

## **Risk Analysis of Sterile Production Plants: A New and Simple, Workable Approach**

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## TECH REPORT

# Risk Analysis of Sterile Production Plants: A New and Simple, Workable Approach

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**ABSTRACT:** A sterile active ingredient plant and a sterile finished dosage filling plant both comprise very complex production processes and systems. The sterility of the final product cannot be assured solely by sterility testing, in-process controls, environmental monitoring of cleanrooms, and media fill validations. Based on more than 15 years experience, 4 years ago the authors created a new but very simple approach to the risk analysis of sterile plants. This approach is not a failure mode and effects analysis and therefore differs from the PDA Technical Report 44 Quality Risk Management for Aseptic Processes of 2008. The principle involves specific questions, which have been defined in the risk analysis questionnaire in advance, to be answered by an expert team. If the questionnaire item is dealt with appropriately, the answer is assigned a low-risk number (1) and if very weak or deficient it gets a high-risk number (5). In addition to the numbers, colors from green (not problematic) through orange to red (very problematic) are attributed to make the results more striking. Because the individual units of each production plant have a defined and different impact on the overall sterility of the final product, different risk emphasis factors have to be taken into account (impact factor 1, 3, or 5). In a well run cleanroom, the cleanroom operators have a lower impact than other units with regard to the contamination risk.

The resulting number of the analyzed production plant and the diagram of the assessment subsequently offers very important and valuable information about a) the risk for microbiological contamination (sterility/endotoxins) of the product, and b) the compliance status of the production plant and the risk of failing lots, as well as probable observations of upcoming regulatory agency audits. Both items above are highly important for the safety of the patient. It is also an ideal tool to identify deficient or weak systems requiring improvement and upgrade, and delivers sound arguments for investments.

Practical experience with this risk analysis, which has already been executed in several production sites in various countries, has demonstrated that it is simple, workable, and delivers valuable information.

**KEYWORDS:** Risk analysis, Sterility, Endotoxins

**LAY ABSTRACT:** Many important pharmaceutical products need to be sterile because they are to be injected into the patient's bloodstream or muscle. *Sterile* means that the product must be free of microorganisms (i.e., bacteria, yeast, and moulds). A non-sterile injection or infusion could lead to very serious or even lethal effects on the patient. Therefore one of the biggest challenges in the pharmaceutical industry nowadays is still the sterile production process itself. Microorganisms are everywhere in the environment, and humans are known to be a significant source of microbial contamination of a sterile product. It is necessary to set up a very effective quality assurance system as well as many quality control analysis tools to assure the sterility of the produced vials/syringes or of the bulk material intended for later filling into vials (bulk material, e.g., 10 kg in bags or cans). Above all, to get an accurate indication of the risk of non-compliance of product quality, regulatory agencies such as the U.S. Food and Drug Administration and the updated E.U. Good Manufacturing Practice (GMP) Guide have made it mandatory to perform a risk analysis of the production process. This provides in advance valuable information about the potential risk of a product's non-compliance with product specifications and GMP requirements, in our case regarding sterility.

The authors set up a new approach for a risk analysis 4 years ago; this approach stems from fundamental experience gained over the past 15 years. Several specific questions are asked regarding various topics that correlate to the sterile production line and associated quality assurance/control systems. If the answer for an item is satisfactory and the best system is in place with regard to sterility, it is assessed with the prime rating of 1. If the topic is not satisfactory and very weak, the response is 5. Risk numbers from 2 to 4 are for intermediate situations. Because each unit of the

production process could have a different type of impact of varying severity on the total product sterility, the average of the answers regarding the unit (e.g., 1, 2) is multiplied by the risk emphasis factor, which could be 1, 3, or 5. To make the rating even more distinct, colors are assigned from green (very good) through orange to red (very weak).

There are currently three different risk analyses available for three different production processes. The results provide the users, that is, production personnel and quality assurance personnel, valuable feedback about the risk for possible non-sterility in their process as well as sound arguments to present to management defending upgrades of their production line and control systems in the case of high numbers and red colors.

Three years of implementation have demonstrated that this new risk analysis approach works and is very useful in identifying potentially risky components of a production process, thus preventing in advance the production of non-sterile product batches for the market, and finally protecting the patient from hazardous products.

## 1. Introduction

Over the past few years, terms such as *risk-based approaches*, *risk management*, and *risk analysis* have become very popular in the pharmaceutical industry. One reason for this is that, for example, the Food and Drug Administration (FDA) started in 2003 its initiative Pharmaceutical cGMPs for the 21<sup>st</sup> Century: A Risk-Based Approach to focus on critical steps in pharmaceutical production and to use this concept for their inspections.

A sterile active product ingredient (API) plant is a very complex production system with regard to the technology, associated cleanroom operations, and the many controls and processes involved. A sterile finished dosage form (FDF) product filling line with liquid or solid product filling seems to be more easily controlled than an API plant, as fewer production steps are required.

The sterility of an aseptically processed product cannot be 100% assured; however, it is essential to keep the risk for the patient as low as possible. It is common knowledge that traditional sterility testing is of very limited help in detecting microbial contamination, and even combined with increased sampling for environmental monitoring and with numerous media fill validations some uncertainty remains.

Microbiology in the pharmaceutical industry is a very challenging field because the root cause of microbial

contamination may not always be discovered. Furthermore, results from microbiological quality control (QC) analysis of a sample are not as reproducible as chemical analyses (e.g., high-performance liquid chromatography) because of the non-homogenous distribution of contaminants throughout the lot.

There are numerous different root causes and possibilities for the origin of microbial contamination: a defective production plant, a leaking primary packaging container, a pressure drop in the cleanroom, poor aseptic working practices of the human operators, an inefficient sterilization step, and so on. To make the situation even worse, these manifold possibilities for the origin of the contaminants are linked with the limited detection rate of microbial analysis as mentioned above.

Regulatory agencies and company management require the quality assurance (QA) microbiologist to perform a successful investigation with a clear and rapid identification of the problem, to define CAPAs (corrective and preventative actions), and, subsequently, to make or propose the correct batch disposition decision both for the sake of the patient and, ideally, for the lowest loss by the company as well. As a result he or she has to write a scientifically sound investigation report that has to fully satisfy all auditors. Therefore, the position of a QA microbiologist is often very challenging. It is therefore no surprise that in worldwide conferences many presentations with topics like "Training in Handling of Microbiological Deviations" are offered to give advice and assistance in reaching the right conclusion.

Imagine this scenario: you are a microbiological laboratory supervisor sitting in your office, the door opens, and your lab technician informs you that "non-sterility" has been detected in your company's most important sterile product that is expected to be launched in

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Aseptic Filling		Unit Risk Emphasis Factor: 3	
Justification: 1- 5		Unit Average Risk Factor	1.14
		Unit Risk Factor	3.43
Questions	Possible Justification		
Q301	Aseptic filling room/ clean room concept 1/2/3/5	Closed isolator (1), mousehole (2), barrier (3), or open manipulations in class A (5)	1
Q302	1/5	If closed isolator: located within classified background (1) or non classified background (5)	1
Q303	Isolator 1/3/5	Glove integrity testing in justified intervals (1) or no integrity testing (5)	1
Q304	1/5	Replacement frequency of gloves defined (1) or not (5)	1
Q305	Clean Room 1/5	Transfer A-B-A: no transfer (1) or transfer of open product/product contact surfaces (5)	1
Q306	1/3	Transfer A-B-A: no transfer (1) or transfer of closed product/equipment/packaging material (3)	1
Q307	Housekeeping 1/2/3/4/5	Housekeeping is good (optical view) (1) or weak (5)	2
Q308	Air Flow Conditions/LF 1/5	Laminar Flow at critical locations or good sweeping (1) or no Laminar Flow or turbulences or "shadowing" (5)	1
Q309	Smoke studies 1/5	Smoke study video during aseptic operations demonstrating uniform air flow (1), or no studies (5) or non-adequate air flow (5)	1
Q310	Material Flow 1/5	All heat stable equipment/material through autoclave/dry heat (1) or not (5)	1

Figure 1

### Example of questions from the questionnaire regarding the sterile API plant and the aseptic operations unit.

the next week. This presents a serious problem. The question is (a) does the microbial contamination originate from your microlab and is thus not correlated with the product (false positive result); (b) does it originate from the production plant, thus actually contaminating the product; or (c) is it a non-product/process-related sampling problem. There are no quick answers available, and while the identification of the contaminant may help to identify the root cause of the contamination, even with the species name the origin is mostly unknown.

You are immediately aware that your final decision has a dramatic impact on the patient as well as on your company, and the investigation must be performed immediately and in the best way. Your decision must be correct and defensible. Additional difficulties would arise if you are not familiar at this time with what goes on in your lab and in production, or you have no knowledge about the sampling procedure.

In order to prevent such a scenario or at least be better prepared, it would be a good idea to walk through your laboratory to experience what is going on and also to walk through the production plant including the clean-room operations, at least from the outside, to become familiar with common practice. In combination with the activities mentioned above, it is nowadays required (e.g., in the updated EU GMP Guide) to perform a "risk analysis of the process and product."

This was also the main reason why the authors decided to set up "Risk Analysis for Sterile Products/Pro-

cesses" in mid-2006 and combine all their technical expertise, knowledge, and past experience within a questionnaire. Many of the questions are based on personal experience and come from daily practice in sterile production and aseptic processing. The last 3 years have shown that this risk analysis approach does indeed work, is practicable, and, in conclusion, provides the required information while also serving as a good tool to go directly into the CAPAs.<sup>1</sup>

## 2. Risk Analysis Methods

### 2.1. Description of the Method

This risk analysis method is very easy to comprehend and perform and is not linked with the probability of the occurrence and detection of a failure, as is the case in a failure mode and effects analysis (FMEA). Specific questions are asked about technical issues, clean-room concepts, QA/QC microbiological controls, and so on. A question can be answered on a scale of 1 to 5. The answer is given as 1 if this point is perfect, and as 5 if very poor or missing. The numbers 2 through 4 are for interim situations, but have been pre-defined in the questionnaire (Figure 2). In addition to the numbers, colors are also added, from green to orange to red (Figure 3).

<sup>1</sup> In part, this topic was presented at the PDA Pharmaceutical Microbiology Conference in Berlin on February 23, 2010.

Possible Responses	Explanation
1	Yes and very good
2	Partially yes and good
3	Rudimentarily yes and average
4	Almost no and poor
5	No and very poor

Figure 2

### Explanation of responses 1–5.

Ultimately, the target and optimum situation are low numbers and green colors. A low number and a green color for a production plant/line and a product signifies a low risk of producing non-sterile product or problems with endotoxins in the product.

The production plant is separated into individual units, between 3, 4, and 5. Each unit is linked to a specific *risk emphasis factor*, either 1, 3, or 5, to adjust for the fact that the overall impact on sterility can be different for each unit. A potential separation in 5 units of the sterile API plant is listed in Figure 4.

These risk emphasis factors are based on the personal experience of the authors; the authors are aware that this might be different from organization to organization. It is important to know that this risk analysis is based on the assumptions derived from experience acquired in a well-run cleanroom showing that human operators do not represent the highest risk for microbial contamination. Rather, this type of contamination is most possible in units involving significant pressure differences. In such cases, the lower pressure inside the drug substance container or working area combined with the non-integrity of the surrounding barrier (production vessel/pipework or primary packaging container) can allow the entrance of non-sterile air or contaminated fluids. Therefore, the impact on the summarized total risk for non-sterility is high for this type of unit and is assigned the maximum unit risk emphasis factor of 5. In contrast, cleanrooms and aseptic operations have a lower vulnerability with a unit risk

Unit Average Risk Factors	
1.0–1.9	Low
2.0–2.9	Medium
3.0–3.9	High
4.0–5.0	Very high

Figure 3

**Unit average risk factors: low numbers and green colors indicate a low risk for non-sterile product, high numbers and red colors a high risk.**

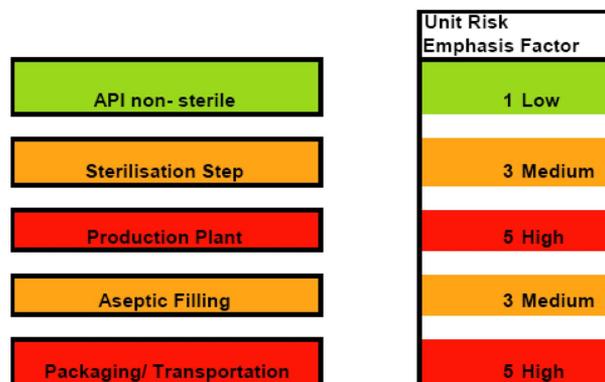


Figure 4

### Unit risk emphasis factors (1/3/5) for the sterile API plant with different impacts on the sterility.

emphasis factor of only 3. Another example is that the non-sterile API, which is the starting material, has the lowest impact (a unit risk emphasis factor of 1) because the bioburden has little influence on the sterility of the product, as the prefiltration and sterile filtration steps are qualified and validated, respectively, to remove microbiological contaminants. (Detailed explanations for these assumptions are given later.)

The average unit risk factor is calculated for each unit as the mean from all results. Based on this value, the unit risk factor is calculated by multiplying the average unit risk factor with the unit emphasis risk factor (Figure 5).

The total risk factor is achieved as the final result (Figure 6) by summarizing these 3, 4, or 5 unit risk factors.

The resulting number of the total risk factor and the associated color of the analyzed production plant offer very valuable information about (a) the risk for microbiological non-compliance of the product regarding sterility and endotoxins, and (b) the GMP-compliance status and the probability of successfully manufacturing the product and passing upcoming regulatory audits.

### 2.2. Sterile API Plants

Sterile API production plants are very complex systems in which initial non-sterile solid drug product ingredients are sterile-filtered, crystallized or lyophilized, centrifuged and dried, and the solid sterile drug product finally aseptically filled into API cans or bags

**Unit Risk Factor = Unit Average Risk Factors X Unit Risk Emphasis Factor**

**Total Risk Factor = Sum of all Unit Risk Factors**

**Figure 5**

**Calculation of the unit risk factor and the total risk factor.**

(for example, 10 kg in size). This bulk material, in the authors' case mostly antibiotics, is intended later to be aseptically filled into final dosage forms (e.g., 1 g/vial used for the patient) in a FDF plant.

The risk analysis divides the process into 5 units, as shown in Figure 4.

The process starts with the non-sterile API unit. Generally, as stated above, the impact of the bioburden on sterility is low because prefiltration and sterile filtration are performed before the liquid formulation is passed to the next process step (e.g., crystallization or drying). Six questions (Q001–006) are asked, and because of the above reasoning the unit risk emphasis factor is 1. For endotoxins, the impact may be higher because the sterile API process (e.g., sterile filtration, crystallization, separation of liquids and solids, dry-

ing, and aseptic filling) is not an endotoxin reduction step. As the endotoxin level of the non-sterile API is controlled together with the bioburden in the incoming material testing, the impact may be regarded as low.

The second unit performs the sterile filtration step. Although it is known that sterile filtration itself is not a terminal sterilization as is heat sterilization or gamma irradiation, it is a well controlled step and validated, and therefore its risk is regarded as average (unit risk emphasis factor of 3). Furthermore, by performing filter integrity testing, it can be assured that a sterile filtrate is obtained by passing the non-sterile liquid through uncompromised sterilizing filters. The impact of bacteria close to 0.22  $\mu\text{m}$  and smaller may be disregarded in most sterile API plants (e.g., those that produce antibiotics and organic solutions) and up to now no public health hazards have been reported.

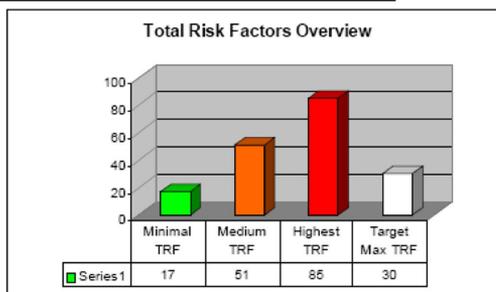
Total Risk Factors	
17 - 33	low
34 - 50	medium
51 - 67	high
68 - 85	very high

Best:

$$1 + 3 + 5 + 3 + 5 = 17$$

Worst:

$$5 + 15 + 25 + 15 + 25 = 85$$



**Figure 6**

Table and diagram of total risk factors for the sterile API plant, the white bar showing a target value, which has been established internally.

- For sterile API plants, risk factors of 17–33 have been defined by the authors as being low total risk factors (green), and risk factors of 68–85 as very high total risk factors (red).
- For sterile liquid FDF plants, risk factors of 10–19 have been defined by the authors as being low total risk factors (green), and risk factors of 40–50 high total risk factors (red).
- For sterile solids FDF plants, risk factors of 11–21 have been defined by the authors as low total risk factors (green), and risk factors of 44–55 high total risk factors (red).

Thirteen questions (Q101–Q113) are asked, and the unit risk emphasis factor is 3.

The third unit is the sterile API production plant itself, the last production unit prior to the aseptic filling step. In most cases, the product plant is comprised of many stainless steel vessels and pipework in a closed system, utility systems such as water for injection as well as much technical equipment. This unit might be a “black box” for the QA microbiologist. Furthermore, since vacuum pressures are involved and required in the vacuum driers, vacuum tank filter, or lyophilizers, the risk for microbial contamination is regarded as very high and the unit risk emphasis factor is defined as 5. If a vacuum is involved in the process, there might be a considerable risk for ingress of non-sterile air or fluids (e.g., the back-siphoning of fluids from the drain system) should the integrity of the production system be compromised. Therefore, maintenance of the production line and associated pipework and equipment including valves and seals is very important. Even in a modern, state-of-the-art production plant, negative surprises may arise. In particular, back-siphoning could lead to a very heavy microbial contamination with a much higher contamination rate of the product than from a cleanroom operator executing a wrong intervention during the last aseptic filling step. If the contamination occurs upstream of the blender in the API plant, then homogenous and heavy contamination is the result in contrast to the often mentioned “single event” happening in cleanrooms. Such events have happened in the past and may still pose a threat if no preventative actions and controls are implemented into the process. Thirty-one questions (Q201–Q231) are asked, and the unit risk emphasis factor is, in this case, 5.

The fourth unit is the aseptic filling unit. In the cleanroom, many factors are involved, and the main risk involves manipulations by the cleanroom personnel. Since humans are involved, mistakes can be expected; single incidences may happen that could compromise the sterility of the product. Therefore the training of the personnel with regard to correct gowning and proper behavior, such as slow movements during aseptic processing, are a key element in most companies’ efforts to maintain and improve quality. Indirect controls like environmental monitoring also offer some information about the quality of the aseptic operations, while the identification of environmental isolates may help reveal the route of entrance to the cleanroom, thus aiding in establishing preventive actions. The

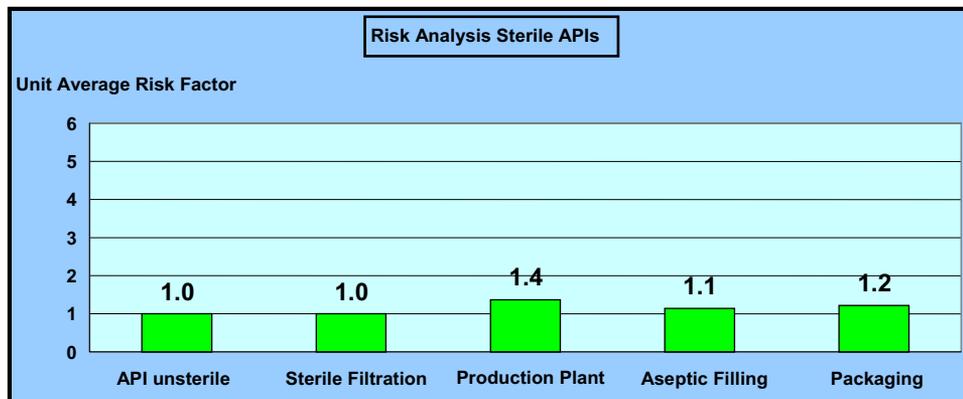
authors have the opinion that this unit has an average risk in comparison to the total contamination risk because no vacuum is involved and the interventions of the fully gowned operators with sterile tools bear a low risk if proper technique is used. Furthermore, these activities are simulated in the media fill validation, and the environment within the cleanroom or even in the isolator has a very low bioburden. Therefore this unit has a unit risk emphasis factor of 3, and 41 questions (Q301–Q341) are asked.

The fifth and last unit is the packaging/transportation unit. Sterilization by heat (such as used to sterilize aluminum cans) or by gamma irradiation (as used on polyethylene bags) of the primary packaging material is a well controlled and validated step. Incorrect storage of sterilized containers in the cleanroom can lead to microbial re-contamination of the container. However, the key point is that during transportation, the primary packaging material might be exposed to high temperature and pressure differentials, especially in the case of aluminum containers. Bags are also exposed to fluctuations, but if filled under ambient conditions with residual air left in the bag, the temperature/pressure effects seem to have less influence. In the case of cans, this means that during storage at lower temperatures (filled at room temperature, storage at +4 °C or lower), the air inside in the headspace tightens and the cold headspace sucks in non-sterile air from the environment. This may occur with containers that are not hermetically closed, and microbial contaminants that entered with the non-sterile air are trapped and can survive, resulting in an unsterile API material. In addition, the properties of the rubber stoppers or sealing material of drums at low temperatures may also be affected. A similar effect compromising sterility also occurs during flight in an airplane because under-pressure conditions exist even inside the passenger cabin, with a pressure similar to an altitude of 6000 ft to 8000 ft (2000–2700 m) above sea level, similar to that on a mountain peak. The reader has most likely experienced after a flight that a shampoo bottle inside the toiletry bag has opened and the toothbrush is covered with shampoo. Similarly, when the integrity of the primary packaging material is not 100%, sterile air is pulled out during the flight and after landing non-sterile air enters, contaminating the product. An aluminum can with a large rubber stopper (>13 cm) that is not sealed in a sterile outer bag over the aluminum container represents a risky primary packaging material.

Production site:	Super API Plant XY
Product:	Sterile Antibiotic
Evaluation Date:	05.05.2009

Unit Average Risk Factors	
1.0 - 1,9	low
2.0 - 2,9	medium
3.0 - 3.9	high
4.0 - 5.0	very high

Total Risk Factors	
17 - 33	low
34 - 50	medium
51 - 67	high
68 - 85	very high



$$\text{Unit Risk Factor} = \text{Unit Average Risk Factor} \times \text{Unit Risk Emphasis Factor}$$

	Unit Average Risk Factor	Unit Risk Emphasis Factor	Unit Risk Factor
API non sterile	1.0	1	1.0
Sterile Filtration	1.0	3	3.0
Production Plant	1.4	5	6.9
Aseptic Filling	1.1	3	3.4
Packaging	1.2	5	6.1
<b>Total Risk Factor</b>			<b>20.0</b>

The plant shows a Total Risk Factor of 20.0 Therefore the probability for product unsterility is low

Figure 7

**Sterile API plant with a low risk for non-sterility.**

The authors have become aware of this high potential of contamination after getting seriously contaminated, externally sourced products shipped in risky cans and without outer bags. An internal action performed for more than 14 years involves sealing all cans in a double-sterile bag, heat-sealing, and, furthermore, the use of another type of aluminum can with better container-closure integrity (CCI). Finally, CCI testing is also now performed by exposure to under- and over-pressure; the results are now satisfactory.

Eight questions (Q401–Q408) are asked. The unit risk emphasis factor is based on past experience and is established for this unit as 5.

*2.3. Sterile Finished Dosage Form (FDF) Plants (Aseptic Filling of Sterile Solid or Liquid Product without Sterile Filtration of the Liquid)*

In FDF plants for sterile solid or liquid products, the sterile API material (internal or external source) is filled under aseptic conditions from a bulk container

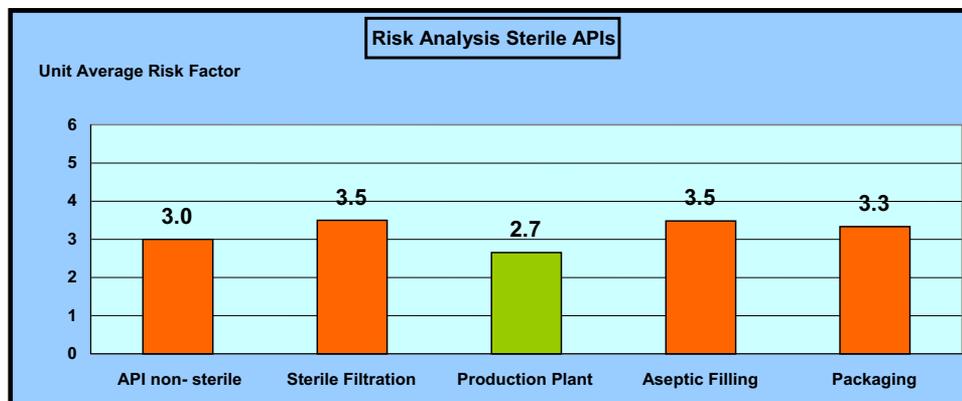
(cans or bags) into vials. The filling line can be conventional under class A within a class B environment or a class A isolator located within a classified area. The quality of the sterile API material is crucial, and the most modern filling line cannot render a non-sterile API product sterile. Therefore, the supplying sterile API plant has to be well known and audited in detail, especially if a company is sourcing from an external supplier. It is also clear that the sterility of the entire API material cannot be assured by the sterility testing of API samples because sterility testing is just a quick and random inspection and does not offer much information.

The risk analysis for FDF plants (sterile solids) consists of three units. The first unit is the sterile API handling unit. Its impact on the sterility of the vial is very high, therefore a unit risk emphasis factor of 5 has been established. The questions are similar to those regarding the sterile API plant addressed above and transportation and storage aspects of packaged

Production site: **Disaster Plant**  
 Product: **XY**  
 Evaluation Date: **25.01.2010**

Unit Average Risk Factors	
1.0 - 1.9	low
2.0 - 2.9	medium
3.0 - 3.9	high
4.0 - 5.0	very high

Total Risk Factors	
17 - 33	low
34 - 50	medium
51 - 67	high
68 - 85	very high



	Unit Average Risk Factor	Unit Risk Emphasis Factor	Unit Risk Factor
API non sterile	3,0	1	3,0
Sterile Filtration	3,5	3	10,5
Production Plant	2,7	5	13,3
Aseptic Filling	3,5	3	10,5
Packaging	3,3	5	16,7
<b>Total Risk Factor</b>			<b>54,0</b>

$$\text{Unit Risk Factor} = \text{Unit Average Risk Factor} \times \text{Unit Risk Emphasis Factor}$$

The plant shows a Total Risk Factor of **54.0** Therefore the probability for product sterility is **high**

Figure 8

#### Example of a sterile API plant with a high risk for non-sterility.

material are also included. Thirty-four questions are asked (Q001–Q034).

The second unit is the aseptic operations part of the process. As discussed above for the sterile API aseptic operations units, the risk for microbial contamination is considered by the authors to be “average” if the cleanroom is well run and the cleanroom operators are qualified and educated. Therefore the unit risk emphasis factor is 3. Fifty-five questions are asked (Q101–Q155).

The third unit is the packaging and transportation step. The primary packaging material for the FDF material is smaller and more robust in comparison to the bulk material primary packaging material, thus the pressure and air exchange effects observed for the large API cans (e.g., 20 L volume size) have less impact, based on the temperature and pressure fluctuations. The vials are smaller and more compact and the remaining air in the headspace is much less than in aluminum cans. The unit risk emphasis factor is therefore average and defined as 3. Three questions are asked (Q201–Q203).

#### 2.4. Sterile Finished Dosage Form Plants (Aseptic Compounding/Filling of Liquid Product, with Sterile Filtration Leading to a Liquid or Solid Product)

FDF plants for sterile liquid products are different from the FDF plants for filling sterile solids because the former plants consist of four units and, in principle, are a combination of the two risk analyses as explained above. The first unit, non-sterile API, is identical to unit 1 of the sterile API plant and has a unit risk emphasis factor of 1. Six questions are asked (Q001–Q006).

The second unit, sterile filtration, is also identical to unit 2 of the sterile API plant and has a unit risk emphasis factor of 3. Thirteen questions are asked (Q101–Q113). The third unit, aseptic operations, is similar to unit 2 of the FDF sterile solids plant and has a unit risk emphasis factor of 3. Sixty questions are asked (Q301–Q360). The fourth unit, packaging and transportation, has a unit risk emphasis factor identical

to unit 3 of the FDF sterile solids plant above, and again three questions are asked (Q 401–403).

In summary, the following number of questions have to be answered:

- Sterile API plant: 99 questions
- Sterile solids FDF plant: 92 questions
- Sterile liquids FDF plant: 82 questions

### 3. Results (Examples)

Figures 7–9 show three examples of how the final result of the risk analysis works and what the results looks like:

plies valuable information about potential microbial contamination risk. This procedure is a simple and effective risk assessment approach, because it works along with relevant questions and multiple-choice answers, with no “probability of . . .” evaluation included, thus making the approach simpler.

All questions regarding the risk analysis are based on practical experience and result from a comprehensive knowledge about sterile plants, aseptic processing, and associated systems like production technology, QA/QC microbiology methods, and current requirements of the regulatory agencies.

If new experiences or requirements arise based on actual problems or weaknesses in daily routine work,

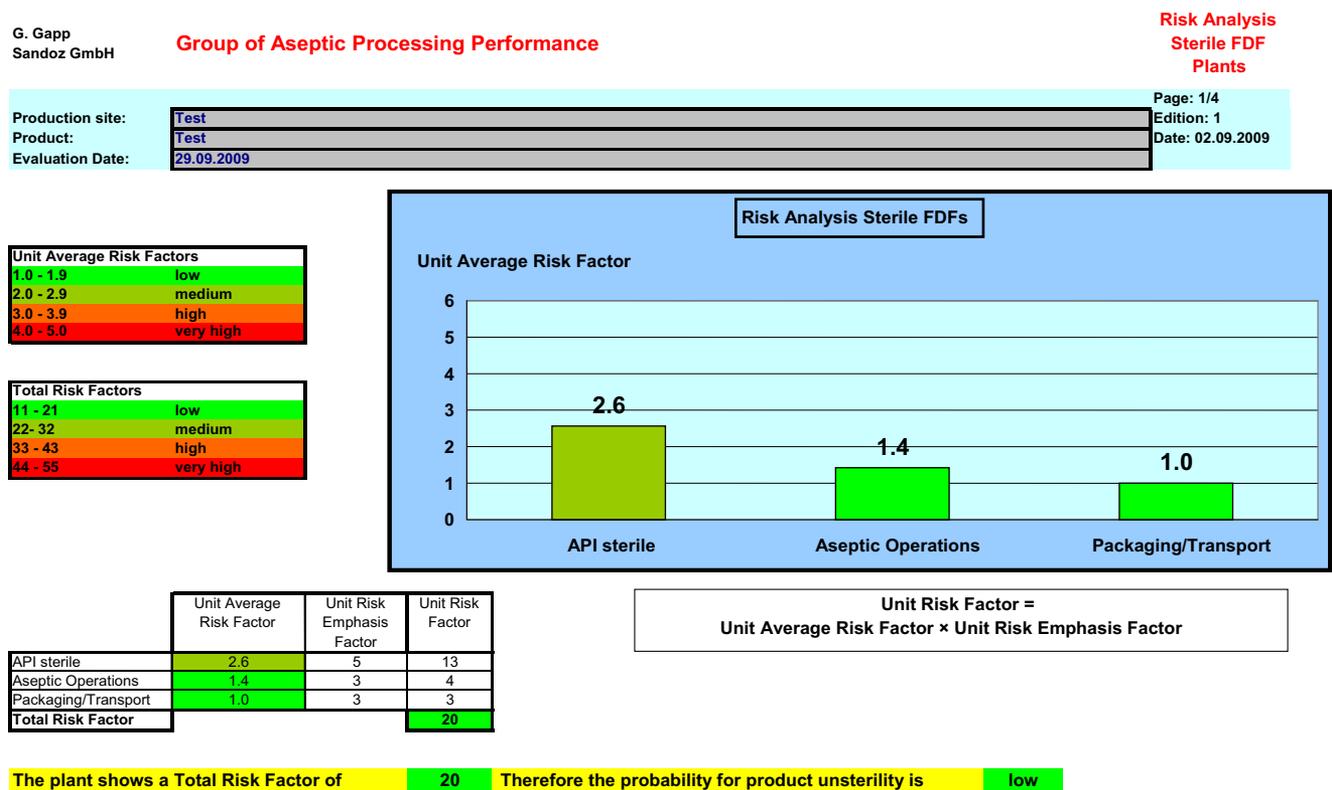


Figure 9

Example of a sterile FDF plant with a low risk for non-sterility but bordering on medium risk due to the medium risk in unit 1 (medium risk sterile API source).

### 4. Discussion

Three years’ performance of this risk analysis method, carried out at different production sites all over the world, demonstrates that the concept works and sup-

or even from justified audit findings, these can be immediately incorporated into the questionnaire and thus result in an updated version. An added plus is that this risk analysis also offers others the possibility of detecting their deficiencies in advance, thus avoiding

the repetition of problems previously appearing somewhere else in the world.

Again, the key to this method is that, for a correct answer to be chosen, long and well-funded experience in advanced, sterile production technologies, microbiology QA/QC, and regulatory agency requirements is needed. Most importantly, the responses must be honest and based on a thorough consideration of the issue.

In addition, the management of the authors' company highly appreciates this new concept, as it is a valid benchmarking tool for comparing the sterile production plants within the company. Finally, because most managers have little expertise in sterile production and aseptic operations, they may feel confident with those production plants that achieved low numbers/green range in the risk analysis with regard to possible product contamination incidences and, as a consequence, adverse drug reactions leading to market withdrawal, and finally also low compliance risks in regulatory audits.

In conclusion, since there are so many microorganisms in the world everywhere around us, and since microbiology is such a complex field, negative surprises can and still will happen, but this will be hopefully only be

a very rare event in "green colored" and "low number" sterile plants.<sup>2</sup>

#### *Conflict of Interest Declaration*

The authors declare that there are no financial or non-financial competing interests related to the manuscript presented.

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#### **Reference**

1. Technical Report 44. Quality Risk Management for Aseptic Processing. *PDA J. Pharm. Sci. Technol.* **2008**, 62 (S1).

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<sup>2</sup> The risk analysis questionnaires can be requested from the author [guenther.gapp@sandoz.com](mailto:guenther.gapp@sandoz.com) and is the property of Sandoz. In the meantime also a Risk Analysis for Terminally Sterilized Products has been established.

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