Worldwide Regulatory Requirements and Standards for Inspection of Sterile Drugs – Container Closure Integrity Test

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Intro and Background

- Over the last years:
  - Growing needs as regulatory expectations
  - Product and package systems are becoming more complex

- Regulatory Requirements and Standards

  I. US FDA Guidelines

  II. Revised EU GMP Volume 4 Annex 1

  III. USP <1207>

  IV. PDA Technical Report “TR” 27 and new PDA TR on CCI

Food and Drug Administration (FDA) Guidelines

"Container and Closure System Integrity Testing *in Lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products" – February, 2008

- Recommendations to manufacturers
- Use validated physical methods other than sterility testing to confirm CCI as a part of the stability protocol for sterile drugs
- Does not require a comparison of physical methods to microbial ingress risk
- Instead, validation data are required demonstrating test method container closure defect detection capability

Food and Drug Administration (FDA) Guidelines

"Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004)

- Inspection of Container Closure System
- Guidance for Industry
- *"Any damaged or defective units should be detected, and removed, during inspection of the final sealed product"*
- *"Any defects or results outside the specification established for in-process and final inspection are to be investigated in accord with § 211.192"*

European Commission – Annex 1

EU GMP Annex 1, Manufacture of Sterile Medicinal Products”

- *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*
- *Need to correct historical ambiguities and inaccuracies*

Revised EU Annex 1 – Details

Items related to Container Closure Integrity

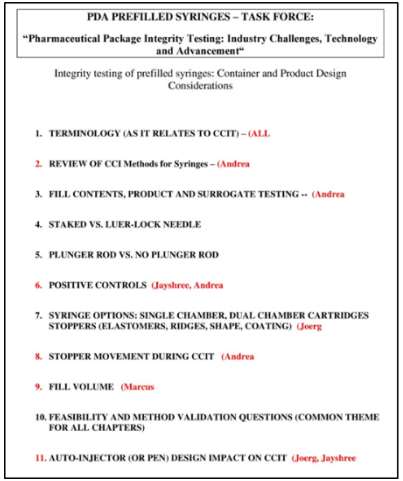
- *Containers should be closed by appropriately validated methods.*
- *Containers closed by fusion, e.g. Form-Fill-Seal Small Volume Parenteral (SVP) & Large Volume Parenteral (LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing.*
- *Samples of other containers should be checked for integrity utilizing 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*

US Pharmacopoeia “USP” Chapter <1207>

- USP <1207> “Sterile Product – Package Integrity Evaluation Introduction”
  - Published 1998, Revised 2016
  - Guidance on the integrity assurance of nonporous packages intended for sterile pharmaceutical products
- Detailed recommendations are presented in three subchapters
  - <1207.1> Package Integrity and Test Method Selection
  - <1207.2> Package Integrity Leak Test Methods
  - <1207.3> Package Seal Quality Test Methods

PDA – New TR on Package Integrity Testing

- Technical Report “TR” XX:
  - Not an update of the existing TR27
  - Replacement / evolution of the previous report
- Main sections:
  1. Challenges with complex systems
  2. Case studies
  3. Emerging integrity testing technologies
  4. Future directions for CCI

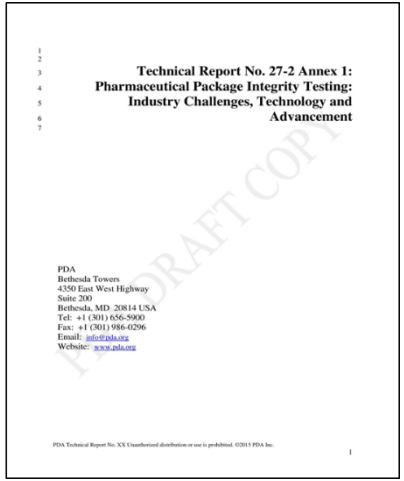


PDA PREFILLED SYRINGES – TASK FORCE:

“Pharmaceutical Package Integrity Testing: Industry Challenges, Technology and Advancement“

Integrity testing of prefilled syringes: Container and Product Design Considerations

1. **TERMINOLOGY (AS IT RELATES TO CCIT) – (ALL**
2. **REVIEW OF CCI Methods for Syringes – (Andrea**
3. **FILL CONTENTS, PRODUCT AND SURROGATE TESTING -- (Andrea**
4. **STAKED VS. LUER-LOCK NEEDLE**
5. **PLUNGER ROD VS. NO PLUNGER ROD**
6. **POSITIVE CONTROLS (Jayshree, Andrea**
7. **SYRINGE OPTIONS: SINGLE CHAMBER, DUAL CHAMBER CARTRIDGES STOPPERS (ELASTOMERS, RIDGES, SHAPE, COATING) (Joerg**
8. **STOPPER MOVEMENT DURING CCIT (Andrea**
9. **FILL VOLUME (Marcus**
10. **FEASIBILITY AND METHOD VALIDATION QUESTIONS (COMMON THEME FOR ALL CHAPTERS)**
11. **AUTO-INJECTOR (OR PEN) DESIGN IMPACT ON CCIT (Joerg, Jayshree**



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