(NON-STERILE RESULTS)

ASEPTIC PROCESSING HOT TOPICS & PRACTICAL EXPERIENCES

FROM THE VIEW OF A SENIOR QA MICROBIOLOGIST IN USAGE OF STERILE RISK ASSESSMENT TOOLS

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CHALLENGES IN ASEPTIC PROCESSING

- **Non-sterile results** in sterility testing (ST) & media fills create a high risk for the patient AND the company.
- All parties (production / engineering / quality assurance (QA) / quality control (QC) / management) are required to develop and realize preventive action plans and implement corporate culture in every day procedures.

THE REALITY >>

- Non-sterile results in aseptic processing cannot be prevented indefinitely - they will happen!
- QC microbiological primary testing results are not reproducible (in contrast to several chemical QC-release assays), no „retesting" is allowed or possible.
- Contaminants are not equally distributed in the sample or product.

THIS RESULTS IN SERIOUS CHALLENGES FOR QA MICROBIOLOGISTS >>

- Immediate action required (investigation / field alert / global escalation)
- Correct release decision under deadline pressure required
- Pressure to identify the root cause: microlab (ST) or sampling procedure? Process or product?
- Often the root cause remains undetected

HOW TO BE BETTER PREPARED

1 SUCCESSFUL CORPORATE CULTURE

MANAGEMENT LEVEL

Long standing employees (> 10 years) are of great value.

- CAUTION: Considerable staff turnover in global companies!
- Try to retain the skilled employees and treat them well.

Recognize the impact of highly motivated production personnel.

- CAUTION: QA should have no „police function", but should act as a strong partner!
- Appreciate and encourage shop floor personnel; provide the feeling that they are extremely important for the quality.

Common practice to separate QA and QC microbiology departments.

- CAUTION: Microbiologist experts lose oversight during investigations!
- Strengthen teamwork
- Support collaboration

STAFF LEVEL

High commitment to good aseptic working practices of the production and cleanroom personnel is of utmost importance for effective risk management and the quality of the final product.

- CAUTION: Cost saving programs result in understaffed production departments. The lack of cleanroom personnel requires fast working and mistakes are more likely to occur.
- Invest in training and a commitment to quality of shop floor operators and cleanroom personnel.
- Provide regular presence of a strong QA department at the shop floor.
- Ensure extensive knowledge of QA within operations (including sampling).

PREVENT

LEAN MANUFACTURING - COMMUNICATION ERRORS
(e.g. making shop floor operators believe that the quantity of filled units is more important than the quality)

COST SAVINGS THAT LEAD TO UNDERSTAFFING
(e.g. resulting in rapid movements in cleanrooms, compromised QA oversight)

INADEQUATE SALARY OF CLEANROOM OPERATORS

PRESSURE ON CLEANROOM PERSONNEL
(e.g. not to run into environmental monitoring (EM) deviations: tightening of EM limits within grade A (target = 0 colony forming units) by industry → leads to false negative results with additional lack of information)

2 RISK ASSESSMENT

IMPLEMENT PAPERWORK FOR A SYSTEMATIC INVESTIGATION

- Have good SOPs, checklists and simple flow charts ready to hand.
- Define details for escalation in advance.

IMPLEMENT PROACTIVE RISK MANAGEMENT

- Have a structured quality risk management (QRM) in use.
- Perform quality risk analysis proactively and periodically.

BENEFIT FROM

- Early identification of weak points for remediation.
- All parties being familiar with the process prior to running into deviations.
- Strengthened teamwork between QA / production / engineering.

RISK ASSESSMENT TOOLS

Each sterile manufacturing production site is required to have a risk analysis tool in use.[1]

Nearly a decade ago, the author developed a detailed questionnaire based on his knowledge and experience in the field of QA/QC microbiology, sterile production, aseptic processing and regulatory audits. Over the course of years the questionnaire evolved into three independent hazard operability analysis (HAZOP) tools that are today employed in numerous sterile active product ingredient (API) and finished dosage form (FDF) plants worldwide.[2]

To reflect the variable contamination risk inherent in the different types of production plants, the production steps are classified into individual **UNITS** according to the process flow. Additionally, a **RISK EMPHASIS FACTOR (REF)** is introduced to account for the impact of the underlying process step on the overall sterility. The unit REF can take on value 1 (low), 3 (medium) or 5 (high), depending on the inherent contamination risk and the standard of equipment of the respective unit. (see Fig 1)

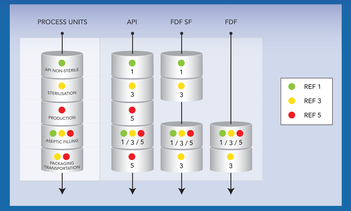


Figure 1. *Schematic overview of process units and related Risk Emphasis Factors (REFs)*

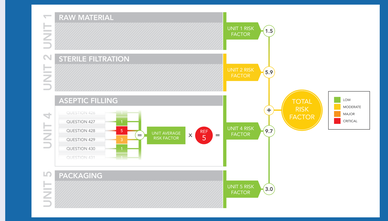
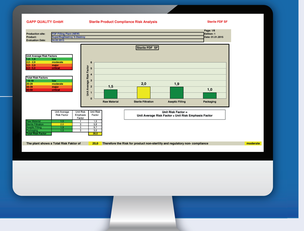


Figure 2. *Schematic overview of the sterile product compliance risk analysis tool*

For each unit, a multitude of specific questions are asked, encompassing all areas of risk involved in aseptic processing. Each question can be answered on a scale from 1 (excellent) to 5 (very poor or missing). The sum of all answered questions from one unit is averaged to give the **UNIT AVERAGE RISK FACTOR**. The smaller the Unit Average Risk Factor, the lower the evaluated risk to the production plant with regard to the quality of its sterile product.

The finally calculated **TOTAL RISK FACTOR (TRF)** provides definitive information about the overall risk of microbial contamination (sterility/ endotoxins) for all production steps of an aseptic processing operation. Furthermore, it allows the user to estimate the compliance status, as well as possible observations of future regulatory audits of the sterile plant. (see Fig 2)



THREE DIFFERENT RISK ASSESSMENT TOOLS ARE AVAILABLE:

Sterile API plant:	Units 1/2/3/4/5	238 questions
Sterile FDF plant (with SF):	Units 1/2/4/5	203 questions
Sterile FDF plant (without SF):	Units 4/5	175 questions

3 MEANINGFUL INVESTMENTS

RAW MATERIAL QUALITY

- CAUTION (for sterile bulk production plants without sterilisation of bulk material by SF)
  - External low price bulk material may be a black box.
  - Filling non-sterile bulk renders the best FDF plant useless.
  - Inadequate transportation materials from external suppliers may result in contamination due to temperature and pressure differentials during the transportation.

INVEST IN

- In-house high quality sterile bulk production plants and maintenance.

HIGHER TRANSPARENCY IN CASE OF INVESTIGATION!

STERILITY TESTING FACILITY

INVEST IN

- Isolators
- Training of QC lab technicians

A MODERN, WELL CONTROLLED ST FACILITY WITH ISOLATOR MINIMIZES THE RISK OF CONTAMINATION!

DISINFECTION & CLEANING

- CAUTION: Often set-up (only one bucket method) and qualifications are weak or details are missing in cleaning protocols.

INVEST IN

- Qualification and training of the staff
- Good cleaning / disinfection programs

VACUUM EFFECTS

- CAUTION: The co-occurrence of leakage and interior vacuum (e.g. vacuum driers, lyophilisators,...) especially in sterile API plants may cause heavy microbial contamination by backsiphonage of drain water or environmental air.

INVEST IN

- Integrity of the systems (piping / seals / valves / ...)
- Good maintenance of production plants

TAKE CARE OF VACUUM EFFECTS AND PREVENT LEAKAGES!

CONCLUSION

Improving quality and safety in aseptic processing demands a change in corporate culture. Avoid cost saving programs that result in increased workloads and pressure on production personnel as well as in understaffed QA departments. Rather, strengthen teamwork, support multidisciplinary collaboration and invest in training and commitment of the production personnel.

HAZOP risk assessment tools are effective and useful measures for reducing microbiological contamination risks and for complying with regulatory requirements in the pharmaceutical industry to assure safety for the patient. The risk analysis tools described here are simple to use and ensure a high level of functionality and performance. At a senior management level they help to control the GMP compliance status and to monitor the risk of non-complying products, whilst at an executive management level they provide solid arguments for investments.

However, the successful use of risk assessment tools requires a competent and highly professional multidisciplinary risk assessment team. If these requirements are lacking, or if there is not sufficient time available, the benefit and outcome will be compromised.

REFERENCES

1. U.S. Food and Drug Administration Department of Health and Human Services: Pharmaceutical cGMPS for the 21st Century – A Risk Based Approach. Final Report – Fall 2004 [Internet].
2. Gapp G, Holzknecht P. Risk analysis of sterile production plants: a new and simple, workable approach. PDA J Pharm Sci Technol. 2011 May-Jun;65(3):217-26.

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