**Practical Applications and Benefits of Sterile Product Compliance Risk Assessments**

**Reality Check & Responsibility**
- Microorganisms are omnipresent in the environment.
- A variety of potential sources can lead to non-sterile product results.
- The volume and kind must meet the purity and endotoxin standards for medical products.
- Automated equipment procedures in any case very risky for the patient.

**Risk Assessments Are Required**
- Each process must be a risk analysis to have risk analysis in use.
- Conduct with FDA, DOE, and/or Pharmaceutical SMEs for the 21st century.
- Support the implementation of EU-CHQ, G3, and GS1.
- Mandatory risk analysis. The EU Good Manufacturing Practice (6) Guidelines.

**Risk Analysis Tools**
- Uncover latent and process steps that are lacking controls.
- Provide information about potential medicinal risks and ensure the necessary risk management in the sterile product.
- Are in support of in process deviations and batch disposition decisions.

**Scope and Objective of SPCRA Tools**
- SPCRA serves as investigative tool in case of deviations and as proactive tool for the prevention of non-compliance during product quality and regulatory audits.
- Objective: to assess risk for product contamination.
- Admits the use of advanced technology tools and computer-based simulation and/or assessment of product risk in market (e.g. field tests – tooling up) complementing experienced human judgment.
- SPCRA's bench mark 65% - 75% of product assessments.
- Rating scoring should be done by an independent expert / 3rd party.
- In case of good outcome, very valuable tool to prove and improve process and product quality (e.g. Proof of SPCRA for warning letter cited sites).
- SPCRA should be used proactively and not to identify the root cause of quality issues.

**Gapp Quality SPCRA Tool – Facts**
- Based on more than 30 years experience in the pharmaceutical industry.
- Simple, flexible, and comprehensive approach to risk assessment of sterile plants.

**Gapp Quality SPCRA Tool – Method**
- The manufacturing stage is classified into individual manufacturing steps or process flow. For each such unit multiple of specific questions are asked, encompassing all areas of risk involved in process production. 
- The following production units are evaluated using specifically (H40SP) analysis risk analysis method (for 21st plant).

**Gapp Quality SPCRA Tool – Amendments**
- Variable Unit REFS.
- Knock-Out Questions.

**Variable Unit REFS**
- Variable REFS reflect the standard of equipment and otherwise filling technology used in ‘Non-Filling Unit’. This makes it possible to reveal advanced equipment technology (e.g. isolation) that has a lower inherent contamination risk.

**Knock-Out Questions**
- Certain questions have a disproportionately high impact on overall compliance results. 
- They represent deficiencies that could lead to production non-sterility or endotoxin (3rd party). 
- To ensure that such risks are flagged and appropriately prioritized, a score of 100 is assigned to negative answers.
- These questions are referred to as ‘Knock-out questions’. (420SP).
- A non-sterile product (HAS/AGN) is rated as MODERATE, which should be considered unacceptable for a production grade.
- Prevents a series of risk factors being utilized when assessing all endotoxin questions.
- Where critical parameters that allow effective measures to be taken and the implementation of remedial actions and/or investments are involved.
- As well-controlled sealed manufacturing process plant not a question in 420SP.
- This is primarily a question of the plant to be shut down, but Defect REFS should be implemented with the highest priority.

**Gapp Quality SPCRA Tool – Targets**
- The first 25% should be in a ‘green range’ (score 10-19) for DEF 3.
- No ‘KO-Question’ should be answered with “100”.
- Identified scored 100-CAPAs have the highest priority for remediation measures.
- No “KO-Question” should be answered with “100”.

**Real World Experience – Gapp Quality SPCRA Tool**

**Case #1 / Minimizing risk from MODERATE to LOW within one year**
- Experience client: aseptic filling
- 2015 risk assessment: MODERATE, risk for product non-sterility and regulatory non-compliance (TRF = 21.4)
- After risk assessment: 2016, improvements were implemented:
- MODERATE to LOW, risk for product non-sterility and regulatory non-compliance (TRF = 17.7)

**Case #2 / Assuring sterility compliance when faced with an FDA warning letter**
- Client with isolator filling cited with warning letter
- 2016 risk assessment: MODERATE, risk for product non-sterility and regulatory non-compliance (TRF = 20.1)
- After risk assessment: 2017, improvements were implemented:
- MODERATE to LOW, risk for product non-sterility and regulatory non-compliance (TRF = 19.2)

**Summary sheet of SPCRA Tool (Case #2)**

**References**
1. FDA Final rule: announcing a new rule and guidance for pharmaceutical manufacturing and process control.
2. Quality System: a Risk-Based Approach – Fall 2004 [Internet]
6. ISO 14971:2007 - Application of risk management to medical devices [Internet]
7. Strengthen teamwork, support multidisciplinary cooperation
8. Successful quality management / risk assessment requires a skilled and experienced multifunctional team
9. Provide resources, invest in advanced technologies
10. Commitment to forewarning during execution of SPCRA
11. Successful teamwork, evident multidisciplinary cooperation
12. Provide enough time (3-6 weeks) for risk assessment procedures

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**Figure 1**: Schematic overview of process units and related Risk Emphasis Factors (REF)