Report from the International Regulatory Panel

ISPE Aseptic Conference
14MAR2022, Bethesda, MD

#sharing challenges
and solutions in practice

Part of PharmaCongress – Düsseldorf/Neuss, 31 May–1 June 2022

Supported by

Jörg Zimmermann

Chair, International Board of Directors of ISPE

- Pharmacist by education
- Over 26 years of experience in the pharmaceutical industry
- Working for Vetter Pharma in Germany, CDMO for sterile dosage forms (syringes, vials, cartridges etc)
- Focus Areas: sterile and biotech products, aseptic processing, process and product development, lyophilization
- ISPE volunteer since 2000
- Speaker, track leader, conference chair, trainer and training development, reviewer for Pharmaceutical Engineering® Magazine etc
- Member of the International Board of Directors since 2016

ISPE Aseptic Conference 2022: 14/15MAR, Bethesda, MD

- Approx. 350 people on site
- 80 participants virtual
- Regulators virtual
- Full exhibit hall with good interactions

Participants in the Regulatory Panel

- **Alonza Cruse** — Director, Office of Pharmaceutical Quality Operations, FDA/ORA
- **Paul A. Gustafson** — 2022 PIC/S Chair, Sr. Corporate Regulatory Compliance & Enforcement Advisor, Regulatory Operations and Enforcement Branch (ROEB), Health Canada
- **Rick Friedman** — Deputy Director, Office of Manufacturing Quality, CDER/FDA
- **Brooke Higgins** — Senior Policy Advisor for the Global Compliance Branch 3, FDA
- **Robert Sausville** — Director, Division of Case Management, FDA/CBER/OMPT/OCBQ
- **Thomas J. Arista** — Consumer Safety Officer, FDA/ORA






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Technical and GMP Questions

What's the direction you see for ATMP manufacturing regulation? Currently its practice is looser than c-GMP requirements, I believe. Will the requirement for ATMPs be similar to c-GMP?

- **Paul:**

- Same general requirements for ATMPs in PIC/S with **PIC/S GMP guide part 1+2**
- **Annex 1** also applies
- **Annex 2 a** specifically for ATMPs
- Autologous therapies: one batch for one patient
- Provisions for working with multiple batches in the same area with appropriate controls
- Elevated GMP requirements for human cells and tissues:
  - **Traceability** of starting materials
  - Traceability of raw materials
  - Longer periods of time for record keeping

Eudralex Volume 4 has provisions for investigational ATMP guidelines. Is there an equivalent guidance document from US FDA?

- **Bob:**
- There is a guidance document, cGMP for phase 1 Investigational Drug Products, which was published in July of 2008. This was for CDER and CBER (maybe also for CVM). Anything past phase 1, we expect adherence to cGMPs under 501 A and B of the Food, Drugs and Cosmetics Act.

What data integrity issues are inspections uncovering in aseptic manufacturing operations?

- **Thomas:**

- Incubation of blank or clean plates for environmental sampling
- Pre-completion of batch records
- The findings always question the culture of the company
- Authenticity of all data is in question

- **Paul:**

- Data integrity issues are found in production and quality control
- PIC/S has a document on the topic:
  “Guide to good practices for data management and integrity in regulated GMP environments”

Should regulatory bodies set acceptable residual hydrogen peroxide levels specifically for biologic drug fills? And if so, at what ppb levels?

- **Bob:**

- FDA cannot set limits here
- Limits need to be developed product-specific and need to be scientifically justified
- Biological products are very varied

What kind of usage are you expecting for enzyme indicators for H_2O_2-decontamination? Do you see any possibilities that enzyme indicators replace biological indicators?

- **Thomas:**

- **Biological indicators** give you **quantitative data**
- Full process characterization can be done: spore reduction at a certain location, using a certain decontamination agent at a certain concentration.
- **Chemical or enzmye indicators** will give you only **qualitative data**
- Don‘t see enzyme indicators fully replace biological indicators

- **Rick:**

- Hybrid approach is possible
- Combination of air flow pattern visualization, showing potential turbulences with indicators to develop the decontamination process

What was the FDA's approach to approving new isolated technology, for example, of VANRX for commercial manufacturing? More specifically, how did you approach compliance with the current regulations and requirements?

- **Rick:**

- cGMPs are open to technological options
- Let‘s talk about **„robotic isolators“** in general
- New technologies are encourraged through FDA‘s **Emerging Technologies Team**
- Companies must know the **failure modes** of their systems
- Robotic isolators remove the risk from operators
- **Mechanical failures** with air quality or piping issues (in CIP/SIP) remain

- **Thomas:**

- **Environmental monitoring** is often overlooked in the design of these systems
- This includes microbiological and particulate sampling

What is the expectation on environmental monitoring in an automated line? Do we need to conduct all settle plates, contact plates and active sampling by robots or manually?

- **Thomas:**

- What do you want to accomplish by monitoring your facility?
- Automation means less interventions, which might mean less monitoring to control the process
- **Monitoring strategy** must be **risk-based** and must achieve the goal of **proper product control**

- **Rick:**

- For example, in an isolator, you might be able to do less monitoring: surface and glove monitoring at the end of a campaign instead of daily.

If filters are 100% integrity tested prior to integration into a non-sterile single use system, is there a risk that the single use irradiation process will create defects in the membrane that would require PUPSIT (post-sterilization, pre-use integrity testing)?

- **Paul:**

- Let‘s focus on the risk of the **radiation process**
- Responsibility is with the manufacturer
- Needs to have a quality risk management framework
- **QRM** must be be based on the **knowlege of the process**
- QRM must be based on the impact of any irradiation process
- **Supplier qualification** is important

Do you expect or prefer incubators for aseptic ATMP manufacturing to be decontaminated? It's usually one of the riskiest parts of the ATMP aseptic manufacturing.

- **Bob:**

- Assume this is an incubator for the growth of a product in early stage processing
- Since it is a risky part of the process, **we would expect a decontamination**

- **Paul:**

- PIC/S Annex 2 for ATMPs:
- Good quality risk management must be applied
- Many specific process questions are discussed in this Annex

There was a recent Federal Register Notice with a request for input from industry on the Quality Metrics Scheme. Can anyone comment on this?

- **Rick:**

- FDA is reporting lessons learned from the pilots
- FDA is seeking feedback
- Notice includes descriptions of what a modified quality metrics program might look like
- Office of Quality Surveillance in the Center for Drugs is running the program
- Commenting is until June 7th

- *[ISPE is collecting comments from industry and will provide them to the FDA]*

Considering the significant investment in manufacturing capabilities seen in the past few years, can the panel speak to the vision to keep up? What should the industry do to aid the regulatory ramp up?

- **Rick:**

- Industry has driven the upgrades to isolators and barrier systems
- Bob and Rick have been involved in the discussions for 25 years
- ISPE survey data has been instrumental in shaping the technology
- GMPs allow for these innovations
- Annex 1 draft calls for **Contamination Control Strategy (CCS)**
- From a product standpoint, it is a Contamination Prevention Strategy
- FDA encourrages industry to report on new technologies via the Emerging Technologies Team at FDA

Can you give some background to the recent draft guidance for industry from FDA on the visual inspection that came out recently?

- **Rick:**

- Draft was issued in December 2021
- Filling the void between USP requirements and cGMPs
- Intrinsic and foreign particles are a patient safety risk
- Holistic risk-based approach to improve the performance of industry

The leaked version of Annex 1 (version 13.1) had guidance values replaced by minimum requirements. Is this going to be also in the final version?

- **Paul:**

- Language was adapted to explain that where specific limits or frequencies are mentioned, they are considered a **minimum requirement**
- They are based on historical regulatory experiences
- There is flexibility with quality risk management
- Example:
  - Autoclave leak testing has a recommended frequency of once per week
  - If you are not using the autoclave on a weekly basis, there is no need to test

When will the final version of Annex 1 be published by EMA and PIC/S?

- **Paul:**

- Current expectation is **between July 2022 and the end of September 2022**
- Joint document between the European Commission, WHO and PIC/S
- Within PIC/S, the Annex is in the final approval steps

Not interrupting first air in RABS and isolators is a goal in Annex 1. In practice, we know that this will not always be possible. How should this be approached?

- **Thomas:**

- Interrupting first air should be avoided at all costs
- Airflow pattern evaluation and visualization will help
- Strongly encourage to include operators and those performing environmental monitoring in the design of your RABS or isolators
- Minimize first air interrupting activities
- When interruption is unavoidable, demonstrate that those have no negative impact on the quality of the product and to not lead to potential contamination

What is your stance on continuous process verification and using it to replace time based, for example, annual or biannual requalification?

- **Rick:**

- Qualification and validation are conflated in this question
- Equipment is qualfied
- Processes are validated
- Continued Process Verification (CPV) can be combined with continous manufacturing
- On-line-measurements can provided feedback to control the process
- For sterile products, this is not possible: sterility cannot be verified continously
- 100% fill weight checks however are a good way forward

What role do you foresee single use systems playing in the future, given the push towards sustainability and sustainable technology?

- **Paul:**

- Regulators and industry should work together on sustainable approaches
- Environmental impact of single-use systems should be evaluated
- Compare to the conventional process that is being replaced by single-use systems
- Can waste be used for energy systems?
- Bio-hazard risks need to be considered

We only have warehouses and we distribute drug products for the US market. What are the primary processes and systems and FDA inspection would focus in on for this type of facility?

- **Thomas:**

- Basic material management
- Incoming material controls
- Storage conditions suitable for the products
- When product is shipped: when does ownership change?
- If at the loading dock: transport is the responsibility of the customer
- If at the customer: transport is the responsibility of the supplier

Inspection Related Questions

Data integrity citations in financial year 2021 dropped significantly, and the lack of physical inspection is widely considered part of the reason. How will this be addressed going forward?

- **Alonza:**

- Domestic inspections in the USA have resumed
- Mission critical inspections have continued through the pandemic (pre-approval inspections, official action indicated inspections, for cause compliance inspections)
- Additional resources were put into the ISPE India office
- On-site inspections still represent the best way to audit a facility

- **Brooke:**

- Encourage industry to self-report any data integrity issues that are identified
- Be transparent and work with the agency to resolve the issues

Could FDA please comment on how they're going to work through the backlog of foreign inspections with so many open positions in the inspectorate?

- **Alonza:**

- 80 new investigators were hired in the last two years
- Training continued internally
- Extensive use of Mutual Recognition (MRA)
- Information was also requested on inspections conducted by EU member countries outside of Europe
- FDA requested local European authorities to inspect certain sites in Europe
- EU authorities requested FDA to inspect certain sites in the US

Do you have any comments on learnings from COVID and ways to modernize inspection approaches and a path forward with industry?

- **Alonza:**

- **Record requests** under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374(a)(4)] were used intensively
- **Remote Interactive evaluations** (teleconferencing) will continue
- Working on best combination of record requests and physical inspections

- **Paul:**

- Workshop held at PIC/S with 315 inspectors from 54 participating authorities
- Preference for on-site inspections
- Working group is developing a process for Distant Assessments and hybrid strategies
- ICMRA has published some reflection papers on the topic on their webpage

The FDA has resumed both domestic and foreign inspections. However, our company has noticed FDA is scheduling foreign surveillance inspections within MRA countries for no obvious reason. Could FDA perhaps elaborate?

- **Alonza:**

- International inspections are for mission critical pre-approval inspections primarily
- If another site is in close proximity or the same country, it might be inspected at the same time
- Requests for MRA are sometimes beyond the scope of the inspectorate of the EU member country, so it needs to be done by FDA

Summary

- Many detailed technical questions on the production of sterile products were answered
- Inspection learnings from the pandemic were discussed
- Good, clear voicing of the current thinking of the agencies
- A summary of the panel will be published as an online exclusive for Pharmaceutical Engineering Magazine

Thank you for your attention

QUESTIONS ?

joerg.zimmermann@vetter-pharma.com
Chair, ISPE International Board of Directors