

Risk Analysis for Aseptic Processing: The Akers-Agalloco Method

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ABSTRACT: Aseptic processing is considered by many in this industry to be among the more difficult activities to execute properly. The number of variables that affect the safety of sterile products manufactured aseptically is substantial. In the design and operation of an aseptic production facility, it is essential that risk to the patient be minimized. This article presents a new approach to risk assessment for aseptic processing that emphasizes the contributions of personnel.

KEYWORDS: aseptic processing, risk analysis methods, sterile manufacturing, validation, aseptic filling, lyophilization, decontamination, isolation, microbial contamination.

INTRODUCTION

In September of 2004, FDA issued a number of guidance documents and regulatory initiatives. Among the guidance documents made available was the long awaited guidance on Sterile Drug Products Produced by Aseptic Processing.ⁱ At essentially the same time, FDA also published "Pharmaceutical CGMPs for the 21st Century - A Risk-Based Approach."ⁱⁱ Each of these documents makes reference to the other, but there is no substantive information offered in either to assist the practitioner in establishing a true risk-based approach for the design, and control of contemporary aseptic processing operations.

Numerous, pre-existing risk analysis methods have been adapted for use in the pharmaceutical industry including:

- Fault Tree Analysis - FTA
- Failure Mode and Effect Analysis - FMEA
- Hazard Analysis and Critical Control Point - HACCP
- Hazard and Operational Studies – HAZOP
- Failure Mode, Effect and Criticality Analysis – FMECA - adds "criticality" to FMEA

These methods have proven to be successful in a variety of applications; however, none was ever specifically intended for application with aseptic processing, which relies on a large number of variables and has the least

tolerance for failure of any process in the entire industry. Simply put, failure in aseptic processing is unacceptable and a suitable risk analysis method must incorporate all of the myriad factors impacting product sterility, and thus patient safety. The risk analysis approach utilized must be compatible with the recognition that there is no acceptable level of risk associated with sterile products, regardless of the method of manufacturing. The goal is, and must always be, perfection in all elements of sterile product manufacture, even where they are made using an aseptic process.ⁱⁱⁱ With this in mind we embarked on an evaluation of prior risk evaluation methods models applied to aseptic processing,

RISK & RISK EVALUATION METHODOLOGIES

Regardless of the risk analysis method there is a clear need to focus on those activities that are essential for success. This is normally embodied by a concern for 'criticality' as an essential criterion, as not all of the supportive activities for a process being evaluated have the same impact on the end result. Risk as defined within FMECA is a multiplication of the criticality of the occurrence by the frequency of occurrence. This is a definition that can seemingly be applied directly to aseptic processing. However, what is generally difficult in aseptic processing is actually measuring what is an "occurrence". One could argue (perhaps incorrectly) that environmental monitoring results can provide a measure of "occurrence", but this is theoretical at best. Environmental monitoring, especially in the ISO 5 environments commonly utilized for aseptic processing activities can hardly be considered a quantitative, nor fully effective

tool. In the typical ISO 5 environment microbial contamination is only rarely detected, and even the most aggressive sampling plans only sample a limited amount of the air or surfaces.¹ A further drawback of viable environmental monitoring is that using common growth and recovery methods results are unavailable in real time. Non-viable particle monitoring which is available in near real-time, has never been agreeably correlated to viable data and we consider it of limited value in aseptic risk assessment.

We believe that there is a straightforward way to analyze risk in aseptic processing. Risk is by general agreement a function of the release of human-derived contamination into the operating environment. The full dimension of human contamination risk is substantial: a gowned operator may release as many as 10,000 CFU or more per hour.^{iv,v} These estimated values are derived from immediately after sterile gowning on operators performing controlled and defined movements. These methods merely provide a way to estimate the intensity of the contamination source from activities substantially different from those performed during aseptic processing. Direct application of this data to aseptic processing is unfortunately not possible given the differing environments, and activities.

Dr. W. Whyte developed a risk assessment model based upon his work on microbial deposition, an extension of his earlier efforts with settle plates.^{vi,vii,viii} The premise behind this approach recognizes that personnel are the primary source of contamination, but it assumes the mechanism for dispersion of that contamination is airborne deposition.

Number of microbes deposited on product = $C \times S \times Pd \times Pa \times T$

Where,

C = concentration of microbes in the source (people)

S = quantity of air or material dispersed from a source over time (usually CFU/M³/s)

Pd = proportion of organisms effectively transferred

Pa = proportion of organisms that arrive into the product area

A = area onto which the organisms are deposited

¹ Note - We do not support increases in environmental monitoring in these already very clean environments in a misguided effort to find what should not be present. Increasing monitoring scrutiny typically increases the number of interventions and thus increases risk of contamination. In any case, there are no means to prove the absence of microorganisms from an environment; so additional samples provide no benefit.

T= time during which microbes could be transferred.

Dr. Whyte has also proposed a slightly simpler deposition model for risk evaluation in which the risk from microbial contamination is defined as

Risk= $A \times B \times C \times D$

Where,

A = microbial contamination on or arising from a source (glove touch/airborne)

B = ease of dispersion or transfer

C = proximity of the source from critical area (i.e. could assume contamination falls off at a square of distance)

D = effectiveness of control method (isolator, RABS, automation, sealed container, intervention frequency etc.

For each of the four terms in the previous equation provide an estimate of risk Dr. Whyte chose five levels of risk - 0= no risk, 0.5= very low, 1=low, 1.5=medium, 2=high. In the case of factor D (effectiveness of control) he suggests 0 for "full barrier control". This means that should a truly full barrier exist overall risk would be effectively zero. Logically products such as sealed vials would fall into the "full barrier control" category although they might get there quite differently than we might expect.^{ix,x}

The authors' major problem with this risk model is that it may underestimate process risk, because it implies that an exclusionary process such as aseptic processing could produce a level of contamination control effectively equivalent to terminal sterilization. Certainly aseptic processing at the present state-of-the-art cannot be considered equivalent to terminal sterilization. While it may be possible in the future for extremely advanced aseptic processing to achieve levels of actual product safety that are hard to distinguish from those of terminal sterilization processes, there are no aseptic systems in present operation that can attain comparable process capability to a terminal sterilization process. Furthermore, the destructive control afforded by terminal processes enables scientists and engineers to far more reliably assess risk than is possible in aseptic processing.

The deposition models for contamination risk analysis have their advantages and disadvantages. They take into account the technical conditions that have been included in informal risk assessment for years:

- The size of container opening
- Exposure time for the container
- The estimated microbial content of the surrounding air

We believe a major disadvantage is the inherent assumption that deposition of microorganisms from the air represents the only vector for contamination. Having observed numerous aseptic processes over the years, we find that approach limiting. In many aseptic processes, operators must approach sterile materials with tools and protective measures. It seems to us that focusing on personnel is more appropriate, and while deposition may be the mechanism of dispersion, we must not be so focused on the containers that we ignore the potential presence of microorganisms on other parts of the aseptic process. We have developed an approach that is much broader and is not limited to the impact on the container alone.

Also, we believe that assumptions regarding the microbial content of air are potentially misleading. It is tempting to consider that the worst case content of air borne microbial contamination is that given in the common international recommendations, e.g. $1\text{cfu}/\text{m}^3$

We see contamination potential in aseptic processing holistically, with potential contributions from a variety of sources. Figure 1 presents a vision of risk assessment that we have utilized for many years.^{xi} This effort draws upon that foundation and incorporates concerns that influence each of these tasks and the others that affect sterility assurance for aseptically produced sterile materials.

Validation of Aseptic Processing

Task	Ease of Validation	Reliance on Personnel	Associated Risk
Sterilization	Easy	Low	Low
Room Design	N/A	N/A	Moderate
Monitoring	Moderate	Variable	High
Sanitization	Difficult	High	High
Gowning	Difficult	Very High	Very High
Material Transfer	Difficult	High	High
Aseptic Technique	Difficult	Very High	Very High
Aseptic Assembly	Difficult	Very High	Very High

Figure 1

There are a number of basic concepts that result from this perspective of aseptic processing personnel impact on the aseptic process is all-important, and we must base risk to sterility predominantly on the human activities required to execute the process. Other factors can be included, but fixation on the contribution from personnel must be paramount. We should consider risk to be directly related to the number of human interventions required during the

process— the fewer interventions required, the lower the risk of contamination. We also believe that interventions can be scaled relative to criticality. The type of interventional activity performed and the varying proximity of that activity to sterile materials suggest that some form of weighting of their impact is appropriate.

There are varieties of other factors in contamination exposure, some of which are described below:

- The container-opening diameter (smaller being clearly preferred following the deposition models described earlier).
- The length of time the container is exposed to the environment from its initial entry until closure.
- The length of time the closure is exposed to environment prior to sealing of the container.
- Lyophilization can increase the exposure risk due to extended exposure time of the unsealed container and due to a need for additional interventions.
- Ampules are low risk relative to vials, the can be filled at relatively high speeds, require no closure, and thus fewer interventions.
- A high degree of automation can significantly reduce the need for operator interaction with sterile equipment, and materials.
- Sealed, sterile unfilled containers that can be filled and rapidly resealed offer substantial advantages over the more prevalent open containers we typically employ.
- Complex assembly activities that depend largely on operator skill increase risk.
- Containers and closures that handle reproducibly can reduce risk relative to their less consistent (and presumably less expensive) counterparts.
- Novelty of personnel, equipment or procedures increases risk, because of the inability to draw directly on prior experience.

One of our more fundamental premises is that **all ISO 5 environments are not equivalent in their ability to support successful aseptic processing**. Limitations in microbial detection in these very clean environments make distinction among them subjective; nevertheless we acknowledge that some technologies are clearly superior to others in their ability to limit microbial intrusion and contamination. We have included the environmental conditions in which the aseptic process is performed as a major factor in risk assessment. In our model we have chosen to

apply it as an overall factor. The application of these general principles and others of similar intent form the basis for our risk assessment model.

Often in our industry, we seem to give little consideration to risk mitigation in equipment selection. We give only slightly more consideration to the choice of container or delivery system in risk mitigation. Ease of assembly and operation can make a substantial difference in the risk exposure. Reductions in the number of required aseptic connections are beneficial. Automated component handling is helpful in reducing risk. Low in-process adjustment and maintenance requirements should be a key specification. Equipment that can operate with minimum accumulation time is also desirable - as it reduces exposure.

AKERS-AGALLOCO METHOD FOR RISK ASSESSMENT

Our objectives in this effort are for a method that is:

- Easy to use
- Based upon real world risk factors rather than more theoretical concepts
- Based upon an occurrence and criticality model
- Focuses on the impact of personnel
- Considers fatigue as a factor
- Rewards processes where interventions are reduced to a minimum

Occurrence in our model includes quantity and criticality of interventions as well as other elements of process risk indirectly related to the core activity of aseptic filling. We have included:

- **Background Environmental Risk** (as distinct from the filling environment)
- **Aseptic Compounding Risk** (heavily dependent upon interventions)
- **Aseptic Set-up Risk (heavily dependent upon interventions)**
- **Aseptic Filling Risk** (heavily dependent upon interventions, and calculated separately for manual and machine processes)
- **Lyophilization Risk** (included where present)

We believe that the risk to contamination associated with personnel is such that the contributions for these factors must be weighted more heavily than those derived from the non-human related contributing factors. We have

utilized an extra weighting of 10X for those process steps where personnel presence and close interaction with sterilized products, materials and equipment is mandated: aseptic compounding, aseptic set-up and aseptic filling.

The risk for the overall process is the summation of the contributions from all of the relevant process factors arbitrarily weighted by the authors to consider the differing impact of different practices. Determination of the individual factors varies and includes simple multiplications reflecting the combined influence of variables within an individual process step. We have included weighting factors in the lyophilization and aseptic filling areas to provide a more balanced perspective of these process steps. We have chosen to use addition as the primary means of calculation for the following reasons:

- It substantially simplifies the calculations (at least once the individual contributions have been determined).
- It is consistent with the sense that adding an activity (e.g., lyophilization) to a process adds risk to an existing process (e.g., solution filling). This allows the elements of a larger activity to be addressed individually and directly, and optimized from a risk perspective more easily.

Consistent with the other risk assessment models, a lower score suggests a reduced potential for contamination. The risk contributions for the various process elements that comprise the overall aseptic process are described below, and then quantified in the table that accompanies this text.

The environmental technology utilized for the aseptic process plays a major role in the risk assessment. We have applied a corrective factor to the final score derived based upon the individual contributions of the various process steps. If aseptic compounding and aseptic filling are not performed using the same environmental technology then the contribution risks for each should be separately calculated based upon the technology employed.

FACILITY CONTRIBUTIONS

Facility contributions relate to the types of environments provided for the supportive tasks associated with aseptic processing including sterilization unloading, personnel gowning, and background environment for the fill zone. Additional contributions from the facility derive

from the sanitization method utilized and the frequency of treatment. Similar considerations are pertinent to the use of isolators, but the factors and weighting are adjusted to suit the differences in technology. We have included restricted access barrier systems (RABs) within the cleanroom category, as this is the technology that it most resembles.

Cleanroom contribution = Sanitization Interval Factor X Sanitization Process Factor X Background classification Factor

Or

Isolator contribution = Decontamination Interval factor X Decontamination Factor X Background classification factor

The interval between sanitization and type of process applied are multiplied together, and added to the contribution from the background environments. Smaller facilities where one room serves multiple purposes (e.g., filling and unloading) receive a lower score because of their simplicity.

ASEPTIC COMPOUNDING CONTRIBUTION

Processes that require substantial amounts of aseptic processing during formulation have an increased risk associated with those activities that must be factored separately from the aseptic filling process. Factors in this area are the numbers of personnel interacting with the sterile materials, the duration of the process, including set-up and execution (exclusive of hold times where the sterile material are secured and there is no supportive personnel activity in the environment), and the technology utilized for the process. As these processes generally entail frequent human intervention to accomplish the process steps, interventions are not considered separately. This contribution is present for even the simplest products where the only post-filtration activity with sterile materials is associated with sampling or verification of filter integrity.

The process time (including any required aseptic set-up for compounding) is multiplied by a novelty factor (based upon experience of personnel, equipment & process) to determine the aseptic compounding contribution to process risk.

Aseptic Compounding Risk Contribution = Process Duration X Novelty factor

Aseptic Set-up Contribution

The assembly / set-up of filling equipment requires direct human manipulation of sterilized equipment and tools within the critical environment. In some firms, only the most experienced personnel whose proficiency in the required task has been confirmed by a successful media fill are allowed to perform this task. The hands-on nature of this activity often requires separate evaluation from that of the fill process itself. Factored into this activity should be the duration of the set-up which indirectly assesses the sophistication / complexity of the filling equipment and the uniformity of the components. As this activity is almost entirely human, related processes interventions are not considered separately. Typically included in this activity are product connection / introduction, initial weight and closure systems checks and any other relevant activity including environmental monitoring during this assembly / set-up process. The expected additional set-up concerns for suspensions, creams, ointments, powders are factored into the set-up duration time as are other elements such as stopper / vial uniformity; inert gassing system installation as well as the more demanding requirements for double chamber filling and other more complex package designs. Product formulation factors are incorporated into contributions from the aseptic execution as well. The location of sterilizing-grade filter(s) in the product delivery system affects the risk of contamination entering a filled container.

The risk is the result of multiplication of the process time, a complexity factor, a product delivery factor, technology factor and a novelty factor to determine the compounding contribution to process risk.

Aseptic Setup Risk Contribution = Set-up Duration X Complexity Factor X Product Delivery Factor X Novelty Factor

ASEPTIC FILLING PROCESS CONTRIBUTION

INTERVENTIONS = RISK! The perfect intervention is the one you don't have to perform. In evaluating aseptic processing we must be fixated on the need to avoid interventions, and where they are unavoidable to minimize their impact as much as possible. Intervention management during aseptic processing has received increased attention in recent years as recognition of the importance of interventions has grown.^{xii} In a recent article addressing intervention management the following definitions and examples related to aseptic filling activities (as opposed to set-up or changeover) can be found.^{xiii}

“Routine interventions are activities that are inherent parts of the aseptic process and integral parts of every batch.

Typical routine interventions include:

- Periodic component replenishment;
- Periodic fill weight or volume checking and verification;
- Fill weight or volume adjustment;
- Environmental monitoring;
- Product sampling;
- Filter integrity testing;
- Product container replacement;
- Any other interventional activity which is an integral part of the process.”

Non-routine Interventions represent a significantly greater concern than routine interventions, in that their frequency is intended to be substantially lower than routine intervention, and unlike routine interventions their execution cannot be as narrowly scripted. In the referenced article, the user is encouraged to define how to perform interventions of all types, train personnel in those practices and then adhere to them during both process simulation and routine production. That is sound advice; however, there are simply no means to orchestrate non-routine interventions such that they conform to the pre-defined practices. During an actual process, non-routine interventions may vary somewhat from the rehearsed expectations and the firm will be forced to rely on adaptations by the operator to execute them successfully. For this reason, we have chosen to place greater emphasis on any non-routine interventions that must be performed. The following definition and list comes from the same reference.^{xiv}

“Non-routine interventions are activities that are predominantly corrective and may not be a part of every batch. Although in theory non-routine interventions may not be necessary during the aseptic process, in practice such interventions are almost always required to correct some anomaly. Some common non-routine interventions involve:

- Stopper miss-feeds or clumping;
- Fallen, broken, or jammed containers;
- Defective seals on containers;
- Product spillage or leakage;
- Product filter change;
- Sensor adjustments or replacement;
- Filling needle replacement;
- Fill-pump replacement;
- Stopper bowl changes;
- Timing adjustments;
- Conveyor or guide rail adjustments;
- Any other line malfunction requiring manual correction.”

This can be determined using an approach designed strictly for manual fills and a more general method for machine fills in which personnel play only a supportive role.

MANUAL FILLS

The intervention risk is simply the number of times the individual parts of the package (i.e., vial, stopper, etc.) are handled in order to prepare a single filled container. The result is incorporated with the other relevant factors for aseptic filling found in the table to define the overall risk for manual aseptic filling.

Touches per unit = Intervention risk for manual filling (I_R)

Manual filling must be considered the most risky of all aseptic processes, because the minimum number of required interventions (I_R) to fill and seal a container is greater than one.

MACHINE FILLS

Interventions during machine filling are substantially lower in number and thus impact relative to manual fills. Intervention risk (I_R) with respect to criticality factors considered is the distance from exposed product contact parts and components. Critical interventions (e.g., replacement of fill pumps or other critical dosing equipment) are scored as 5, as are any aseptic connections made/remade after the initial set-up. All other interventions within one foot of exposed product contact parts or components parts are scored as “3” on every occurrence. Interventions within two feet are scored as “2”. Interventions outside two feet are scored as “1”. Routine interventions that are an inherent part of every process are weighted at one, while non-routine (corrective) interventions are weighted as two.

NUMBER OF INTERVENTIONS

Calculate or visually confirm during the process for a period of not less than one hour all of the interventions (routine and non-routine) required during the process. Multiply each by the appropriate proximity and type score. Determine the weighted number of interventions per hour by summing these values.

Example:

4 routine interventions within 1 foot
 $4 \times 1 \times 3 = 12$
2 routine interventions within 2 feet
 $2 \times 1 \times 2 = 4$
1 non-routine intervention within 3 feet
 $1 \times 3 \times 1 = 3$
2 non-routine interventions within 1 foot
 $2 \times 3 \times 3 = 18$
1 critical intervention
 $1 \times 5 \times 3 = 15$

Weighted interventions / hour
 $12 + 4 + 3 + 18 + 15 = 52$

The score should be based upon maximum number of interventions observed or allowed. The ideal number of required interventions is always zero.

The weighted number of interventions (normalized for criticality and proximity) / hour should be determined first. A longer evaluation period provides a more accurate assessment, as does averaging of the number of observed interventions over the entire or even multiple batches. In determining intervention risk in this manner, the role of container / closure consistency in determining handling requirements is intrinsically included.

Containers / hour (this is the actual number of units produced during a 1 hour period and is not the theoretical line speed per minute multiplied by 60). Determination of this value over a longer period is preferable in order to be more accurate. Do not include downtime periods when filling is intentionally stopped for activities such as lunch, breaks, or shift change. Include in the calculation those times when the fill is interrupted by interventions of any type. Divide these values by each other to determine interventions / container – here again a lower number is desirable. This value is the Intervention Risk (IR).

Adjusted Product Filling Risk

Estimate the total risk from filling (for either manual or machine fills) by incorporating the remaining variables associated with the filling process: container size, complexity, container introduction method, closure handling technology factor and process duration.

The Intervention Risk (IR) is multiplied by the process duration in hours, the container design factor; container feed factor; closure feed, a weighting factor of 10, and the technology factor.

The longer the process duration, the larger the potential that at least one unit will be contaminated due to the increased number of interventions. Multiplying the Intervention Risk (IR) by the length

of the process emphasizes the impact of filling speed, and includes consideration of fatigue as a factor in inducing contamination.

Further multiplication by the product and technology factors adjusts for the varying levels of contamination potential associated with differing aseptic technologies and product formulation types. Thus the risk contribution for filling could be determined by the following equation:

(Normalized Interventions / hour) / containers / hour) = interventions / container or Intervention Risk (IR).

Intervention Risk (IR) X Fill Duration X Container Factor X Container Feed Factor X Closure Feed Factor x Novelty Factor x Product Factor = Contribution to risk from aseptic filling

LYOPHILIZATION RISK (WHERE PRESENT)

The risk is associated with the time filled components are exposed to the environment between first exposure and closure, as well as the handling practices, lyophilizer sanitization/sterilization practices and the ever present environmental technology factor.

Lyophilization Risk Contribution = Loading Time X Lyophilizer Sterilization Factor X Load Factor X Transfer Factor X Tray Factor X Tc Factor

ENVIRONMENTAL TECHNOLOGY RISK

Once the risk contributions from the components of the overall aseptic process have been determined we recommend an overall adjustment based upon the environmental technology utilized to provide the aseptic conditions. If aseptic compounding is a substantial part of the process, and not performed using the same technology, the environmental factor should be applied separately and then summed. As we have done throughout this document, we have placed an arbitrary weighting on the various technologies. As we stated earlier, consistency in the evaluation of an aseptic process will come through in the overall risk assessment regardless of the specific values chosen.

CONCLUSION

It is apparent that through the application of this method a glaring difference is apparent in risk analysis “score” between conventional manned aseptic processing and advanced technologies. Manual processes will fare ever poorer still. We believe that the distinctions this method reflects among different aseptic technologies are real and

properly represent the realities of the risk to contamination. The reader may disagree at the detail level with the numerical weighting factors we have selected, but the rationale for them, and hence their general correctness, is largely irrefutable. We acknowledge that it is possible to debate our recommendations in an absolute numerical sense, but we believe such a debate would result in rather subtle changes and would not materially affect the objective assessment of the differences among the various practices we have evaluated. We do not mean to suggest that this method should be used to score "acceptable" or "unacceptable" in absolute terms, but rather as a means of identifying opportunities for process improvement regardless of the practices and technologies being utilized. There may come a time when a system similar to this one could be used to define acceptability of practices for products; clearly, however, that time has not yet arrived. We also see potential for this method in the selection of technologies to be utilized.

Perhaps even more importantly, we believe that our risk analysis model can serve as an aid in determining an appropriate level of validation (and revalidation) suitable to the technology employed. Aseptic technologies that with automation or separative technologies either mitigate the risk of human intervention or eliminate such activities are inherently safer than technologies that allow direct human intervention. It follows that the more reliant a technology is on human intervention the more risky it must be. Logically then, such traditional tests as the media fill are far less likely to provide value in assessing the performance of truly advanced technologies. Thus, media fill test frequency could be reduced as could sample size, particularly in systems that allow direct real time control and evaluation of the environment and the process.

In fact, we propose that it is possible using risk analysis to draw a clear line of demarcation between "advanced" aseptic technologies and more conventional systems. We suggest that in order for a technology to be considered advanced there must be no direct human interventions allowable at any time. For example, a RABS system would be considered advanced if and only if there were never under any circumstances direct human interventions, through temporarily opened barriers. Similarly, a blow, fill and seal system would be considered advanced only if after an intervention, no containers were put at risk and the fluid path was subjected to sterilization-in-place prior to the resumption of manufacturing. In our view, firms that invest in technologies that can be

objectively demonstrated to mitigate risk and in which key control parameters can be measured and controlled in real time should benefit from reduced validation, revalidation and traditional microbiological monitoring requirements. Imposing the same validation pathway for advanced technologies as for more risk intensive alternatives not only provides no safety benefit; it does actual harm.

We consider this document as a positive step in an effort to assess risk in aseptic processing. We believe because we have broadened the perspective of risk relative to aseptic processing we have increased awareness that risk can vary substantially in what are perceived by many to be equivalent (and thus equally acceptable) practices and technologies. We welcome constructive criticism of this effort in the hope that it will lead to a clearer definition of risk issues and evaluation approaches as it relates to aseptic processing

POST SCRIPT

As a further guide to the reader, we have applied this method to different facilities utilized for aseptic processing as examples to the reader of how this method might be utilized (see Appendix 1). The facilities are all based upon real installations, though we have altered some of the characteristics to disguise them. The risk assessment of these facilities was utilized to fine tune the model utilized. The authors believe the relative (and of course subjective) capabilities of the facilities are consistent with the values obtained and demonstrate the potential utility of our model for application in aseptic risk assessment. Had the reader visited each of them we believe they might have developed a similar perspective.

Table 1
Risk Factors in Aseptic Processing

<i>Facility Considerations (Use cleanroom or isolator section as appropriate for filling)</i>		
Background Environment to aseptic processing (cleanrooms including RABs)	ISO Class	Risk Contribution
	5	1
	6	2
	7	5
	8	10
	>9	15
Gowning Environment for aseptic processing (cleanrooms including RABs)	ISO Class	Risk Contribution
	5	1
	6	2
	7	5
	8	10
	9 or greater	15
Cool-down location for sterilizer & oven unloading (cleanrooms including RABs)	ISO Class	Risk Contribution
	5	1
	6	2
	7	5
	8	10
	9 or greater	15
Sanitization Regiment (cleanrooms)	Practice	Risk Contribution
	Manual	5
	Non-sporicidal Fog	3
	Sporicidal Fog	1
Sanitization Frequency (cleanrooms)	Practice	Risk Contribution
	Daily	1
	Every Other Day	2
	Every Third Day	3

	Weekly	7
Background Environment for aseptic processing (isolators)	ISO Class	Risk Contribution
	5	1
	6	2
	7	3
	8	4
	9 or greater	5
Decontamination Regimen for Isolators	Practice	Risk Contribution
	Manual Non-sporicidal	4
	Manual Sporicidal	2
	Automated Sporicide	1
Decontamination Frequency for Isolators	Practice	Risk Contribution
	Each Batch / Daily	1
	Weekly	7
	N Day Campaign	N
Aseptic Compounding		
Process Duration (include all aseptic setup time in the process duration)	Practice	Risk Contribution
	1 Minute	1
	2 Minutes	2
	N Minutes	N
Novelty Factor (apply all relevant factors in making the calculation)	Practice	Risk Contribution
	Experienced Personnel & Process	1
	New Personnel (less than 1 year)	2

	New Process (<10 batches)	2
	New Equipment (<10 batches)	2
Aseptic Personnel Factor	All Processes	10
<i>Aseptic Filling Set-up</i>		
Time Required	Practice	Risk Contribution
	1 Minute	1
	2 Minutes	2
	N Minutes	N
Novelty Factor (apply all relevant factors in making the calculation)	Practice	Risk Contribution
	Experienced Personnel & Process	1
	New Personnel (less than 1 year)	2
	New Process (<10 batches)	2
Set-up Complexity (relates to practices for the majority of the components required for the fill)	New Equipment (<10 batches)	2
	Practice	Risk Contribution
	Autoclaved / assembled	10
	Assembled / autoclaved	2
Product Delivery	Sterilized in-situ	1
	Tank – sterilizing filter – tank – sterilizing filter – filler	0.75
	Tank – sterilizing filter – tank – polishing filter – filler	1.1
	Tank – sterilizing filter – tank – filler	1.0
	Tank - sterilizing filter – filler	0.90
Aseptic Personnel Factor	All Processes	10
<i>Aseptic Filling</i>		
Novelty Factor (apply all relevant factors in making the calculation)	Practice	Risk Contribution
	Experienced Personnel & Process	1
	New Personnel (less than 1 year)	2
	New Process (<10 batches)	2
Container Design	New Equipment (<10 batches)	2
	Type	Risk Contribution
	Closed ampule / vial	0.10
	Open container >5 mL	1
	Open container <5 mL	1.5
	Syringe / cartridge	1.25
Container Feed	Multi-chamber	2
	Practice	Risk Contribution
	Oven Fed	1
	Tunnel Fed	0.25
Closure Sterilization / Feed	Tub Fed	0.50
	Practice	Risk Contribution
	No Closure	1
	Open Tray Fed	3
	Sealed Bag / Box	1
	Tub Fed	1

Product	Formulation	Risk Contribution
	Solution	1
	Suspension / Emulsion	2
	Cream / Ointment	3
Filling Duration	Powders	4
	Time	Risk Contribution
	N Minutes	N
Aseptic Personnel Factor	All Processes	10
Lyophilization Process (if present)		
Exposure Time (placement of first stopper on first container until placement of last container in lyophilizer)	Practice	Risk Contribution
	1 Minute	0.1
	2 Minutes	0.2
	N Minutes	N/100
Vial to Tray Loading	Practice	Risk Contribution
	Manual	3
	Automatic	1.5
	No Trays	1
Transfer to Lyophilizer	Practice	Risk Contribution
	Trays on Cart	4
	Trays on LF Cart	2
	Conveyor	1
Tray to Lyophilizer Loading	Practice	Risk Contribution
	Manual	5
	Automatic	2
	No Trays	1
Lyophilizer Sterilization	Practice	Risk Contribution
	Sanitization	4
	Sterilization - Chamber Only	2
	Sterilization – Chamber & Condenser	1
Lyophilizer Thermocouples	Practice	Risk Contribution
	Each Shelf	3
	One Shelf	2
	None	1
Environmental Technology		
	Practice	Risk Contribution
	Vertical Laminar – No Barrier	3
	Vertical Laminar – Soft Barrier	1.5
	Vertical Laminar – Soft Barrier w/gloves	1.25
	Vertical Laminar – Hard Barrier	1
	Vertical Laminar – Hard Barrier w/gloves	0.75
	Horizontal Laminar	0.75
	RABs	0.10
	Isolator	0.01
	BFS/FFS	0.01

Appendix I Application of the Method

In this appendix we have utilized our proposed methodology to evaluate five different aseptic processing systems with which we are familiar.

Execution of the methodology defines the facilities better than a written summary, but a brief description of each is provided by way of introduction. In each of the facilities we utilized a freeze-dried formulation for the purposes of the evaluation. For the purposes of this exercise we have chosen to simplify the process by providing the weighted interventions, line speeds, process duration and thus the intervention risk for each system. We encourage the use of the method described in the text, but in the interest of brevity we have eliminated that step in these examples. The intervention risk for each of these is included in the listing below

Facility A - An older facility of producing a variety of small volume parenterals of differing formulation and configuration. Weighted interventions per hour 90, fill speed 120 vials per minute, process duration 6 hours. Intervention Risk (I_R) = 0.0125 interventions per container.

Facility B - A heavily automated facility of late 80's construction dedicated to the production of a single freeze-dried product in multiple containers and strengths. Weighted interventions per hour 5, fill speed 300 vials per minute, process duration 5 hours. Intervention Risk (I_R) = 0.00027 interventions per container.

Facility C - An early generation isolator based facility intended for a variety of products and formulations. Weighted interventions per hour 60, fill speed 80 vials per minute, process duration 4 hours. Intervention Risk (I_R) = 0.0125 interventions per container.

Facility D - A small volume suite for the production of clinical materials. Weighted Interventions per hour 60, fill speed 30 vials per minute, process duration 2 hours. Intervention Risk (I_R) = 0.033

Facility E - A low volume clinical suite relying on manual filling. Interventions required per container is 4, thus the intervention Risk (I_R) = 4. Process duration is 4 hours

<i>Facility Considerations (Use cleanroom or isolator section as appropriate for filling)</i>			A	B	C	D	E
Background Environment to aseptic processing (cleanrooms including RABs)	ISO Class	Risk Contribution					
	5	1				1	1
	6	2		2			
	7	5	5				
	8	10					
	>9	15					
Gowning Environment for aseptic processing (cleanrooms including RABS)	ISO Class	Risk Contribution					
	5	1				1	1
	6	2		2			
	7	5	5				
	8	10					
	9 or greater	15					
Cool-down location for sterilizer & oven unloading (cleanrooms including RABs)	ISO Class	Risk Contribution					
	5	1					
	6	2		2			2
	7	5	5			5	
	8	10					
	9 or greater	15					
Sanitization Regiment (cleanrooms)	Practice	Risk Contribution					
	Manual	5	5	5		5	5
	Non-sporicidal Fog	3					

Facility Considerations (Use cleanroom or isolator section as appropriate for filling)			A	B	C	D	E
Sanitization Frequency (cleanrooms)	Sporicidal Fog Practice	1					
	Daily	1	1	1		1	1
	Every Other Day	2					
	Every Third Day	3					
	Weekly	7					
Background Environment for aseptic processing (isolators)	ISO Class	Risk Contribution					
	5	1					
	6	2					
	7	3			3		
	8	4					
9 or greater	5						
Decontamination Regimen for Isolators	Practice	Risk Contribution					
	Manual Non-sporicidal	4					
	Manual Sporicidal	2					
	Automated Sporicide	1			1		
Decontamination Frequency for Isolators	Practice	Risk Contribution					
	Each Batch / Daily	1					
	Weekly	7					
	N Day Campaign	N			7		
Facility Contribution Risk			625	40	21	25	10
Aseptic Compounding			A	B	C	D	E
Process Duration (include all aseptic set-up time in the process duration)	Practice	Risk Contribution					
	1 Minute	1					
	2 Minutes	2					
	N Minutes	N	15	15	10	200	100
Novelty Factor (apply all relevant factors in making the calculation)	Practice	Risk Contribution					
	Experienced Personnel & Process	1	1				
	New Personnel (less than 1 year)	2			2		
	New Process (<10 batches)	2		2		2	2
	New Equipment (<10 batches)	2					
Aseptic Personnel Factor	All Processes	10	10	10	10	10	10
Aseptic Compounding Risk			150	300	200	4000	2000
Aseptic Filling Set-up			A	B	C	D	E

<i>Facility Considerations (Use cleanroom or isolator section as appropriate for filling)</i>			A	B	C	D	E
Time Required	Practice	Risk Contribution					
	1 Minute	1					
	2 Minutes	2					
	N Minutes	N	15	5	10	20	10
Novelty Factor (apply all relevant factors in making the calculation)	Practice	Risk Contribution					
	Experienced Personnel & Process	1	1				
	New Personnel (less than 1 year)	2			2		
	New Process (<10 batches)	2		2		2	2
	New Equipment (<10 batches)	2					
Set-up Complexity (relates to practices for the majority of the components required for the fill)	Practice	Risk Contribution					
	Autoclaved / assembled	10	10				
	Assembled / autoclaved	2			2	2	2
	Sterilized in-situ	1		1			
Product Delivery	Tank – sterilizing filter – tank – sterilizing filter – filler	0.75			0.75		
	Tank – sterilizing filter – tank – polishing filter – filler	1.1					
	Tank – sterilizing filter – tank – filler	1.0	1	1			
	Tank - sterilizing filter – filler	0.90				0.9	0.9
Aseptic Personnel Factor	All Processes	10	10	10	10	10	10
Aseptic Filling Set-up Risk			1500	100	300	720	360
<i>Aseptic Filling</i>			A	B	C	D	E
Novelty Factor (apply all relevant factors in making the calculation)	Practice	Risk Contribution					
	Experienced Personnel & Process	1	1			1	1
	New Personnel (less than 1 year)	2					
	New Process (<10 batches)	2		2	2		
	New Equipment (<10 batches)	2					

Facility Considerations (Use cleanroom or isolator section as appropriate for filling)			A	B	C	D	E
Container Design	Type	Risk Contribution					
	Closed ampule / vial	0.10					
	Open container >5 mL	1				1	1
	Open container <5 mL	1.5	1.5	1.5	1.5		
	Syringe / cartridge	1.25					
	Multi-chamber	2					
Container Feed	Practice	Risk Contribution					
	Oven Fed	1	1			1	1
	Tunnel Fed	0.25		0.25	0.25		
	Tub Fed	0.50					
Closure Sterilization / Feed	Practice	Risk Contribution					
	No Closure	1					
	Open Tray Fed	3	3				3
	Sealed Bag / Box	1		1	1	1	
	Tub Fed	1					
Product	Formulation	Risk Contribution					
	Solution	1	1	1	1	1	1
	Suspension / Emulsion	2					
	Cream / Ointment	3					
	Powder	4					
Filling Duration	Time	Risk Contribution					
	N Minutes	N	360	300	240	120	240
Aseptic Personnel Factor	All Processes	10	10	10	10	10	10
<i>Aseptic Filling Risk</i>			16200	225	180	1200	7200
<i>Intervention Risk (I_R) (from above)</i>			0.0125	0.00027	0.0125	0.033	4
<i>Intervention Adjusted Aseptic Filling Risk</i>			202.5	0.061	2.25	36.6	28800
Lyophilization Process (if present)			A	B	C	D	E
Exposure Time (placement of first stopper on first container until placement of last container in lyophilizer)	Practice	Risk Contribution					
	1 Minute	0.1					
	2 Minutes	0.2					
	N Minutes	N/100	3.6	3.0	2.4	1.8	2.4
Vial to Tray Loading	Practice	Risk Contribution					
	Manual	3					3
	Automatic	1.5	1.5			1.5	
	No Trays	1		1	1		

<i>Facility Considerations (Use cleanroom or isolator section as appropriate for filling)</i>			A	B	C	D	E
Transfer to Lyophilizer	Practice	Risk Contribution					
	Trays on Cart	4	4				
	Trays on LF Cart	2			2	2	
	Conveyor	1		1	1		
Tray to Lyophilizer Loading	Practice	Risk Contribution					
	Manual	5	5			5	5
	Automatic	2					
	No Trays	1		1	1		
Lyophilizer Sterilization	Practice	Risk Contribution					
	Sanitization	4	4				
	Sterilization - Chamber Only	2					1
	Sterilization – Chamber & Condenser	1		1	1	1	
Lyophilizer Thermocouples	Practice	Risk Contribution					
	Each Shelf	3	3				
	One Shelf	2				2	2
	None	1		1	1		
Lyophilization Process Risk			1296	3	2.4	54	144
Facility			A	B	C	D	E
Facility Contribution Risk			625	40	21	25	10
Aseptic Compounding Risk			150	300	200	4000	2000
Aseptic Filling Set-up Risk			1500	100	300	720	360
<i>Intervention Adjusted Aseptic Filling Risk</i>			202.5	0.061	2.25	36.6	28800
Lyophilization Process Risk			1296	3	2.4	54	144
Unadjusted Total Risk			3770	443	526	4837	31314
Environmental Technology			A	B	C	D	E
	Practice	Risk Contribution					
	Vertical Laminar – No Barrier	3	3				
	Vertical Laminar – Soft Barrier	1.5				1.5	
	Vertical Laminar – Soft Barrier w/gloves	1.25					
	Vertical Laminar – Hard Barrier	1		1			
	Vertical Laminar – Hard Barrier w/gloves	0.75					

Facility Considerations (Use cleanroom or isolator section as appropriate for filling)		A	B	C	D	E
	Horizontal Laminar	0.75				0.75
	RABs	0.10				
	Isolator	0.01		0.01		
	BFS/FFS	0.01				
Facility		A	B	C	D	E
Overall Aseptic Processing Risk		11310	443	5.26	7256	23486

As an aside, it should be noted that the latest media fills at each of these facilities were free of microbial contamination, indicating the relative inability of process simulations as an effective means to evaluate relative risk

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