some points of further clarification added. Because of this, organizations had more than two years to start preparing and familiarizing themselves with the text and knew what was coming. That was one of the reasons EMA agreed to a deadline of one year for implementation, reemphasizing that the final published Annex 1 text is based on what regulators already have seen in the industry as a practice and, in essence, is not new.*

*...there were still organizations who confirmed limited familiarity with the (Draft) Annex 1 within their company. Feedback received from multisite facilities indicated that they expect it will be difficult to implement all the requirements within the expected timeframe. For companies using contract manufacturing organizations (CMOs), there is an additional challenge as they depend on the readiness and willingness of the CMO to make changes. This could lead to serious financial costs and time constraints when it comes to regulatory approval of an updated Drug Master File.”*

Similar to the PDA Amsterdam Annex 1 conference/workshop, the PDA Dublin Annex 1 conference/workshop was the first major Annex 1 event in Ireland post issue of the updated Annex 1.

The Dublin event provided a great opportunity for all those present to discuss the final document, instead of previous draft versions.

At the Dublin event, excellent presentations were given by acknowledged industry experts. The presentations were then followed by Q&A sessions and workshops.

This approach ensured that all delegates were informed on the state of the industry and also given the opportunity to raise questions, share ideas and network with their peers, compliance experts and current MHRA regulators.

Presentations will be sent to all attendees and will be available for viewing by PDA members on the PDA Ireland website, <https://www.pda.org/chapters/europe/ireland>

### **PRESENTATIONS**

A very brief summary of some of the items and issues addressed in the excellent presentations is given below, please refer to the actual presentations for more information.

**Andrew Hopkins, Director Operation Quality, AbbVie, discussed Regulatory updates/trends.**

Andrew stressed that PUPSIT is not new and that the principles of CCS are not new. Annex 1 was updated to give more explanation of current regulatory expectations.

Andrew stated that Annex1, EMA guidance on sterilization of medicinal products, CFR 211.113, USFDA Aseptic guidance 2004, all have one main overall aim to minimize contamination risk and emphasizing the need to look at Facility, equipment and process design to achieve this.

Challenges posed by Andrew included:

- Appropriate application of QRM needs to show an understanding and justification of all we do
- Knowledge Management (Industry and Regulators)
- Critical and unbiased thinking
- Keeping up with new technologies
- Less reliance on monitoring

Andrew stated that “**Monitoring or testing alone does not give assurance of sterility.**”

Andrew asked the audience if Annex 1 also applies to ATMPS? The answer is actually Yes and No. It can be applied and where it is applied, it must be based on sound scientific based justification which must be documented. For example, use of a grade A, with grade C background for a low bioburden BDS.

#### **Maik Jornitz, President & CEO, G-CON provided a in depth presentation on PUPSIT and the Impact of Annex 1 revision on filter testing expectations**

Maik gave an excellent presentation on the work of the SFQRM Task Force and their findings to date.

Maik gave an intriguing insight into the science of filter masking and the tests carried out to determine the risks of filter masking.

It was mentioned in the conference that PUPSIT is the norm in Ireland and much of Europe, however this is not currently the case in the US.

#### **Shada Warreth, Senior Training Manager, NIBRT - Academic Spotlight: Automated Environmental Monitoring**

Shada’s presentation on the use of robotics for EM sample collection and handling was a great example of how industry is engaging to comply with the regulators expectations to use new technologies, where possible. Use of robotics can significantly reduce the risk of the greatest source of contamination the Human. Co-BOTS MOC and risk of particle shedding.

Shada’s work was a collaboration of Academia, the Pharmaceutical Industry, Engineering Design Experts and Robot Manufactures – all working together for a common goal – Patient Safety.

#### **Patrick Nieuwenhuizen, Director Senior Consultant, PharmaLex - Case Study: Excursions in Non-Aseptic Areas and the Importance of a Contamination Control Strategy**

Patrick stated that some of the principles of Annex 1 such as a CCS can be used to support the manufacture of products that are not intended to be sterile to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product

Patrick gave an overview of the elements to consider when developing a CCS and stressed that it involves an end to end evaluation of many elements involved in the manufacture of pharmaceuticals, such as manufacturing, shipping, distribution, laboratories, facility design, qualification .....

Patrick presented a case study on mould detected in non-aseptic areas of a pharmaceutical facility, how the investigation was carried out and the outcome.

Patrick provided the following guidance:

- There may not be a single root cause and there may be several direct and indirect contributing factors.
- Data mining is key– what has changed? Monitor trends. Data is key.
- Experience is key – involve all disciplines.

In summing up, Patrick mentioned that an action plan was put in place, however not all actions were addressed until mould was found in the sterile core.

### **Corey Bishop, Senior Engineer, Amgen. Visual Inspection and Container Closure Integrity**

Corey is an expert in visual inspection and container closure integrity.

Corey gave very practical advice based on his hands-on experience in Amgen.

The revised Annex 1 includes significantly more information on inspection and CCIT, Cory guided the audience through all this.

Corey also gave excellent advice on inspector training, AVI methods and qualification, defect libraries and CCIT technologies.

Corey was asked if a robot can be used for MVI? Robotics and automation can be used to facilitate MVI and carry out some tasks and these options are available from MVI suppliers.

In addition, MVI operations are continually policed to ensure that MVI inspection techniques are being performed correctly.

### **Maria Ginnelly, Senior Process Specialist, MSD - Sterilisation of Indirect Contact Parts**

Maria gave an excellent presentation on the challenges faced when sterilizing and maintaining the sterility of indirect product contact parts. It has been well documented that VHP cannot be claimed to sterilize these parts. This means that operating companies with isolated Filling lines that relied on VHP to sterilize the stopper bowl and other indirect product contact parts will need a new approach such as sterilizing the parts in an autoclave.

Maria explained that handling of parts post sterilization poses many challenges to ensure that the parts are not contaminated post sterilization and that grade A continuity is maintained.

Potential risk areas include storage hold times, wrap integrity and robustness, unwrapping procedures and environment.

Knowledge of the process steps is critical for clearly identifying risks that may reintroduce bio load/contamination post sterilisation. Maria recommended that it is essential to GO SEE on the floor.

Carry out risk assessments and be aware that level of maturity on site of risk assessments can vary.

A consensus was reached during the Q&A session that sterilised parts such as tongs, tools in bags should ideally be kept wrapped when being placed/hung-up in the Filling Line Isolator and the wrapping removed post isolator VHP.

### **Bernadette O'Brien, Director, Quartz Quality Ltd - Contamination Control Strategy: Preparation and Pitfalls**

Bernadette provided expert advice to the audience on the preparation of a CCS and pitfalls to be aware of.

Bernadette stated that QRM tools used may be selected based on a company's familiarity however it is important to use the tool most appropriate for the task to ensure that the correct answer is found.

For small organisations having all the required people/skill sets present for the risk assessment can be a challenge as these personnel may not be available. The level of maturity on site of risk assessments can also vary.

Pitfalls identified by Bernadette included:

- Striving for perfection.
- Excessive use of FMEA
- Inappropriate risk ratings
- Absence of contamination focused governance
- Aging sites not keeping pace with technology

### **WORKSHOPS**

Workshops were held in the afternoon after lunch.

Everybody registering for the conference was requested to submit Annex 1 relevant topics that they would like discussed.

The following top 7 topics submitted by the delegates were selected for the workshops,

1. Contamination Control Strategy and Application of QRM to Annex 1
2. Gap Assessments and Mitigation Plans for Annex 1 Readiness
3. Sterilization of indirect product contact parts
4. Clean room practices - impact of Annex 1 and best practices
5. Single Use systems and the increased focus on sterility assurance
6. CMO Annex 1 compliance / oversight
7. Impact of annex 1 on container closure integrity

Each Annex 1 workshop topic was assigned to a team of 14 delegates who were tasked with identifying challenges, developing solutions and reporting on their findings to the audience.

For each of the workshop topics, any questions that the individual workshop team and the audience had were later shared with the expert panel for resolution and comment.

The A1 flip chart worksheets from each of the workshops were collected and all notes taken at each of the workshops will be collated by the PDA and sent out to each of the delegates.

Questions raised by delegates on the Slido interactive platform during the event will be reviewed with the experts and replies posted to all attendees in the coming weeks.

### **Q&A SESSIONS - On the couch...Panel Discussion and Q&A on Annex 1 Topics with Speakers and Experts**

Two Q&A sessions were held.

Delegates were asked to submit questions by raising their hand or at any time during the day via the Slido software platform. Priority was given to questions raised from the floor.

All questions raised from the floor were answered, it was not possible to answer all questions raised via Slido due to time constraints.

However, unanswered questions raised by delegates on the Slido interactive platform during the event will be reviewed with the experts and replies posted to all attendees in the coming weeks.

We had four current and past regulatory inspectors present for the Q&A sessions, there was great interaction between Paul Sexton, Ciara Turley, Greg McGurk and Andrew Hopkins, and between all the delegates and the expert panel of speakers/regulators.

Some highlights from the Q&A sessions are detailed below:

1. Cleanroom practices – focus should be on education and not just training. All parties need to understand the science and the impact of their actions on product quality and ultimately patient safety.
2. PUPSIT is the norm in the Republic of Ireland.
3. How frequently should the CCS be updated? It is a living document – however a formal update every 12 months is considered good practice.
4. You must sterilize indirect product contact parts
5. Integrity of closures bags/wrapping on autoclaved parts - it is not a regulatory requirement to test this at the moment.
6. CMO – what documentary evidence does the releasing site need from a CMO site?
7. You do not always get the full picture from the CMO. If something happened in the facility when operating for a different client may not be shared.
8. Buyer beware!
9. Does the CMO site reflect the same culture as the releasing site?
10. Annex 1 is part of PIC/S and FDA were involved in writing Annex 1
11. Capacity utilization and impact of CCS - if a facility is operating at the limit – any increase in throughput may cause the facility to fall over.
12. Older sites will need to comply with Annex 1 by deadline – including sterilization of indirect product contact parts.
13. Companies must comply with all requirements by 25 August 2023, with the exception of point 8.123 which has a deadline for coming into operation of 25 August 2024. The reason for this is the time required to implement the requirements of 8.123.
14. There was a lot of discussion around the sterilization of indirect product contact parts, notably stopper bowls and other parts that are not designed for removal and autoclaving. The use of VHP is not acceptable for sterilization of parts. VHP is used to decontaminate not sterilise.
15. Concern was raised that CMOs may not comply with Annex 1 requirements by 25 August 2023 – if only required to do so by smaller clients.

16. For CMO companies with several customers it is important not to share confidential information in the CCS document. Customer specific CCS may be required in addition to an over-arching CCS.
17. The CCS is a living document and drives continuous improvement. Monitoring/trending of production data (process, utilities, environmental) is very important in ensuring that the CCS is robust and will assist in rapidly identifying remedial actions required.
18. The PDA are preparing a technical report on the development of a CCS that will be a valuable reference guide for the Industry.
19. The FDA and PIC/S have been involved in the review of Annex 1 which requires PUPSIT as the norm. PUPSIT is currently the norm in Ireland and is expected to be the norm in the rest of Europe.
20. CCIT must be part of the storage/transportation as transportation/storage at low temperature -80 deg C can impact the vial/stopper seal for example.
21. Knowledge management, we have a lot of new people coming into the industry which is great, a challenge may be how we ensure old knowledge (when things went wrong) is shared and understood.