

**2017** PDA Annual Meeting

# One Simple Way to Manage Aseptic Risk Assessments

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Aseptic processing presents many risks to sterile product. How can manufacturers address these risks to effectively prevent contamination?

In 2006, I created a sterile risk assessment tool, the Hazard Operability Analysis (HAZOP). This tool proactively identifies microbial contamination risks for aseptically filled sterile products. I have since refined this tool into what I now call the Sterile Product Compliance Risk Assessment (SPCRA).

Like any risk assessment tool, I caution that it is only as good as the individual or team behind it. In my years in the industry, I've seen companies use various risk assessment tools to justify all sorts of weak quality practices. When implemented appropriately, however, this simplistic tool potentially offers many benefits for manufacturing sites.

## The Risk Analysis Concept

The SPCRA tool, which is comprised of a comprehensive list of specific questions, is a deep dive assessment into the manufacturing process and controls for product quality, spanning microbiological laboratory, quality culture, manufacturing facility and filling technologies, media fills and environmental monitoring. Furthermore several questions are related to current regulatory requirements, audit findings and best practices.

To reflect the different microbial contamination risks inherent in the various types of aseptic manufacturing, these are separated into individual units according to process flow (*I*). For example, a sterile API plant is a complex, five-step process. A sterile finished dosage form (FDF) manufacturing line for liquid or solid product filling, with or without sterile filtration, incorporates either two or four production steps. A four-step FDF site consists of raw materials, sterile filtration, aseptic filling and packaging units for FDF lines to render liquid product sterile. A two-step site consists only of aseptic filling of sterile liquid or solid API and a final packaging step.

With this in mind, I've created three different SPCRA tools. The one for a sterile API plant consists of 263 questions. The one for a two-step FDF plan consists of 203 questions and the one for a four-step FDF plant consists of 243 questions. In general, the greater the number of questions, the more detailed the specific production units assessed. And the number of questions can be changed based on new information and regulatory requirements.

Within each analysis, a number of specific questions are asked for each step to address areas of potential risk involved in aseptic manufacturing. Each question can be answered on a scale of 1 (excellent) to 5 (very poor).

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 carried a higher impact on overall sterility assurance than others. To ensure that a negative answer has an impact, a value of 100 is assigned. Questions scored with a 100 are now referred to as "Knock Out Questions" as their answers indicate a high impact on the sterility of the product if the requirement is not met. A rating of "100" increases the sum and renders the whole unit to a higher risk. The latest version incorporates 36 Knock Out questions.

For each step, the sum of the numbers resulting from the question-answer scale is divided by the number of questions to provide the **Unit Average Risk Factor**. The smaller the Unit Average Risk Factor, the lower the evaluated risk with regard to sterile product quality and potential for audit findings.

Each production unit has an inherent risk on the overall sterility of the product, therefore **Risk Emphasis Factors (REF)** have ➤

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been defined with different impact factors: 1 (low), 3 (medium) or 5 (high) (**Figure 1**). For example the raw material unit, which carries a lower risk of contamination in the final product, is assigned REF 1. Sterile API production units that use significant pressure differences are considered especially risky, so they are assigned the maximum value of REF 5. For aseptic filling units, to correctly address lower contamination risks of advanced filling isolators, a variable unit REF was introduced. This ensures that an isolator is rewarded a significantly lower REF (such as 1) than a conventional open filling line (likely 5), even if the respective individual unit average risk factors are identical. I based these numbers off my previous industry experience.

Each Unit Average Risk Factor is multiplied by its corresponding Unit- REF to achieve the **Unit Risk Factor**.

$$\text{Unit Risk Factor} = \text{Unit Average Risk Factors} \times \text{Unit REF}$$

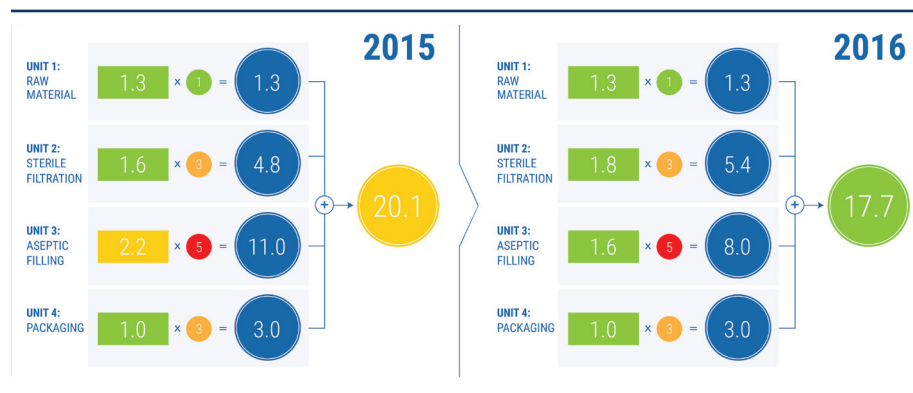
The SPCRA analysis is finally concluded by calculating the **Total Risk Factor (TRF)**, which is the sum of all Unit Risk Factors (refer to **Figure 2**).

$$\text{TRF} = \sum \text{Unit Risk Factors}$$

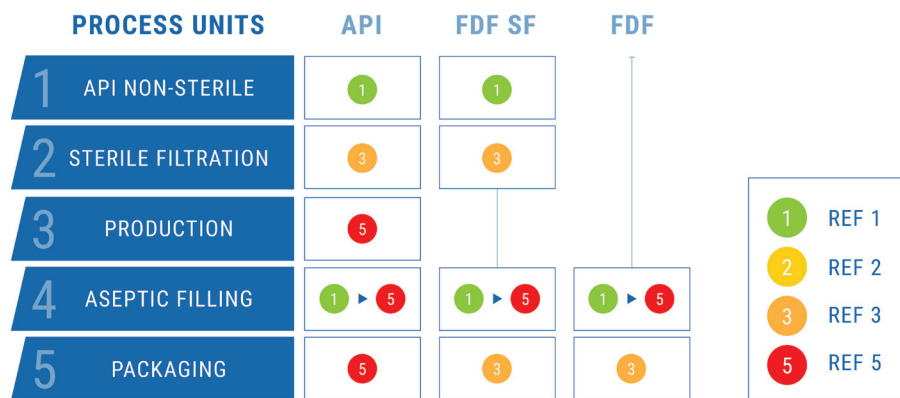
### The SPCRA Tool in Action

But how does the tool actually work in action?

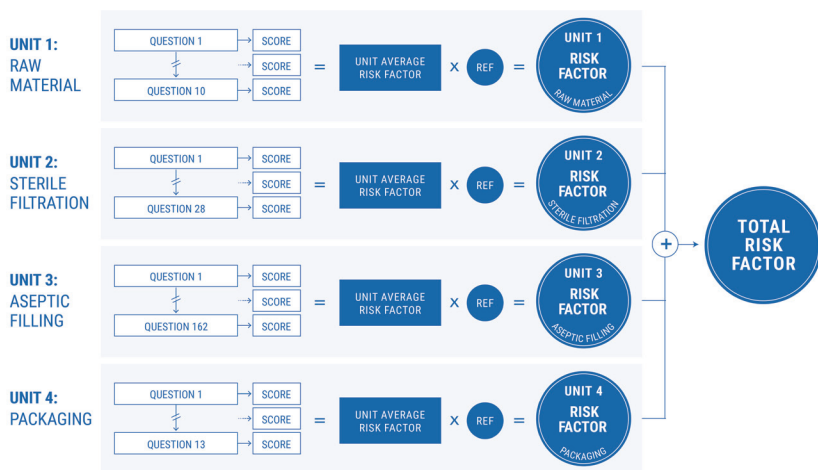
An executed risk analysis using the SPCRA tool at a specific FDF site (with sterile filtration) resulted in a considerable improvement of the TRF after one year of implementing recommended CAPAs. The improvements have been mainly made at the aseptic filling unit, rendering



**Figure 3** One Year Following Risk Assessment



**Figure 1** Schematic Overview of Process Units and Related Risk Emphasis Factors (REFs)




**Figure 2** Schematic Overview of the Sterile Product SPCRA Risk Assessment

an acceptable low risk range for the site (**Figure 3**).

The benefit of the tool is its simplicity, since the TRF provides for valuable information about the overall risk of microbial contamination. It enables companies to estimate compliance status and make potential observations in advance of upcoming regulatory audits. By providing simple numerical and color-coded answers in each unit questionnaire, the SPCRA tool serves to uncover potential weaknesses in the process, enabling CAPAs for further systematic improvement. The target should always be green colored with a low TRF, and no Knock Out Questions answered with 100.

So far, this tool has been proven to be a very effective and useful measure for reducing microbiological contamination risks and to comply with regulatory requirements. But while this tool provides a simple way to conduct microbial risk assessments, its success depends on the honest of the reviewers combined with a high level of expertise. For this reason, I recommend the tool be used by an independent third party, or at least moderated by an external expert. This is particularly important if the

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outcome will be used to compare different manufacturing sites.

**[Editor's Note:** This article is based on the author's poster at the 2017 PDA Annual Meeting.]

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## About the Author

Since 2013, the microbiologist **Guenter Gapp** has been working as an independent consultant for different clients around the globe. 



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