Risk assessment and environmental microbial monitoring practices to be used in food applications

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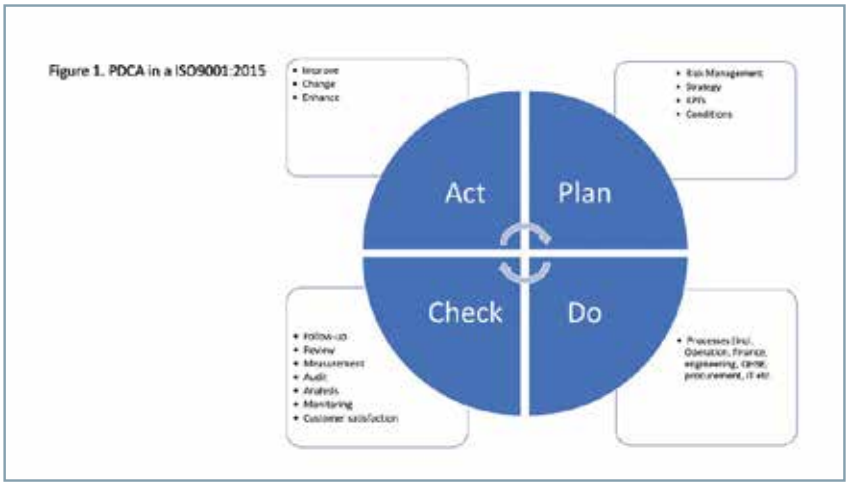
Risk assessment is generic in the methodology, no matter how people perform it or how it is called. The risk assessment is pivotal for safe production in food environments, as well as for any production involving products intended for human intake. The hazards in food processes depend on the contaminants that can be lowered using correct protection level. This is dependent on the nature of the product, the raw materials and the processing stage. In this review aspects of risk assessment are presented along with considerations of environmental monitoring and barrier technology, which are specifically directed towards food applications. The cleaning and disinfection issues will be dealt with in the first RT-issue 2024. This review and the one about cleaning and disinfection are both based on presentations from the R³ Nordic Symposium 2023, held in Elsinore, Denmark.

HELPFUL STANDARDS

Standards describing current best practices are central for many industries. These standards are typically issued by either ISO (international) or EN (European) or as joint publications. The pharmaceutical industry is accustomed to the use of standards e.g., the standards in the ISO 14664 family. to support compliance with good manufacturing (GMP) requirements, which are legal requirements. The food industry worldwide adheres mainly with the legislation, in Europe the EU regulations are the prevalent acts to follow. The food safety requirements in this legislation are derived from the Codex Alimentarius, which prescribes that risk assessment according to the Hazard Analysis Critical Control Point (HACCP) principles is recommended.

In the presentation "The helpful standards" Marianne Vidkjær from Danish Standards gave examples of standards which can support the general work on risk assessment and quality assurance. These includes the management standards as ISO 9001 Quality Management, ISO 14001 Environmental Management, ISO 45001 Occupational, ISO 31000 Risk management, ISO 27001 Information technology, and ISO 50001 Energy management. An excellent tool in ISO 9001 is the Plan, Do, Check and Act (PDCA). Factors affecting the four phases are given in Figure 1. In some presentations at the symposium it was reported that where the first three phases are often performed the resources may not stretch to perform the last and most important one for sustainable optimisation of processes i.e., Act.



The Act contains improve, change, and enhance.

Two standards which may be more sparsely applied but are helpful too are ISO 31010 Risk assessment techniques and ISO 19011 Audit. The first supports ISO 31000 Risk management. This standard describes a wealth of tools that may be applied for risk assessment for various purposes. The second contains guidance for performing audits of varying scope and size, which are applicable in large or small organisations.

RISK ASSESSMENT, GAP-ANALYSIS & CONTAMINATION CONTROL STRATEGY

In the presentation "Management of Risks to Product Safety, Quality and Sustainability" Roland Cocker from Cocker Consulting Ltd. emphasized that HACCP offers a simplification-process which leads to identification and control of the most critical risks in an efficient manner. He also warned that sometimes a critical hazard with a low probability may be perceived to be negligible or absent. This obviously may lead to catastrophic situation. Therefore, training of risk assessment and HACCP teams as well as due diligence is necessary to assure the needed food safety. Roland also presented EHEDG Guideline Document 34 on integration which includes a cradle-to-cradle scheme for facilities and processing equipment consisting of 10 steps:
1. Designing, 2. Building, 3. Operating,
4. Cleaning, 5. Maintaining, 6. Shutting-down,
7. Dismantling, 8. Re-commissioning,
9. Re-selling and 10. Recycling.

After step 10 learnings should be captured as input for step 1 in a new project to utilise knowledge in optimising risk reduction and elimination. Figure 2 shows the steps in Risk Management.

In the talk about "Risk assessment in practice" Kari Solem (COWI) refers amongst other standards to ISO 31000 and 31010 and exemplifies some of the applicable types of risk assessment: Brainstorming as well as HAZOP, SWOT analysis, Fault tree analysis (FTA) and structured what-if-technique (SWIFT) analysis. Risk matrix and scenario planning based on table test are also mentioned. The appropriate

(either qualitative or quantitative) method depends on the desired outcome and the level of knowledge available. It is emphasized that risk assessment is important in the planning process, should be a continuous process in an organisation and be a tool for communication up and down in the organization. The process is always to define scope, choose a method, in which SWIFT is recommended, and invite the relevant stakeholders. SWIFT is about thinking ahead and anticipating potential issues before they arise, planning for them, and taking action to avoid or minimize them. This approach has been proposed by other experts in the field and is directly applicable in food and pharma production.

"Contamination control strategy (CCS)" was at the core of Kirsten Jorsal's (ELLAB) presentation. In the pharmaceutical industry CCS is a major document in GMP audits. CCS is the way to ensure contamination prevention in a specific process, it is not a way to compensate for bad design, it includes exact controls based on risks identified in the process to mitigate those risks. CCS is not a Gap analysis in itself. But the backbone of the CCS can be a Gap-analysis of identified risks and strategies to mitigate these identified issues. Thus, CCS is a quality document that identifies and assesses risk, explores the mitigating options, and defines the preventive actions.

In the presentation "PHSS CCS Guidance Contamination Control Strategy and supporting FMECA" James Drinkwater from Pharmaceutical & Healthcare Sciences Society (PHSS) focused on how to navigate the regulatory maze and supporting guidance for pharmaceutical companies. Notable to extract from this talk is that GMP regulation shift to risk based, holistic and proactive methodologies. Failure Mode, Effects & Criticality Analysis (FMECA) is introduced for CCS, which is focused on documenting the strategy taken in control of contamination i.e., bioburden control, and prevention of contamination of sterile products.

This CCS approach is quite similar to that applied in HACCP. The main difference seems to be the target industry. There is something to learn from risk control in both food and pharma manufacturing i.e., when looking at each other's approaches.

ENVIRONMENTAL MONITORING

The "The challenge of microbiological contamination control and the role of the ISO 14644 family of "dashes"" presentation presented personal opinions of Conor Murray, who is a subject expert in Cleanrooms, and Convener of ISO/TC 209 WG2, Microbiological Contamination Control. The content follows: 1) Ability to control the physical environment, 2) Challenges of the invisible, diverse microbial world, 3) Management of people versus environment, 4) the role of new technology and 5) a link to standards in the ISO 14644 family including the new ISO 14698 "Biocontamination control", which is based on EN 17141, into the ISO 14644-family as ISO 14644-20. The challenges in manufacturing based on good manufacturing practices (GMP) in cleanrooms are under increasing regulators' emphasis, which can be divided into variety, complexity, and toxicity of drug products. Furthermore, the shelf life, access patient safety risks and costs of drugs distributed across the globe are crucial for both maintain high life standards and lifesaving medication.

For many years traditional microbiology has dealt with uncertainties around living matter, and microbiological sampling using a lag indicator i.e., enumeration of colony forming units (CFU) after incubation. In sterilised products and non-sterile products, the emphasis is on bioburden and spoilage microbes. In an aseptic environment a huge effort is spent on culturing clean samples leading to a lot of zero counts. Microbiologists have to understand both spoilage and benign microbes of the production, because specification of what are measured differ in both risk and impact even though engineers have been able to rely on simple and standardised real time airborne measurements. HACCP-based qualitative risk management (QRM) applications in microbial control have been used in food manufacture, healthcare, life science, life science medical devices, microelectronics, optics etc. In life science the drivers are to make improvements without adding more regulations

and in fact standards are not designed to add new regulations. The drivers in product quality and patient safety due to that contamination of medical devices can cause serious harm to patients. The contamination can be prevented by aseptic processing. Drivers in infection control i.e., in clean controlled environment are based on infection control, and biosafety as well as preventing cross contamination. The drivers in food manufacturing are based on absence of pathogens in food manufacturing because they cause illness or death, deterioration of food quality and product spoilage, because growth in retail outlets in either case also cause economic loss. The concern with the spread of bacteria, yeasts, and moulds, which are carried by air currents throughout the food plant, is that they can grow in moist process areas. The objective is to control that air in the vicinity of the food being processed is free from microbes. The fundamental in this process is to establish and demonstrate a proper contamination control strategy. The presentation gave an overview of core cleanroom standards, which have been updated and revised.

Sabine Bessières Recasens from Millipore gave a presentation on new regulatory trends: What impacts microbiological monitoring of clean environments? The norms and guidance in environmental microbial (EM) monitoring is based on EU GMP ANNEX 1 (2022) Requirements for EM and equipment, PIC/S guidelines (2018): Requirements in sterile manufacturing, ISO 14698/EN17141: Validation biological and physical efficiency, FDA Aseptic Guide (2004): Requirements EM and equipment, EN 14644: Classification of cleanroom with regards to particle levels, PDA Technical Report #12 (2022): Requirements for EM and Equipment and FDA (2018) Questions and answers to data integrity. In the guidance of viable particle monitoring, it is stated that each nonconformity discovery requires an investigation. It is also stated that results should be considered in routine batch certification: The monitoring plan should be documented, and a microbial identification strategy should be followed. The follow-up can also be based on rapid, automated methods after that they have been validated. New texts referring to alternative, e.*g.*, rapid, methods include appropriately justified methods.

BARRIER TECHNOLOGY

In the "Contamination control of isolator" by Yuanzhong Wang from Novo Nordisk presented isolators, which protect sterile components and products from the surrounding environment and people. This study presented three (3) plates with growth. They were found among 20000 environmental plates. These three plates were contaminated with contaminants from human skin (Micrococcus lutes and Staphylococcus warneri) as well as human mucous membranes (Corynebacterium tuberculostearicum). He stated that the environmental monitoring shall be meaningful based on risk assessment and sampling methods.

CLEANING & DISINFECTION

The studies on cleaning and disinfection at the Elsinore symposium in May 2023 will be presented in more detail in the first issue of Renhetsteknik 2024. In that review we will describe the studies held by Jette Holt from Statens Serum Institut (topic: What is clean? – And when is clean, clean enough?), Nadine Hoffmann from Nadine Pharma Consulting (topic: Aseptic behaviour – cleaning & disinfection), Peter Tønning from UV Medico (topic: New shades of ultraviolet light disinfects air and surfaces around us with no harm to humans by and the importance of detecting and effectively removing disinfectant residues in the GMP environment) and Juliana Nassette from Ecolab (topic: The importance of detecting and effectively removing disinfectant residues in the GMP environment). The outcomes of these studies can be applied in studies on collaborative robots (cobots). Furthermore, the cobot hygiene study financed by the research fund of Töysä Savings Bank and performed at Seinäjoki University of Applied Sciences was presented in Renhetsteknik 2:2023 directly after the symposium.

SUMMARY

The basis of the risk analysis is openness and honesty. Reasons for identified risks should be sought through risk management. The aim is to find faults, not guilty persons. The process should be documented as it really is, not as it should be. All risk assessment should be based on HACCP, but if there are too many critical control points. They will impede smooth running of the process, i.e. it is a big no-no. The prioritization of risks should be performed according to severity and probability. The measures needed should be based on essential factors in the process and key risks. The most important steps in risk analysis are to agree measures, implementation and follow-up in the risk management. In the risk assessment team, there should be representatives of all working groups including experts. All representatives should be present, not just on-site.

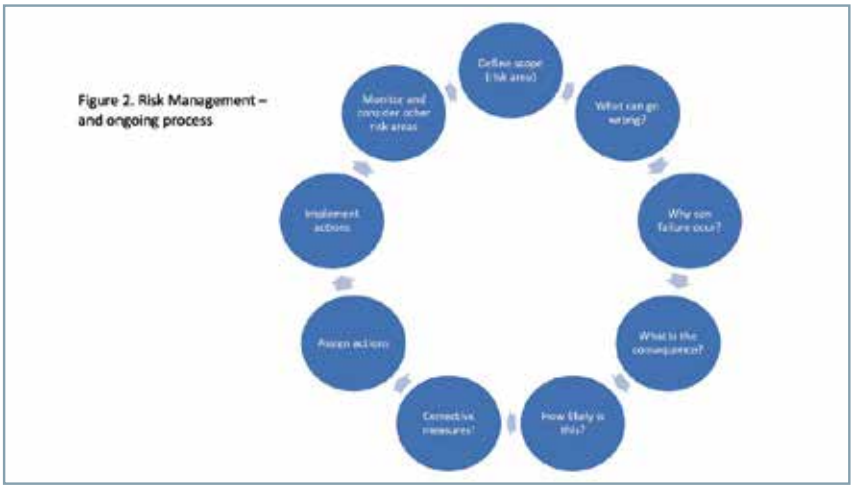


Figure 2. Risk Management – and ongoing process

References

This review is based on the following presentations given at the R3Nordic Symposium in Elsinore in May 2023:

- Sabine Bessières Recasens, Merck (France) - Environmental microbial sampling
- Roland Cocker, Cocker Consulting Ltd (Ireland) - Management of risks to product safety, quality, and sustainability
- James Drinkwater, Franz Ziehl (United Kingdom) - Overview of PHSS published guidance on contamination control strategy preparation and experience from application
- Ina Glamheden-Helle, Bavarian Nordic (Sweden) - GAP-analysis according to Annex 1
- Kirsten Jorsal, Ellab (Denmark) - Implementation of Contamination Control Strategy
- Conor Murray, 3dimension (Ireland) - The challenge of microbiological contamination control and the role of the ISO 14644 family of "dashes"
- Kari Solem Aune COWI A/S (Norway) - Risk assessment in practice
- Marianne Vidkjær, Danish Standards (Denmark) - The helpful standards
- Yuanzhong Wang (DK) Novo Nordisk (Denmark) - Contamination control of isolator