“Summary delle attività degli interest group e task force di PDA, Hightlights su Revisione Annex 1“

Assemblea Annuale

PDA Italy Chapter

Milano, Mercoledì 24 gennaio 2018

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Agenda

- Latest updates on

1. *PDA Interest Groups (IGs)*
2. *PDA Task Forces and Forum*
3. *EU GMP Volume 4 Annex 1*

PDA IG Task Forces and Forum – Update

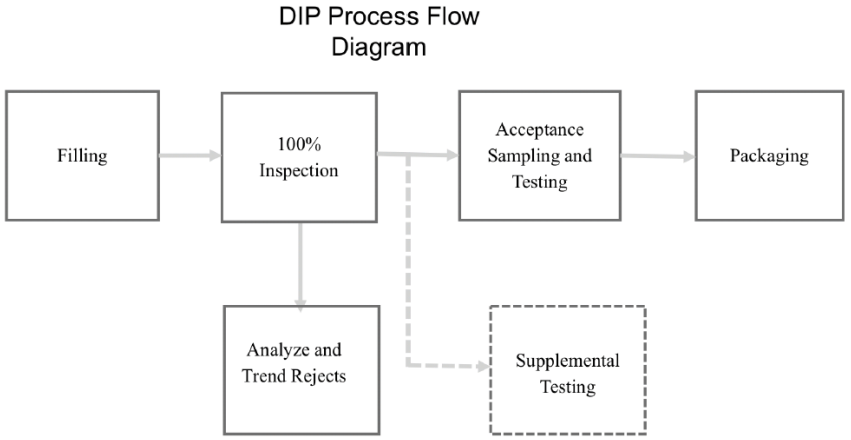
- Themes of current interest
  1. *Visual Inspection*
  2. *Container Closure Integrity*
  3. *SUS, Prefilled Syringes*
  4. *Blow-Fill-Seal*

1. Visual Inspection: DIP

- PDA TECHNICAL REPORT NO. XX: Particulate Matter Control in Difficult to Inspect Parenterals
  - ✓ *Draft available – PDA VI IG and volunteers into PDA Community*
  - ✓ *Points of interest:*
    - ➢ *opaque and deeply colored solutions, lyophilized cakes, powders, concentrated suspensions, and emulsions*
    - ➢ *plastic syringes, blow-fill-seal packaging, flexible bags, specialty containers, and medical devices*

1. Visual Inspection: DIP (Cont'd)

- Current Directions
  - ✓ *where 100% inspection is not fully effective in removing visually detectable particulate matter, companies should put in place a robust lifecycle approach and utilize the appropriate statistical destructive inspection or testing*
  - ✓ *a supplemental, statistically-based reconstitution or other destructive test is needed as a quality check for each batch to determine how frequently and what types of intrinsic/extrinsic foreign particulates are present*



1. Visual Inspection: DIP (Cont'd)

- PDA Survey on DIP Products
  - ✓ *101 respondents worldwide*
  - ✓ *The survey indicated that only about 50% of the companies producing DIP products currently comply with the guidance in USP <1> and USP <790> for supplemental destructive testing*
  - ✓ *Most reported products are packaged in clear glass vials or syringes (85%). Other common DIP container types are amber glass (29%) and plastic syringes (17%)*
  - ✓ *DIP formulation types: lyophilized (93%), suspensions (51%) and opalescent to milky solutions (29%)*

1. Visual Inspection: DIP (Cont'd)

- Methods of Destructive Testing
  - ✓ *Reconstitution and inspection of Lyophilized and Powder forms*
  - ✓ *Membrane filtration or sieving for a variety of product formulation types*
  - ✓ *Clarification by adding a solvent, acid, or base for suspensions and emulsions*
  - ✓ *Transfer to a clear container and inspection (may significantly increase the chance of lab contamination)*
- Other results
  - ✓ *Use of external or contract services for particulate characterization is increasing (42%)*
  - ✓ *Some firms (9%) do not perform any particulate characterization on their products*

1. Visual Inspection: DIP (Cont'd)

- Recommendations
  - ✓ *Combination of methods AVI, SAVI, MVI*
  - ✓ *Use various illumination sources (e.g. backlight, Tyndall lighting, IR)*
  - ✓ *Defect standards / qualification set*
  - ✓ *Thorough evaluation of the product lifecycle is required in order to minimize foreign particulate in each of the upstream process steps. Raw materials, API, expendable product contact materials, reusable equipment, and primary components should be routinely monitored for foreign particulate control*
  - ✓ *Robust in-process fill and seal particulate generation controls must be considered for glass breakage events, operator intervention, and routine equipment maintenance cycles.*
  - ✓ *Evaluation of rejected product provides an understanding of the particle populations present, identifying opportunities for mitigation or reduction.*

2. Container Closure Integrity: New TR

- PDA TECHNICAL REPORT NO. XX: “Pharmaceutical Package Integrity Testing: Industry Challenges, Technology and Advancement“

- This report:
  - ✓ *Is not an update of the information described in the existing TR27*
  - ✓ *Is a replacement of the previous report and represents an evolution of the package integrity information covered by the previous report*
  - ✓ *Provides current thinking on the challenges faced by industry when utilizing complex packaging systems*
  - ✓ *Describes emerging technologies in the field of package integrity testing*

2. Container Closure Integrity: New TR (Cont'd)

- This report:
  - ✓ *Is an influential document for industry*
  - ✓ *Is not intended to be used as a regulatory guidance*
  - ✓ *Is focused to be complimentary to USP <1207> as resources of current technologies in package integrity*
- Three main sections:
  1. *Challenges with complex systems & associated case studies*
  2. *Emerging integrity testing technologies*
  3. *Future directions for pharmaceutical package integrity*

2. Container Closure Integrity: New TR (Cont'd)

- Current status:
  - ✓ *USP <1207> issued and acknowledged*
  - ✓ *Revision of contents to avoid redundancies and to introduce technology updates*
  - ✓ *Harmonization of thinking with Annex 1*
  - ✓ *Task force team reorganized*
  - ✓ *Advisor board approval planned by 2018 end*

3. SUS, Prefilled Syringes: CCI

- PDA TECHNICAL REPORT NO. XX: “Pharmaceutical Package Integrity Testing: Industry Challenges, Technology and Advancement“ – Integrity testing of prefilled syringes: Container and Product Design Considerations

1. *Fill Contents, product and surrogate testing*
   - CCI decisions related to product physical properties
   - WFI fill is widely accepted were needed
2. *Staked VS Luer-Lock needle, Luer Slip, or Luer Cone*
   - Several different syringe designs and elastomeric closures available
   - Proper interference fit between closure system and syringe barrel is also an essential requirement to ensure container closure integrity
   - Additional considerations for this interface include performance requirements such as permeability to sterilizing agents, removal forces, torqueing forces, and device compatibility

3. SUS, Prefilled Syringes: CCI

3. *Plunger Rod VS No Plunger Rod*

   - Since the addition of these secondary items may impact the different seal points on the syringe, CCI of the finished syringe should be assessed
   - Plunger rod insertion may potentially impact the seal on the plunger stopper, and deserves careful evaluation

4. *Positive Controls*

   - Usage is required when performing CCIT method development and validation, even if they are not thoroughly representative of real container closure integrity defects

5. *Cartridges – Single Chamber / Dual Chamber*

6. *Stoppers*

   - The design of the plungers per ISO 11040-5 all employ three ribs
   - Excess lubricity coating while good for plunger/piston functionality and movement in use, may result with the plunger/piston moving too freely during transit causing breeches in CCI

3. SUS, Prefilled Syringes: CCI

7. *Stopper movement during CCIT*

   - In the case of the test methods exploiting a pressure differential between the container interior and the test chamber (ex. vacuum decay and mass extraction), stopper movement should be minimized.

8. *Filling and stoppering method impact*

9. *Fill volume / headspace*

   - Fill volume of samples should be sufficient to conduct the testing method
   - Minimum headspace volume for headspace gas analysis

10. *Feasibility and Method validation*

    - It might be necessary to validate different drug products, even if used in the same delivery system, depending on what method is used to evaluate CCI.
    - Each method should be independently validated for its limit of detection

3. SUS, Prefilled Syringes: CCI

11. *Auto-injector (or Pen) and safety system design impact on CCIT*

    - Best practice for deterministic methods for use in process validation and throughout stability would be a two-pronged approach consisting of a high voltage leak detection method for evaluating the isolated primary package as well as a pressure-based analysis to evaluate the assembled combination product

12. *Plastic Syringes*

    - Container closure integrity requirements expected for glass syringes throughout product life cycle phases as outlined in this chapter are also applicable for plastic syringes.
    - However, polymer materials, along with its manufacturing processes, may present a unique set of risks for forming and maintaining seal integrity throughout drug product life cycle

13. *Functional secondary packaging: plunger rod placement, finger flange placement, labeling, placement into a tray, and carton insertion*

4. Blow-Fill-Seal

- The Manufacture of Sterile Pharmaceuticals and Liquid Medical Devices Using Blow/Fill/Seal Technology – Points to Consider

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4. Blow-Fill-Seal (Cont'd)

- Updates:
  - ✓ *PDA BFS Interest Group*
  - ✓ *Strong interest by PDA – joint meeting*
  - ✓ *Revision of PTC document planned: introduction of new aspects*
    - ➢ *Parenteral products into BFS packages*
    - ➢ *Visual inspection – difficulties in the detection of foreign contaminants for injectable products*
    - ➢ *Container Closure Integrity – potential compromise of product stability and sterility after leak detection*

EU GMP Volume 4 Annex 1 – Outline

- Annex 1 first issued in 1989 and partially revised in 1996, 2003 and 2007
- There has not been a complete review of the document since it was originally issued
- Since its issuance, advances in technologies and significant changes in GMP following the adoption of the ICH Q9 (Quality Risk Management) and ICH Q10 (Pharmaceutical Quality System)
- In recent years, it has become evident that the current Annex 1 has not kept pace with current regulatory and technological advancements and hence a complete review is necessary
- The need to correct historical ambiguities and historical inaccuracies are also behind the need for a revision

Annex 1 – Update

- Recent updates to Ph. Eur. regarding methods of production of Water for Injection which now allows methods other than distillation is yet another reason why an update to the current Annex is required.

- As the current guideline is used to provide guidance on the conditions of manufacture of some non-sterile finished products and the early stages in the manufacture of a range of products, the new revision will include clarification on these areas of applicability using the principles of QRM.

- The scope of the guideline will be broadened to encompass these references.

- Consultation Document on Revision of Annex 1

- https://picscheme.org/layout/document.php?id=1268

Annex 1 – Commenting Phase

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 25 November 2008 (rev.)

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Annex 1
Manufacture of Sterile Medicinal Products
(corrected version)

Document History	
Previous version dated 30 May 2003, in operation since	September 2003
Revision to align classification table of clean rooms, to include guidance on media simultations, bioburden monitoring and capping of vials	November 2005 to December 2007
Date for coming into operation and superseding	01 March 2009[1]

Please note correction on the implementation of provisions for capping of vials!

[1] Note: Provisions on capping of vials should be implemented by 01 March 2010.

Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium. Telephone: (32-2) 299 11 11

Submission of comments on Revision of 'Annex 1: Manufacture of Sterile Medicinal Products'

Comments from:

Name of organisation or individual

1. General comments

General comment (if any)

2. Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Comment: Proposed change (if any):
	Comment: Proposed change (if any):
	Comment: Proposed change (if any):

Note: All comments must be received in the table for consideration by 31Jan2018

Annex 1 – Revision: New concepts

1 **Annex 1**

2 **Manufacture of Sterile Medicinal Products**

3 **Document map**

Section Number	General overview
1. Scope	Additional areas (other than sterile medicinal products) where the general principles of the annex can be applied.
2. Principle	General principles as applied to the manufacture of medicinal products.
3. Pharmaceutical Quality System (PQS)	Highlights the specific requirements of the PQS when applied to sterile medicinal products.
4. Personnel	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance to the qualification of personnel.
5. Premises	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of barrier technology.
6. Equipment	General guidance on the design and operation of equipment.
7. Utilities	Guidance with regards to the special requirements of utilities such as water, air and vacuum.
8. Production and specific technologies	Discusses the approaches to be taken with regards to aseptic and terminal sterilisation processes. Also discusses different technologies such as lyophilization and Blow Fill Seal (BFS) where specific requirements may be required. Discusses approaches to sterilization of products, equipment and packaging components.
9. Viable and non-viable environmental and process monitoring	This section differs from guidance given in section 5 in that the guidance here applies to ongoing routine monitoring with regards to the setting of alert limits and reviewing trend data. The section also gives guidance on the requirements of Aseptic Process Simulation.
10. Quality control (QC)	Gives guidance on some of the specific Quality Control requirements relating to sterile medicinal products.
11. Glossary	Explanation of specific terminology.

This Annex provides general guidance for all sterile medicinal products and sterile active substances, via adaption, using the principles of Quality Risk Management (QRM)

The intent of the Annex is to provide guidance for sterile medicinal products.

However some of the principles and guidance, such as contamination control strategy, room qualification, classification, monitoring and gowning, may be used to support the manufacture of other products that are not intended to be sterile

Annex 1 – Development

- ❑ All sections were expanded and detailed, new sections introduced
- ❑ Reference made to Annex 11, Annex 15, PIC/S guide PE 010-4
- ❑ Relevance given to QRM and QA
  - ✓ *"Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles that provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality.* ***Risk assessments should be used to justify alternative approaches to those specified in this Annex only if these alternative approaches meet or surpass the intent of this Annex.***"

Revised Annex 1 – CCI

- Focus on Container Closure Integrity
  - ✓ *Containers should be closed by appropriately validated methods.*
  - ✓ *Containers closed by fusion, e.g. Form-Fill-Seal Small Volume Parenteral (SVP) & Large Volume Parenteral (LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing.*
  - ✓ *Samples of other containers should be checked for integrity utilising validated methods and in accordance with QRM, the frequency of testing should be based on the knowledge and experience of the container and closure systems being used.*
  - ✓ *A statistically valid sampling plan should be utilized. It should be noted that visual inspection alone is not considered as an acceptable integrity test method*
  - ✓ *Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate, pre-determined period and during shelf life.*

Revised Annex 1 – VI

- Focus on Visual Inspection
  - ✓ *All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. QRM principles should be used for determination of defect classification and criticality. Factors to consider include, but are not limited, to the potential impact to the patient of the defect and the route of administration.*
  - ✓ *Different defect types should be categorized and batch performance analyzed.*
  - ✓ *Batches with unusual levels of defects, when compared to routine defect levels for the process, should lead to investigation and consideration of partial or the whole rejection of the batch concerned.*
  - ✓ *A defect library should be generated and maintained which captures all known defects. The defect library can be used as a training tool for production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling of acceptable containers as it indicates a failure of the original inspection process.*

Revised Annex 1 – VI (Cont'd)

- Focus on Visual Inspection *(cont'd)*
  - ✓ *Where automated methods of inspection are used, the process should be validated to detect known defects with sensitivity equal to or better than manual inspection methods and the performance of the equipment checked prior to start up and at regular intervals.*
  - ✓ *Results of the inspection should be recorded and defect types and levels trended.*
  - ✓ *Reject rates for the various defect types should also be trended.*
  - ✓ *Investigations should be performed as appropriate to address adverse trends or discovery of new defect types.*
  - ✓ *Impact to product on the market should be assessed as part of this investigation.*

Revised Annex 1 – VI (Cont'd)

- *Remarks from the PDA VI SAB*
  - ✓ *PIC/S and EMA have expanded the guidance on visual inspection and container integrity. In general, the points made are consistent with current good practices in visual inspection and agree with other guidance such as that found in USP <1790>.*
  - ✓ *Of note however, is that visual inspection is no longer considered sufficient for assuring container integrity. This is most significant for containers sealed by fusion such as ampoules and flexible bags, where confirmation of all units produced is required.*
  - ✓ *There continues to be an issue with the expectation to be "free" for mAB's, while "practically free" for all other injectable drug products. The reason for the difference and how to comply is still not clear.*
  - ✓ *It also suggests that some form of instrumental leak testing is required on a sample for other containers.*
  - ✓ *Also added more detail on training, classification, trending and use of automated inspection*

Revised Annex 1 – VI (Cont'd)

- *Message from the PDA VI IG (Cont'd)*
  - ✓ *Please review and share your comments and concerns.*
  - ✓ *PDA is planning to respond to this draft and will need your comments by the end of January to meet the deadline for internal review and reply.*
  - ✓ *The PDA VI IG is also planning a 1-day workshop in Bethesda the week of April 23, 2018. This workshop will include discussion of hot topics in visual inspection such as these proposed changes.*
  - ✓ *The PDA TRI course, Introduction to Visual inspection will be taught this same week for those who wish to take advantage of both opportunities in Bethesda.*

Revised Annex 1 – Example of new sections

- Sterilization
  - ✓ *Specific related contents were grouped in dedicated sections*
  1. *Sterilization by heat*
  2. *Moist heat sterilization*
  3. *Dry heat sterilization*
  4. *Sterilization by radiation*
  5. *Sterilization with ethylene oxide*

Revised Annex 1 – Specific recommendations

- Closed Systems and SUS
  - ✓ *Integrity testing, Pin-hole and leakage*
  - ✓ *Risk of particulate contamination*
  - ✓ *Compatibility of materials used for product contact surfaces*
  - ✓ *SUS should be designed so as to maintain integrity during the intended operational conditions and duration, especially the structural integrity of the single use components under extreme process and transport conditions such as during freeze and thaw processes. This should include verification that intrinsic aseptic connections (both heat and mechanical) remain integral under these conditions*

Thank you !!!

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