Aseptic Processing Risk Assessment: The Simplified Akers-Agalloco Method

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Risk Analysis Methods

- Fault Tree Analysis (FTA)
- Failure Mode and Effect Analysis (FMEA)
- FMECA- which adds “criticality” to FMEA
- Hazard Analysis and Critical Control Point (HACCP)
- Hazard and Operational Studies (HAZOP)

However, are any of these methods directly applicable to aseptic processing?

Aseptic Risk- What is it?

- Risk as defined by FMECA = criticality of the occurrence X frequency of occurrence.
- This is a definition that can be readily applied to aseptic processing.
- What is difficult in aseptic processing is actually measuring an “occurrence”
- One could argue that EM provides a measure of “occurrence”, but this is theoretical at best.
- Current EM methods have an uncertain correlation to microbial contamination, and is unavailable in real time.

Risk Assessment by Dr. W. Whyte

No. 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/M^3/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

T= time during which microbes could be transferred.

Deposition Models + and -

- This model takes in account technical conditions that have been included in informal risk assessment for years:
  - Size of container opening
  - Exposure time to the environment
  - Estimated microbial content in air
    - How does that relate to the numbers of microorganisms detected on surfaces (and deposited in the product perhaps?)
      - RODAC® samples
      - Settle plates
- The first two of these are relatively easy to determine; the last can only be estimated.

Another way to look at risk

- Risk is a function of release of human contamination into the environment.
- Dimensions of human contamination risk- a gowned operator may release as many as 10,000 CFU/hour or more (Reinmuller and Ljungqvist; W. Whyte).
- Data from first use gowns with controlled and defined movements.
- It is also agreed that the only significant route of contamination is airborne.

Risk Source = Personnel

Risk Route = Airborne Dispersion

Operators & Contamination

"It is useful to assume that the operator is always contaminated while operating in the aseptic area. If the procedures are viewed from this perspective, those practices which are exposing the product to contamination are more easily identified."

Hank Avallone – 1988

Risk and Aseptic Processing Tasks

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

The Proper View of Interventions

- Interventions always mean increased risk to the patient.
- There is no truly safe intervention.
- The ‘perfect’ intervention is the one that doesn’t happen!

Interventions & Risk

- 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.
- Routine interventions are activities that are inherent parts of the aseptic process and integral parts of every batch.
- Non-routine interventions are activities that are predominantly corrective and may not be a part of every batch.

Types of Interventions

Routine

- Line set-up
- Replenishment of components
- Weight / volume checks / adjustments
- Environmental monitoring
- Breaks, lunch

Non-routine

- Stopper jams
- Broken / fallen glass
- Defective seals on containers
- Liquid leaks
- Other mechanical failures requiring manual correction

Factors in Contamination Exposure

- Size of container opening
- Length of time container is exposed to the environment.
- Length of time closure is exposed to environment.
- In the case of lyophilization we can clearly see the increased exposure risk which arises from exposure time and perhaps from intervention intensity as well.
- Grade A environments are not equivalent in their performance capabilities.

General Principles of Aseptic Risk

- Ampoules are low risk - relatively high speed, no closure, few interventions.
- Small containers filled at high speed are low risk, unless they are prone to tip over.
- Isolators and automation decrease risk.
- Sealed product systems dramatically reduce risk.
- Complex assemblies heavily dependent upon personnel increase risk.
- Open product transfers conducted by personnel increase risk even in Grade A/ISO 5 air.

Equipment & Risk Mitigation

- There is little consideration to risk mitigation in selection.
- Ease of assembly / reduced connections can make a substantial difference.
- Automated component handling is helpful in reducing risk.
- Target minimal need for in-process adjustment and maintenance.
- Equipment that operates with minimum accumulation is always desirable - reduces exposure time of components.

Components & Risk Mitigation

- Container / closures that feed without jams or breakage lower risk by reducing the need for interventions.
- Fills that result in spills of liquid or powder may cause slippage or more likely sticking.
- Small container openings (ampoules, small vials, some pre-filled syringes) may result in more spillage, jams and tip-overs.
- Powder fills often lead to dissemination of powder- leading to equipment problems/jams.

More Factors Impacting Risk

- Automation can significantly reduce the need for operator interaction.
- Sealed, sterile unfilled containers that can be filled and rapidly resealed are less risky.
- Complex assembly activities that depends 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 on prior experience.

Isolators and other “barriers”

- Isolators do not eliminate interventions.
- Isolators that are designed to allow frequent and easy glove access may have more interventions than cleanrooms.
- RABS – the same intervention would be even more risky than in isolator.

- Even where isolators or barriers are involved reducing the number of interventions should be a primary design and operations principle.

The Proposed Method

- Objectives
  - Easy to use, simple math, no statistics used.
  - Based upon identifiable risk factors rather than assumed risks.
  - Uses an occurrence vs. criticality model.
  - Occurrence in our model includes quantity, criticality and proximity of interventions as well as other process risks.

Major Risk Elements

- Aseptic Compounding Risk
  - Some processes have substantial interventions; while others are less invasive.
  - Varies significantly with product formulation.
- Aseptic Set-up Risk
  - A series of interventions.
- Aseptic Filling Risk
  - Calculated differently for manual and machine processes.
- Lyophilization Risk
  - Included only where present.
- Individual Environmental Consideration
  - Compounding, Filling, Lyo can differ in design.

Aseptic Compounding Risk

- The process time (including any required aseptic set-up for compounding) are 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 X Environmental Factor

Aseptic Set-up Risk

- The risk is determined by multiplying the process time, a complexity factor, a product delivery factor, and the technology 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

A Different Approach

- Consider risk to be directly related to the number of human interventions - fewer interventions = less risk.
- Consider that interventions can be scaled relative to criticality.
  - Complexity
  - Proximity to open containers, sterilized components and exposed product contact surfaces.
- Consider the total length of product exposure.

Manual Aseptic Filling Risk

- 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.
- All interventions are critical ones.

- Touches per unit = Intervention risk for manual filling (IR)
- This number is always greater than one.

Number of Interventions (N_i)

- Determine the total number of interventions done during a process.
- Score should be based upon maximum number of interventions observed or allowed.
- Weight the interventions (routine & non-routine) by distance from open container/stopper.
- The goal for every aseptic process should always be zero interventions.

Intervention Risk (I_R)

- Calculate or visually confirm during the process for a period of not less than one hour all of the interventions required during the process. Multiply each by the appropriate proximity and type score. Determine the total intervention risk per hour by summing these values.
- The objective is to minimize this number in every situation.

Intervention Risk (I_R)

- Score Intervention risk (I_R) with respect to criticality factors to be considered are criticality and distance from exposed product contact parts and components.
- A score of zero is possible only if no operators are present within the aseptic processing environment.
- Critical interventions for example replacement of fill pumps or other critical dosing equipment are scored as “5”. All aseptic connections are scored as 5.
- Non-routine interventions are scored as “3”, while routine interventions are score as “1”
- Interventions within one foot of exposure product contact parts are scored as “3”. (i.e. stopper addition), interventions within two feet are scored as “2”.

Intervention risk / hour -

4 routine interventions within 1 foot

4 x 1 x 3 = 12

2 routine interventions within 2 feet

2 x 1 x 2 = 4

1 non-routine intervention within 3 feet

1 x 3 x 1 = 3

2 non-routine interventions within 1 foot

2 x 3 x 3 = 18

1 critical intervention

1 x 5 x 3 = 15

Weighted interventions / hour

12 + 4 + 3 + 18 + 15 = 52

Adjusted Product Filling Risk - 1

- 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.

Adjusted Product Filling Risk - 2

- The intervention Risk (I_R) is multiplied by process duration in hours, the container design factor; container feed factor; closure feed factor; novelty factor and product factor.
- Aseptic Filling Risk Contribution = Intervention Risk (I_R) X Fill Duration X Container Factor X Container Feed Factor X Closure Feed Factor x Novelty Factor x Product Factor

Combining Set-up & Filling Factors

- The individual contributions from aseptic set-up and aseptic filling are summed and multiplied by the environment control factor associated with the prevalent technology utilized for filling.

Lyophilization Risk (optional)

- The risk is associated with time filled components are exposed to the environment between first exposure and placement in the dryer, as well as the handling practices, lyophilizer sanitization / sterilization practices and thermocouple factor.

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

Sum the Individual Contributions

- Aseptic Compounding Risk +
- Aseptic Set-up & Filling Risk +
- Lyophilization Risk =

Total Aseptic Risk

- Lower values suggest lower risk.
- Consider the individual risk values as well as the total to ensure proper attention is paid to all areas.

Aseptic Compounding Risk

Aseptic Compounding Risk

Process Duration (include all aseptic set-up 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
	None	1
	New Personnel (less than 1 year)	2
	New Process (<10 batches)	2
	New Equipment (<10 batches)	2
Environmental Technology	Practice	Risk Contribution
	Vertical Laminar – No Barrier	3
	Vertical Laminar – Soft Barrier	1.5
	Vertical Laminar – Soft w/gloves	1.25
	Vertical Laminar – Hard Barrier	1
	Vertical Laminar – Hard w/gloves	0.75
	Horizontal Laminar	0.75
	RABs	0.10
	Isolator	0.01
	BFS/FFS	0.01
	Fully Closed System	0

Aseptic Filling Set-Up Risk

Aseptic Filling Set-Up Risk

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
	None	1
	New Personnel (less than 1 year)	2
	New Process (<10 batches)	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
	Assembled / autoclaved	2
	Sterilized in-situ	1
Product Delivery	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 Filling Risk

Novelty Factor (apply all relevant factors in making the calculation)	Practice	Risk Contribution
	None	1
	New Personnel (less than 1 year)	2
	New Process (<10 batches)	2
	New Equipment (<10 batches)	2
Container Design	Type	Risk Contribution
	Closed ampule / vial	0.10
	Open container >5 mL	1
	Open container <5 mL	1.5
	Syringe / cartridge	1.25
	Multi-chamber	2
Container Feed	Practice	Risk Contribution
	Oven Fed	1
	Tunnel Fed	0.25
	Tub Fed	0.50
Closure Sterilization / Feed	Practice	Risk Contribution
	No Closure	0.1
	Open Tray Fed	3
	Sealed Bag / Box	1
	Tub Fed	1
Product	Formulation	Risk Contribution
	Solution	1
	Suspension / Emulsion	2
	Cream / Ointment	3
	Powders	4
Filling Duration	Time	Risk Contribution
	N Minutes	N

Aseptic Set-up & Filling Risk

Sum the risk values from set-up and filling.

Multiply by the value in the table.

	Practice	Risk Contribution
Environmental Technology	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

The result is the combined risk contribution from set-up and filling.

Aseptic Lyophilization Risk

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/10
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
	Per Thermocouple (N)	Nx2
	None	1

Aseptic Lyophilization Risk

Multiply the value in the tables on this and the preceding page.

	Practice	Risk Contribution
Environmental Technology	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

The result is the risk contribution from lyophilization.

Discussion - 1

- In the application of this evaluation method that there is a sharp distinction between conventional manned processing and advanced technologies. Manual processes will fare ever poorer still.
- We believe that the distinctions this method creates are real and represent the realities of the risk to contamination properly.
- What we have endeavored to create is a means to perform an objective assessment of aseptic practices.

Discussion - 2

- This method should not be used to score “good” or “bad” in absolute terms, but rather as a means of identifying opportunities for process improvement regardless of the practices and technologies being utilized.
- It might be usable to define acceptability of aseptic practices for products.
- We also see potential for this method in the selection of technologies to be utilized.

Application in the Real World

- 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 (IR) = 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 (IR) = 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 (IR) = 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 (IR) = 0.033.
- Facility E – A low volume clinical suite relying on manual filling. Interventions required per container is 4, thus the intervention Risk (IR) = 4. Process duration is 4 hours.

Results of the Evaluation

Simplified Method

Risk Contribution	A	B	C	D	E
Aseptic Compounding Risk Contribution Subtotal	12	22.5	0.2	300	150
Aseptic Set-up & Filling Risk Contribution Subtotal	571.5	7.56	0.203	303	2,160
Lyophilization Risk Contribution Subtotal	103,680	30	0.24	540	4,320
Overall Processing Aseptic Risk	**104,263.5**	**60.06**	**0.643**	**1,143**	**6,630**

Original Method

Risk Contribution	A	B	C	D	E
Overall Aseptic Processing Risk	**11,310**	**443**	**5.26**	**7,256**	**23,486**

Application in the Real World - 2

	Oldest	Smallest	Largest	Newest	Isolator
Compounding	**20.0**	**20.0**	**20.0**	**20.0**	**20.0**
Filling Contribution	**450.6**	**162.7**	**152.9**	**177.1**	**17.7**
Lyophilization Risk	**103680.0**	**5184.0**	**432.0**	**57.6**	**17.3**
Overall Aseptic Risk	**104150.6**	**5366.7**	**604.9**	**254.7**	**55.0**

Conclusion

This method is an effort to assess risk in aseptic processing. We believe because we have broadened the perspective of risk relative to aseptic processing that if nothing else 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.