The Never-Ending Story of Annex 1 and the Obstacles of Aseptic Processing

A report on the ISPE European Annual Meeting 2018

8 min reading time

by Thomas Peither

Who is involved in Annex 1, to whom is it addressed, what products and institutions are covered? Today I provide you with insights into the discussions on Annex 1 and aseptic processing from the recent ISPE European Annual Meeting. More than 600 industry experts and 30 regulators discussed from 19 – 21 March 2018 in Rome.

Two weeks ago I summed up the highlights from the Pharma 4.0 sessions (LOGFILE 16/2018). This text (and many more) was also published in my live reporting from the conference on Linkedin (#gmppublishing).

The long story of Annex 1 was the topic dealt with by **Andy Hopkins**, MHRA, a well-known speaker at the ISPE conference for years. Annex 1 and the obstacles encountered from 1996 to the present day are still topical. At the end of March 2018 the comment phase ended - now it's up to the agency to proceed to the next step - reviewing all the comments.

Who is involved, to whom is it addressed, what products and institutions are covered? The importance of the document is high and Hopkins also focussed on quality risk management. He saw a loss of knowledge about aseptic manufacturing in the industry.

He provided insight into some important changes in the Annex. Merely for information: GMP Publishing has already published a comprehensive document check. (LOGFILE 07/2018, LOGFILE 08/2018)

Andy Hopkins summed up six key changes:

- Need to have a documented contamination control strategy
- Based on QRM, design is paramount to risk reduction
- Need to use current technologies (e.g. RABS, isolators and even robotics)
- Old 70s technologies such as open "grade A" or curtains will not be acceptable going forward.
- Need to be designed to keep operators outside of grade A
- Once design is optimised:
    - Think about procedural controls and monitoring strategy

- Design needs to be reviewed and updated (as necessary) based on: specific system feedback and broader information regarding technological improvements and advances

Nothing new under the sun of Annex 1 - we have to wait and see what the final version will bring us. No information was given about the anticipated timeline for the final version.

Lifecycle quality risk management in aseptic processing is one of the topics of **Rick Friedman** from the FDA. He is a long-time expert in the aseptic field. The main thing in aseptic processing is: People! And of course, there are a lot of other risks that have to be solved on a daily basis.

Robust unidirectional airflow in ISO 5 areas, smoke studies, manufacturing reliability, design, consistent product quality, risk reduction, media fills, ...; he gave a good overview of areas in industry with room for improvement. "And human error is still the most common reason for contamination", said Rick Friedman (see also Figure 1 on reducing hazard posed by people).

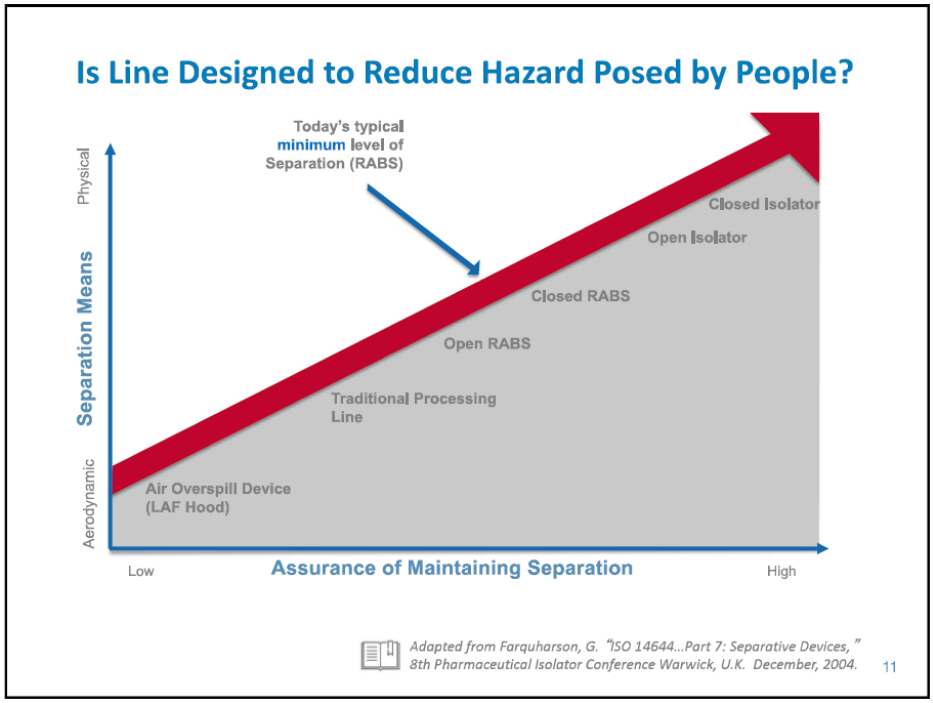

Figure 1: Reducing hazard posed by people by different separation means

He also talked about the different solutions between open and closed systems and referenced Warning Letters to underline the challenges. Modernisation is necessary and „Innovation is a social process", said Friedman - and you have to cover all stakeholders to drive innovation.

We fear that Annex 1 could be used for Non-Sterile Products

"The final release of Annex 1 is expected in December 2018", **Jean-Francoise Duliere** said at the meeting today. He talked about the collaborative work from various ISPE sub-groups on commenting Annex 1.

General comments were: clarification of wording, replacement of "could, should" with "must, shall"; improvement of glossary; improvement of definitions linked to risk; clarification concerning laminar flows and unidirectional flow ; more accurate definitions, e.g. RABS, open, closed. There were also some restructuring recommendations on Chapters 9 and 6.

One concern Duliere expressed, but didn't comment on was that many comments from industry indicate fears that Annex 1 could be used for non-sterile products.

There are many requests for personal aspects like qualification, microbial monitoring, clothing and mobile phone usage. Premises comments covered, for example, HVAC filters, particle size classification, environment background, access to critical areas, air flow visualisation. There were only a few comments on utilities, but many on production and specific technologies: contamination definition, access to sterilisation operations, exit from autoclave, PUPSIT, loading/unloading of freeze dryers, many wording clarifications (see Figure 2).

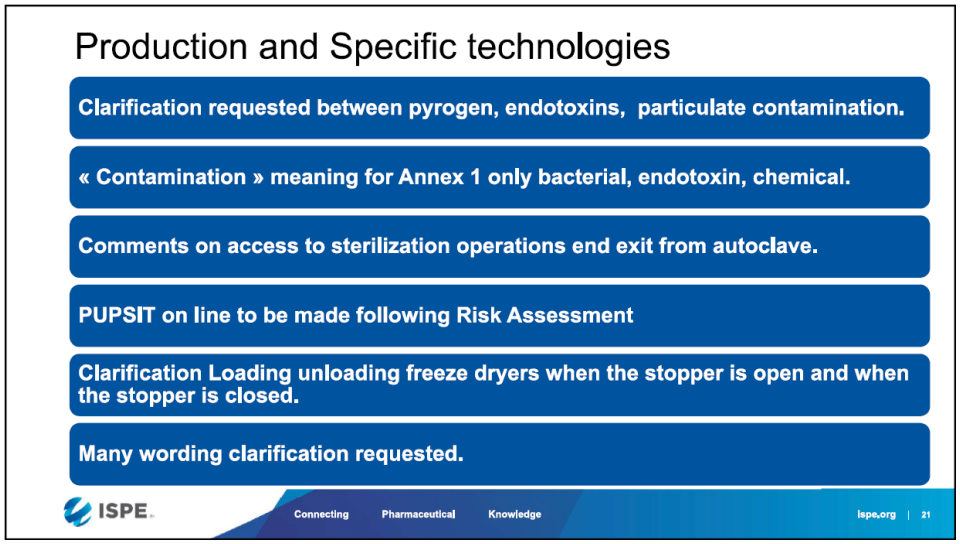

Figure 2: ISPE comments on Annex 1 regarding production and specific technologies

In summary, ISPE received, collected, aggregated and sent a large number of comments to the EMA on 20 March. The presentation of Jean-Francoise Duliere gave good insight into the work done by all the volunteers.

Annex 1: Questions & Answers from the Regulators

The Questions & Answers session with three regulators gave a great deal of input and many tips for the industry. **Vladislav Shestakov**, Russia, **Rick Friedman**, USA, and **Andy Hopkins**, UK, gave good insight into their interpretations of the Annex 1 draft and the upcoming steps.

Andy Hopkins explained that EMA will look at every single comment - they will go through it step by step. Not every comment can be included; some will be contradictory. At the end it will be a consensual document.

The discussion covered the complete annex. It would be too much to go into detail here - we from Maas & Peither GMP Publishing will cover some of the input in later LOGFILE newsletters.

Some of the Q&As:

Q: Which grade is allowed for loading and unloading of lyophilisation products?

A: As long as the stopper is not inserted, it is critical and only grade A is acceptable.

Q: PUPSIT (preuse post-sterilisation integrity testing) - why is it still a requirement?

A: We need PUBSIT - at the moment we see so other way. If you want to change this procedure you shall have to show us a proven scientific approach.

Q: What is understood by personal disqualification?

A: There is frequent documentation of why personnel is allowed to enter the cleanroom (training, monitoring, etc.). But if, for example, you still see increased contamination of employees after a long time of experience and training, you should take action and probably disqualify the person. If someone is ill in a critical way, there should be a disqualification. This is also documented in early GMPs.

„We have ICH Q9 in place - a document that gives you the possibility of making decisions on a risk-based approach."

Sources:

Andrew Hopkins, MHRA: Annex 1 – ISPE Update, ISPE European Annual Meeting 2018, Rome

Rick Friedman, Deputy Director FDA/CDER Office of Compliance: Current Perspectives on Aseptic Processing, ISPE European Annual Meeting 2018, Rome

Jean-Francoise Duliere, Pharmacy Senior Consultant, Technip France: Annex 1 Draft, ISPE Commenting Process, ISPE European Annual Meeting 2018, Rome

Thomas Peither, Live reporting from the conference on Linkedin (#gmppublishing)

Author:

Thomas Peither
Executive Editor
Maas & Peither AG - GMP Publishing
E-Mail: thomas.peither@gmp-publishing.com

