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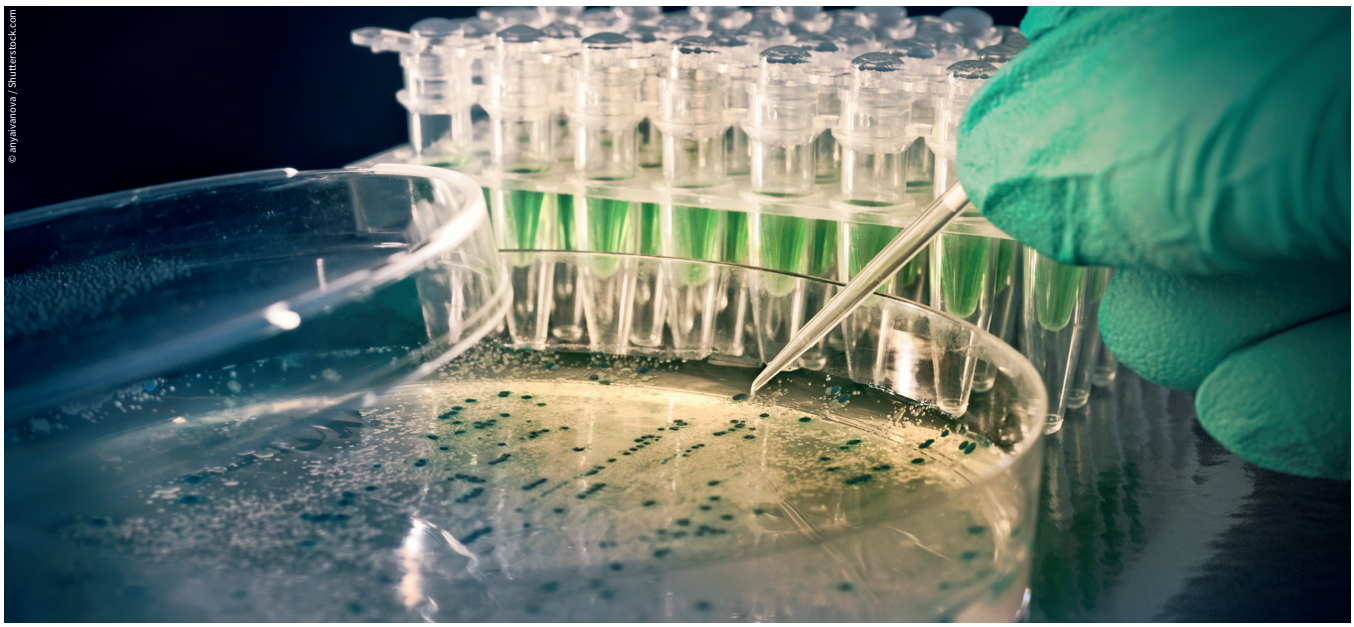

Reducing microbial contamination via sterile risk assessment

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Several years ago, microbiologist Guenther Gapp created a new sterile risk assessment tool (based on a hazard operability analysis [HAZOP] approach) to identify and reduce the microbial contamination and compliance risk of aseptically-produced sterile products and production plants. The following article describes the operating principle of three risk analysis tools with a special focus on the revised 2015 edition. This latest edition incorporates the improvements that have been implemented in recent years, which make the tool more applicable and thus valuable for the user.

Microorganisms are omnipresent in the environment, making sterile manufacturing plants, especially those with aseptic filling operations, highly vulnerable to microbial contamination. There are a variety of potential root causes of non-sterile results. These may include weaknesses of design, insufficient maintenance of the production plant or poor aseptic working practices of the cleanroom operators, to name but a few. Also, it is often unclear as to whether a lack of sterility is due to a systematic weakness of the process or if it has been caused by the often-cited 'single incidence' resulting from an individual human error. As the non-homogenous distribution of contaminants within the product gives rise to low reproducibility when testing, it makes the search for an assignable cause even more complex and hides the impact it may have.

Since only a small number of random samples are examined for sterility testing, the statistical significance of the results is hardly sufficient to draw conclusions about the sterility of the whole batch. Thus, neglecting appropriate precautions would ultimately create a very high risk for the patient. Therefore, it is imperative to understand all possible microbial entry points and to implement quality risk management (QRM) strategies that aim to prevent microbial contamination.

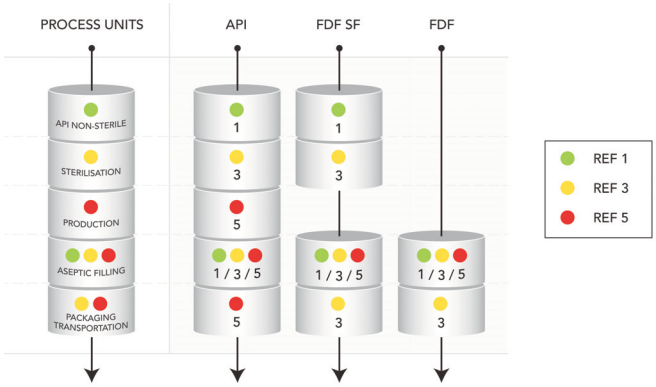

Figure 1: Schematic overview of process units and related risk emphasis factors (REFs)

It is highly recommended that a systematic approach be followed both when developing a proactive microbial control strategy and when performing an investigation of a microbial contamination deviation. Accordingly, each sterile manufacturing production site is required to have a risk analysis tool in use.[1] It allows for a comprehensive risk assessment that uncovers potentially hazardous process steps and lacking controls, and provides information about potential microbial contamination root causes.[2] Thus, in sterile production, risk management and the performance of risk analysis take on a very important role, serving both as investigative tools in case of deviations (for root cause analysis and batch disposition decisions) and as proactive tools for preventing non-compliance during regulatory audits and of the final product.

These tools, such as the ones described below, incorporate a profound understanding of the manufacturing process and product attributes. They are simple, usable and have been relied on for several years.

Managing risk effectively using process-specific risk analysis tools

Starting nearly a decade ago, the author began compiling first-hand information on technical experience and knowledge derived from everyday practice in the field of quality assurance (QA)/quality control (QC) microbiology, sterile production and aseptic processing and generating from this a register of questions. By further incorporating questions relating to regulatory audit requirements and findings and then ranking all questions according to their criticality, the questionnaire evolved into a new risk assessment tool based on a HAZOP methodology. Over many years this tool has been continuously adapted, refined and extended. Meanwhile, three specific sterile product compliance risk analysis tools have been successfully employed in numerous sterile active product ingredient (API) and finished dosage form (FDF) plants worldwide.

GAPP QUALITY GmbH — Sterile Product Compliance Risk Analysis — Sterile FDF SF

Page: 5/6
Production site: FDF Filling Plant (NEW)
Product: SuperBugDestroy X-Destroy
Evaluation Date: 04.02.2015
Edition: 1
Date: 01.01.2015

Aseptic Filling
Justification: 1- 5
Unit Risk Emphasis Factor: 5

		Unit Average Risk Factor	1,93
		Unit Risk Factor	9,66
Questions	possible justification	General	
Q301	1/5	Housekeeping (e.g. no excess material/ sanitizer residuals/ product residuals) is good in all stages of production (visual impression) (1) or not (5)	1
Q302	1/5	Is there a Change Control Procedure in place approved by QA which ensure the microbiologically validated status of the process and /or room layout including impact on aseptic conditions (1) or not (5)	1
		Cleaning /sanitization	
Q303	1/5	Are there good documented cleaning and disinfection procedures in place (1) or not (5)	1
Q304	1/3/5	Is the disinfection for class A/B validated via carrier test with sterile production site surfaces (1) or suspension testing (3) or not (5)	1
Q305	1/5	Are only sterile disinfectants used in grade A/B areas (1) or not (5)	1
Q306	1/5	Is there a regular usage (e.g. monthly) of sporocidial disinfectants for class A/B clean rooms (1) or not (5)	1
Q307	1/5	Are the ready to use disinfection solutions or cleaning agents used in the grade A/B tested at least monthly for bioburden (1) or less (5)	1
Q308	1/5	Are the trend results good and meet the requirements (1) or not (5)	1
Q309	1/5	Are the disinfection or cleaning agents requalified and changed in case of a significant change in 'in house' isolates (1) other (5)	1
		Facility	
Q310	1/2/3/5/100	All aseptic filling operations (e.g. time of exposure of sterilized units until closing) take place in a closed isolator (1) or isolator with mouse hole (2) or RABS with background Grade B (3) or conventional GRADE A filling line with background Grade B (5) or within class B or less (100)	5
Q311	1/5	Is unidirectional airflow and air quality maintained under 'in operations' conditions within the critical area (1) or not (5)	1
Q312	1/5/100	Is a smoke study movie/video/DVD (at rest/ in operation) available demonstrating unidirectional air flow and sweeping over in the critical area for all critical operations (1) or smoke studies performed but no adequate records in place not for all critical operations (5) or no smoke studies available or inadequate air flow (100)	5
Q313	1/5	Is the actual finishing (e.g. floor, walls, windows, ceiling, doors) meeting current GMP- requirements (smooth finish and easy to clean) for grade A and B (1) or not (5)	1
Q314	1/5	Is the layout of the clean room in line with cGMP requirements (1) or not (5)	1
Q315	1/5	Is the final stage of the changing room (at rest) of the same grade as the area it leads to (1) or not (5)	1
Q316	1/5	Is the personnel air lock equipped with separate inlet/ exit, interlocked doors (1) or not (5)	1

Figure 2: Example of the questionnaire showing real-life data

To reflect the variable contamination risk inherent in the different types of production plants, the production steps are classified into individual units according to their process flow. For example, an API plant is a complex multi-step processing system with relation to technology, associated aseptic operations and control mechanisms. Consequently, the risk analysis tool for a sterile API plant consists of five units (**Figure 1**). On the other hand, a sterile FDF filling line for liquid or solid product filling with or without sterile filtration (SF) incorporates fewer production steps. Hence, the risk analysis tools for sterile FDF plants are made up of either two (FDF without SF) or four (FDF with SF) units, depending on the particular manufacturing process employed, as illustrated in **Figure 1**.

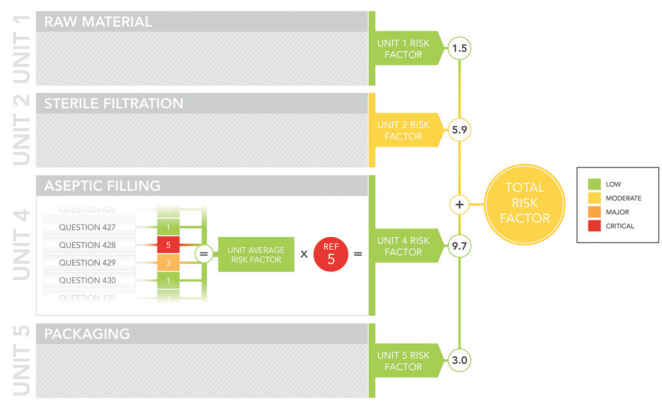

Figure 3: Schematic overview of the sterile product compliance risk analysis tool for an FDF plant with SF combined with real-life data

For each unit, a multitude of specific questions are asked, encompassing all areas of risk involved in aseptic processing (for example, raw material, cleanroom operator qualification and training, QA/QC microbiological controls, packaging, etc.). Each question can be answered on a scale from 1 (excellent) to 5 (very poor or missing) (**Figure 2**).

The sum of all answered questions from one unit is then 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. To provide instant visual information about overall risk and potential problem areas, all answers and calculated results are colour-coded from green to red. A risk analysis target and optimum situation would ultimately be low numbers and green colours.

In addition to tailoring each risk analysis tool to fit the underlying process by using distinct units, it is also necessary to weigh these units according to the impact they have on the overall sterility. To correctly account for these differences, a unit-specific multiplication factor is introduced, termed Risk Emphasis Factor (REF). The unit REF can take on the value 1 (low), 3 (medium) or 5 (high), depending on the inherent contamination risk and the standard of equipment of the respective unit. For example the 'Raw Material Unit', which bears a low risk for contamination, is assigned REF 1. Production units that utilise

significant pressure differences, such as vacuum driers or lyophilisers, are considered especially risky. Similarly, primary packaging materials, such as aluminium cans, harbour an inherent vulnerability for microbial contamination. Therefore, 'API Production Unit' and 'API Packaging/Transportation Unit' are always assigned the maximum value of REF 5. In contrast, small packaging sizes, such as small vials used in FDF filling lines are less prone to pressure-drop related contamination, thus the allocated REF is 3 (**Figure 1**, page 36).

Each Unit Average Risk Factor is multiplied by its corresponding unit REF to achieve the Unit Risk Factor as in the simple equation below:

Unit Risk Factor = Unit Average Risk Factor x Unit REF

The QRM analysis is finally concluded by calculating the Total Risk Factor (TRF), which is the sum of all Unit Risk Factors (**Figure 3**, page 36):

TRF = Σ Unit Risk Factors

The 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. By providing simple numerical and colour-coded answers in each unit questionnaire, as well as by incorporating a unit REF, the risk analysis tool additionally serves to uncover potential weaknesses of the process and enables proactive corrective and preventive actions (CAPAs) for further systematic improvement. Any uncovered weaknesses provide solid arguments for investments in improving the compliance status and, finally, the TRF provides managers with a conclusive score for benchmarking of sterile production plant performance (**Figure 3**, page 36)

Amendments, updates and real-life examples

Variable Unit REFs

In the previous guidance, each unit was assigned a single specific REF (low/medium/high) according to the inherent risk for non-compliance and/or microbial contamination. However, to correctly represent lower contamination risks associated with using advanced aseptic technologies and to create pressure for investments, a variable unit REF was introduced. For example, the 'Aseptic Filling Unit' was initially assigned a REF of 3 (medium),[3] but now has a variable REF according to the standard of equipment and filling technology used. A variable REF thus ensures that an advanced filling line is rewarded a significantly lower TRF than a conventional filling line, even if the respective individual Unit Average Risk Factors were identical.

Knock-out questions

In the initial tool, a five-point scale was applied to all answers in the questionnaire. After some years of practical

experience it became apparent that certain questions had a disproportionately high impact on overall sterility assurance compared to others and that they represented deficiencies that could lead to product non-sterility or a US Food and Drug Administration form 483 finding. To ensure that a negative answer in these cases is appropriately penalised, a value of 100 is assigned and these questions are thus referred to as 'knock-out questions' (KO-questions) (see Example 1).

Example 1:

Q401: Is the sterilisation of primary packaging material validated (autoclave/dry heat/gamma-irradiation) (1) or not (100).

As described above, assigning a value of 100 upon negatively answering this question prevents a severe risk factor being diluted when averaging all unit questions. Although the impact of KO-questions on the Unit Risk Factor score is greater for units comprising fewer questions, a negative answer will in any case push the TRF from LOW to at least MODERATE, which should be considered unacceptable for a production plant.

Ultimately, the purpose of KO-questions is to illuminate critical parameters that allow effective measures to be set and to get the senior management's attention if resources or investments are required for remediation. Typically, in a well-controlled sterile manufacturing plant a negative answer to a KO-question does not, however, necessitate that the plant is shut down.

Latest release (2015)

Three different risk assessment tools are available (refer to **Figure 1**, page 36) in the most recent 2015 release:

- 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)

36 knock-out questions have been defined in total (5 units):

- Raw material: none
- Sterile filtration: 4 KO-questions
- Sterile production: 6 KO-questions
- Aseptic filling: 23 KO-questions
- Packaging/ transportation: 3 KO-questions

Illustrative example

The following example demonstrates the operating principle of the product compliance risk analysis tool for a FDF filling plant with SF consisting of four units (raw material/SF/aseptic filling/packaging) (refer to **Figure 2**, page 36 and **Figure 4**). **Figure 2** (page 36) shows part of the questionnaire for the 'Aseptic Filling Unit', where some of the answers have uncovered specific weaknesses in the system, as illustrated by the score 5 in red, leading to an Unit Average Risk Factor of 1.9 (risk is still LOW). The bar chart in **Figure 4** shows all four Unit Average Risk Factors, whereof only one (SF) displays a MODERATE risk (yellow colour). The summary table (bottom left corner in Figure 4) shows that following multiplication with the respective unit REFs results in a TRF that exhibits a MODERATE risk for product non-sterility and regulatory non-compliance.

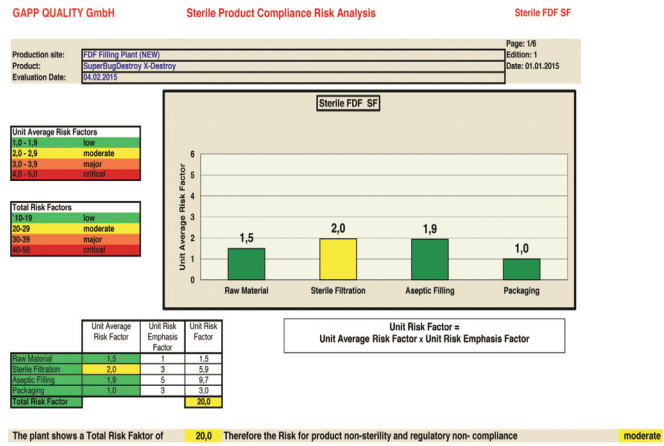

Figure 4: Example showing actual data of a risk assessment outcome in an FDF plant (with SF)-5

Summary

HAZOP approaches 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 sterile product compliance risk analysis tools described here are characterised by simplicity, usability and the option to add new questions based on recent experiences, audit findings and newly published guidelines, which, taken together, ensure a high level of functionality and performance. By enabling a comprehensive and in-depth assessment it serves at a senior management level to help control the GMP compliance status and to monitor the risk of non-complying products, whilst at an executive management level it provides solid arguments for investments. However, the successful use of the tool requires both expertise and honesty in answering the questions, which necessitates a competent and highly professional multidisciplinary risk assessment team. If these requirements are lacking, or if there is not sufficient time available to dig deeper, the benefit and outcome will certainly be poor.

In 2013 microbiologist **Dr. Guenther Gapp** founded the consulting company Gapp Quality GmbH (Austria). Today he divides his time between working as a Senior Associate for Lachman Consulting Ltd. and as an independent consultant. Guenther spent the first 20 years of his career at Biochemie Kundl (Sandoz GmbH), Austria, where he became Head of QA/QC Microbiology. He gained in-depth experience in media fill practices of finished dosage forms and bulk products, environmental monitoring, rapid testing methods, aseptic operations practices and regulatory agency audits. He has been a subject matter expert in more than 20 FDA audits. Several years ago he created a new sterile risk assessment tool (based on a HAZOP approach) to identify and reduce the microbial contamination and compliance risk of sterile products and production plants and subsequently won the 2011 PDA Journal of Pharmaceutical Science and Technology Award. His risk assessment tool has been used worldwide by sterile manufacturing plants.

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