RISK ASSESSMENT FOR STEAM STERILIZERS IN GMP APPLICATIONS – White Paper

A short overview of the methodology

Ms. Carme Carrillo is the Director of Innovation, Design & Development for MATACHANA Sterilizers.

With more than 25 years of experience in sterilization, she is member of PDA and ISPE and also participates in several ISO and EN committees.

Summary

Steam sterilizers used in terminal sterilization or aseptic manufacturing are critical equipment inside the pharmaceutical production of sterile forms. A complete risk assessment, along the life cycle of this equipment shall be performed, in order to warranty the correct sterilization of the products.

Here, a short overview of the different approaches will be given, as well as the main aspects to take into consideration.

THE STEAM STERILIZATION

Some medical devices, parenteral and ophthalmic products and other pharmacological forms shall be sterilized before placing them on the market. Although there are different sterilization methods accepted for terminal sterilization, moist heat sterilization is the preferred system for all these items that are not heat sensitive.

Moist heat sterilization is a well-known system, highly reliable and easy to control. Even though, as any other physical process, the sterilization process shall be well defined and perfectly verified to grant the correct sterilization of all the batches.

In this sense, from the initial design to the end of the equipment's lifespan, all the critical situations that could affect the user, the product or even the patient, shall be considered, evaluated and, if possible, reduced. All this is the product life risk management.

DEFINITION OF HAZARD AND RISK

The risk management shall reduce the presence of hazards and minimise the exposure to these hazards.

But what is the difference between risk and hazard?

HAZARD is a 'potential source of harm' (ISO 14971 and ICH Q9). As a 'potential' fact, hazard is closely related with exposure and effect. Then:

- A hazard can affect in different ways different stakeholders or situations
- A hazard can be detected immediately or its effects are only detectable after a period of time

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- Hazard always exists, it is an intrinsic element of processes and products.

RISK, according to ISO 14971 and ICH Q9, is defined as 'the combination of the probability of occurrence of harm and the severity of that harm'.

Risks can be classified according to their acceptability into 4 categories:

- Acceptable risk: risk that can be allowed without any additional action
- Residual risk: acceptable risk remaining after mitigation actions
- Unacceptable risk: risk that cannot be accepted; it must be eliminated or, at least, transformed into a residual risk
- Unidentified risk: unknown and not assessed risk; commonly, these risks are detected after an incident and must be controlled as soon as possible.

After a correct risk assessment, all the known risks shall be 'acceptable'.

THE RISK MANAGEMENT

A wide bibliographic information (publications, standards, different guides, etc.) about risk assessment and risk management are available. But, focussing in the steam sterilizer, what steps must be taken to properly manage the risks associated with the steam sterilization? Our step-by-step suggestion is as follows:

1. Create your own risk-team: qualified people from different departments with activities related to sterilization process
2. The team will prepare list of all the risks they can anticipate and their consequences: cross-contamination, non-sterile material, damages to people or environment, etc.
3. The risk list shall be pondered and classified following the chosen risk assessment tool
4. For unacceptable risk, mitigation actions must be defined and executed. In this sense, the experience and knowledge of the risk team is a great value to define the optimal solution.
5. After mitigation actions, check that no other risks have been generated.
6. In a periodic basis, or, if an unexpected situation generates an unidentified risk, a complete review of risk assessment shall be done.

This assessment shall be done till the end of the sterilizer's lifetime.

THE RISK ANALYSIS: WHICH METHOD IS THE CORRECT ONE?

Each organization must have defined its own procedures for risk management and risk assessment. These procedures shall be integrated in the Quality System and reviewed periodically.

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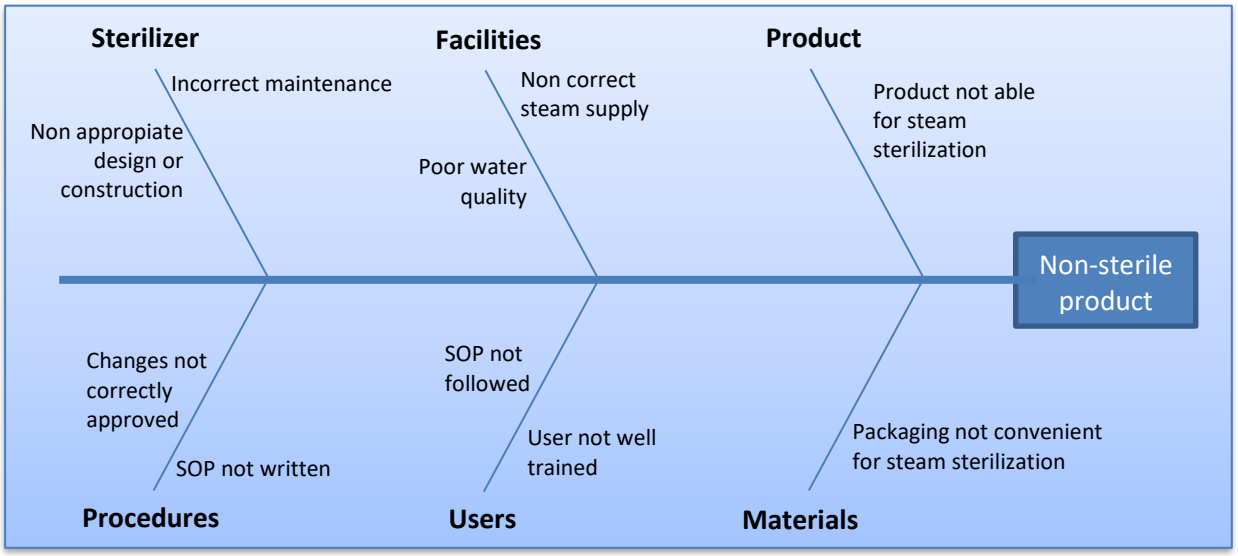
As a general guide, you can consider the following tools:

- For general list of risks and their consequences, the Isikawa (or fish-bone) diagram is a powerful and very visual tool, especially useful for initial brainstorming.



Note: This is just a very simple example, to be expanded and completed according to the needs of each organization.

- To ponder and classify the risks, a wide range of tools are available:
  - Failure Mode and Effects Analysis (FMEA)
  - Fault Tree Analysis (FTA)
  - Hazard Analysis and Critical Control Points (HACCP)
  - Hazard and Operability Studies (HAZOPS)

Additionally, some international standard could help to do the task: the previously mentioned ICH Q9 and ISO 14971, but others as ISO 31000 'Risk management — Guidelines' can be used.

In any case, it is the organization itself that shall establish its own risk management procedure, that can be a combination of the above-mentioned methods.

THE BEGINNING: THE RISK ANALYSIS AT THE DESIGN OF THE STEAM STERILIZER

From the point of view of risk, the steam sterilizers have, mainly:

- The related risks as a 'machine'
- The related risks as a 'pressure equipment'
- The related risks as an equipment that generates 'sterile product'

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All these risks shall be considered, evaluated and, if necessary, mitigated at soon as possible, including the initial steps of design phases.

Regarding 'machinery' and 'pressure equipment', a wide support from guides and standards about risk and risk management are available. A good initial point is the ISO 12100 'Safety of machinery — General principles for design — Risk assessment and risk reduction'. This standard will take us to others guides and standards that will show us the basic aspects of safety in the design phases.

Similarly, the pressure equipment standards applied (ASME, EN 13445 or others) will give us the same support.

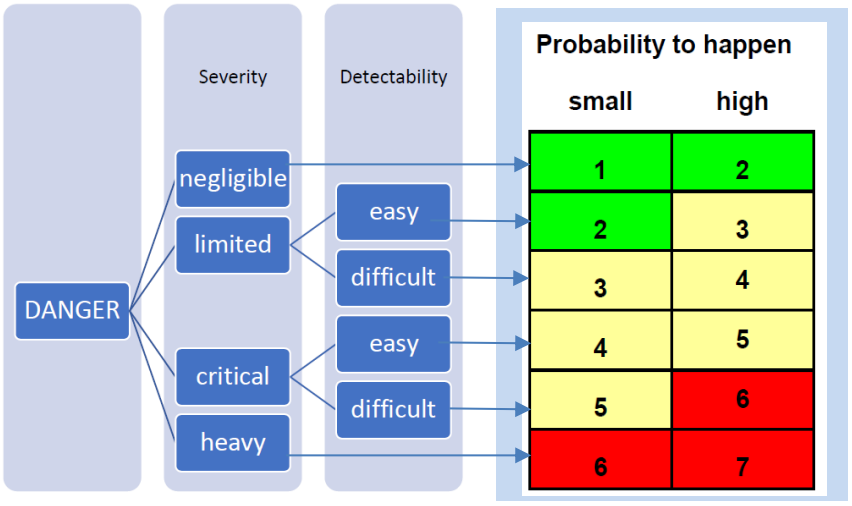
But to warranty that the sterility of the product implies a series of external conditions that cannot always be controlled by design:

- The packaging of the product
- The correct choice of the sterilization parameters
- The correct manipulation of the sterilizer
- And a whole set of conditions related to the sterile production environment.

All these risks must be managed; not only in the sterilizer installation and commissioning, but also in all the lifespan of the equipment.

THE STERILIZER LIFE CYCLE: THE RISK ASSESSMENT IS ALWAYS PRESENT

Let's give an example with this easy risk matrix, that gives a value for each risk assessed:



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Where we consider:

RISK	Evaluation of the safety features, that needs to be applied	Residual risk after safety actions
1	Negligible small risk	The residual risk is acceptable
2	Reduced application without additional safety features possible. Indication of safety features in equipment documentation.	
3-5	Additional safety features (at least indirect safety features, in case may be with indicative safety features supplemented) have to be intended	The residual risk needs to be compared / balanced with the benefit for the process / product. The higher the risk, the higher the benefits need to be.
6-7	Direct risk reduction measures have to be applied; the hazard has to be removed. If this is not possible, because of State of the art or because of the function, the risk needs to be controlled with sufficient effective and validated safety features.	

LOW RISK MEDIUM RISK HIGH RISK

After defining the matrix, we need to create and evaluate the risks list. Just a few lines as an easy hypothetical model:

Phase	Danger	Cause	Sev.	Det.	Prob..	Risk level	Preventive measures
IQ	Failure of vacuum system, the sterilizer cannot work	Not enough cooling water or water too hot	Critical	Easy	High	5	Check and follow installation specification
OQ	Temperature distribution out of specifications	Bad adjustment of instrumentation and/or control software	Critical	Easy	Small	4	Recalibrate instrumentation Validate software Check periodically
PQ	Not sterile product	Bad preparation of the load, the steam cannot heat up uniformly	Heavy	-	Small	6	Validation of process application at the product. SOP shall be documented and used Trained people

It is necessary to repeat this task (risks review) regularly, in order to detect if a new risk has been generated or changed, and, of course, whenever a significant change is made to the sterilizer, the sterilization process or the product.

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CONCLUSIONS

Risk assessment and risk management is a never-end task. But with the correct tools and the correct tracing of changes, risks can be eliminated or at least reduced to an acceptable level.

This will result in better working conditions for all the system and, of course, in the best guarantee of correct elaboration for our products.

Main references:

- ***ISO 14971:2019. Medical devices — Application of risk management to medical devices***
- ***ISO 31000:2018. Risk management — Guidelines***
- ***ISO 12100:2010 'Safety of machinery — General principles for design — Risk assessment and risk reduction.***
- ***ICH Q9 Quality risk management,*** *2006*
- ***Risk-based software validation*** *– Ten easy steps. David Nettleton & Janet Gough. PDA-DHI, 2006*
- ***Risk assessment and risk management in the pharmaceutical industry****. James L. Vesper. PDA-DHI, 2006*