Practical issues on PFS sterilization: an analysis of critical aspects

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COMPANY: Fedegari Group

Prefilled syringes offer several advantages over traditional packaging in vials.

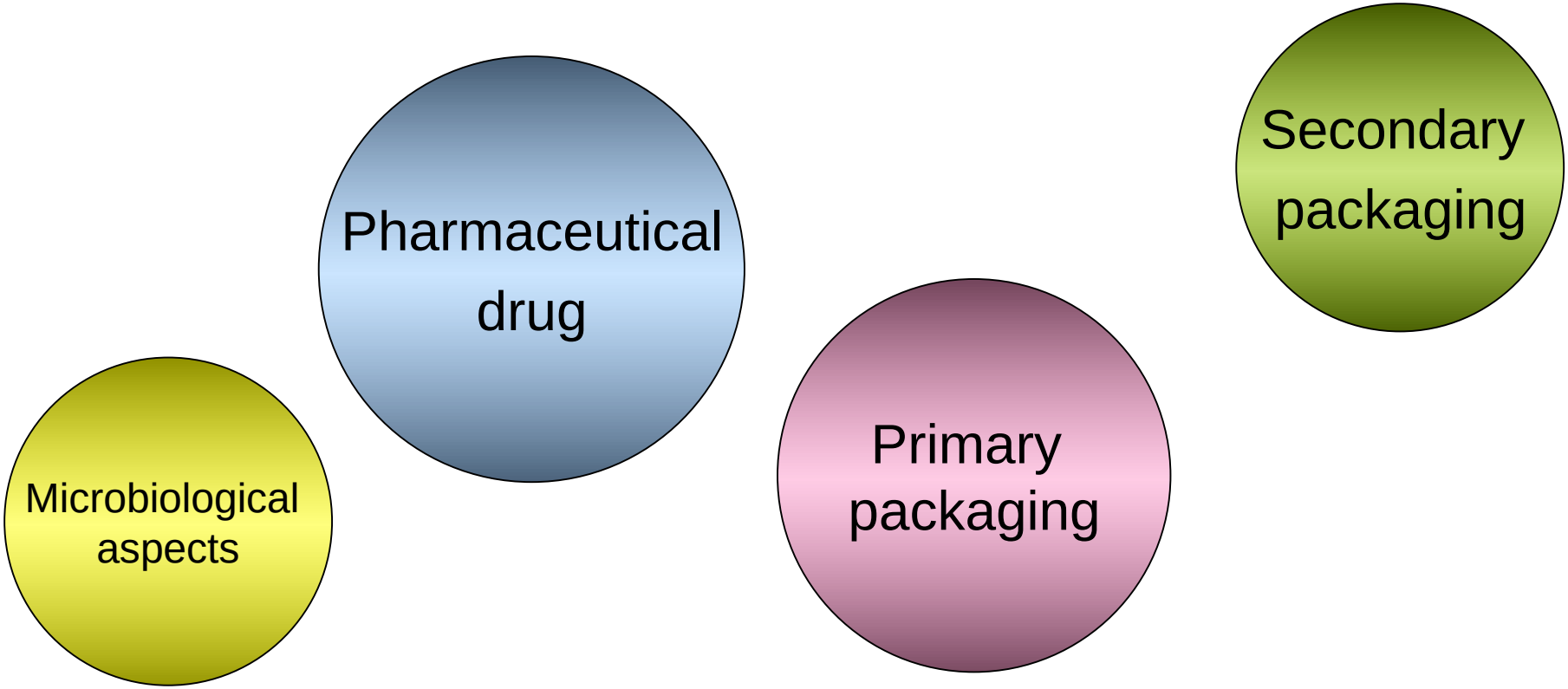
For example, microbial contamination is minimized due to less manipulation.

A method for sterilizing PFSs is performing

a moist heat process.

Steam sterilization of parenteral drugs is the most common and approved method used by pharmaceutical facilities for this type of products.

The main issues to consider while sterilizing PFSs with a moist heat process are:



What happens when a sealed container with aqueous solution is heated?

Inside every sealed container, **the internal pressure increases** during the heating phases of the sterilizing process.

1 - Water evaporates in the head space

Vapor pressure of the liquid, because of a one-to-one correspondence, depends on temperature and is indipendent from the quantity of product.

2 - Dissolved gases leave the solution

They will partially contribute to pressure rise in the head space.

3 - Gases (air) initially present in the head space increase their pressure

Their pressure will rise proportionally to the absolute increasing temperature.

4 -The liquid phase increases its volume.

5 - The container walls expand (in a different way if comparing glass and plastic) and increase the volume of the container.

The **syringe plunger moves** balancing the internal and external pressure.

If the internal pressure increase is too high:

the plunger moves from its original position.

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Liquids expand with temperature increase

Thermal expansion of water becomes important if the head space is (as usually happens) lower than 10-15% of the volume of the container.

The head space volume tends to be reduced due to the expansion of the liquid volume while the pressure consequently increases.

We can't stop liquid thermal expansion

The thermal expansion of an aqueous solution, between ambient temperature and 121°C, is about **6%** of its initial volume: in fact, in the transition, the specific volume of pure water becomes 1.00 l/kg, instead of 1.06 l/kg.

There are no means to prevent thermal liquid expansion: the counterpressure required to contrast it should be about **one thousand bars**.

The expansion of the glass (material commonly used for the carpules) doesn't compensate the liquid one.

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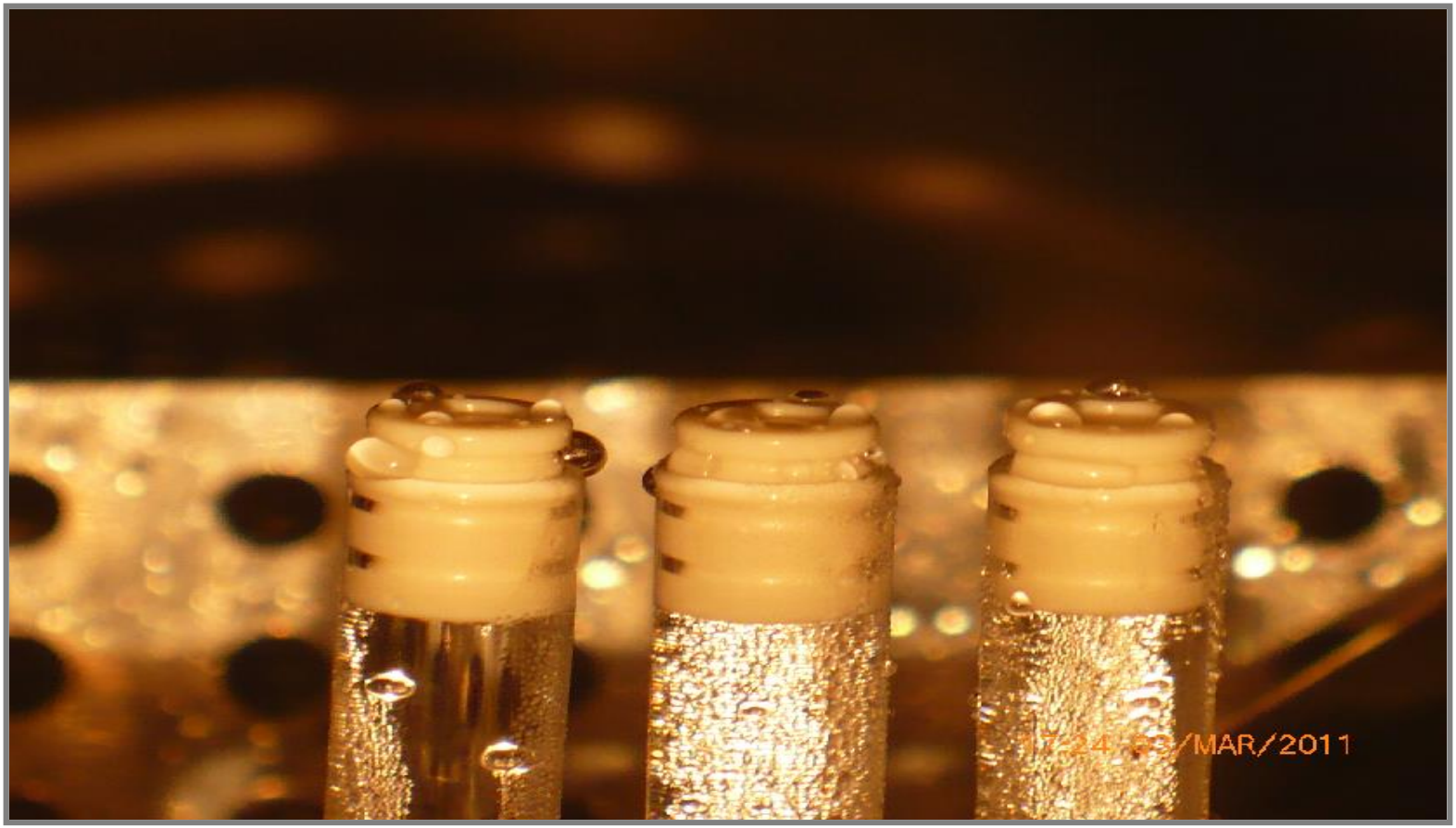

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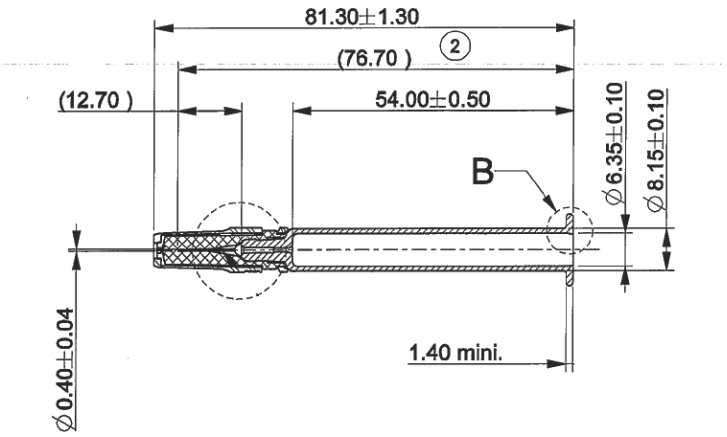
PDA Parenteral Drug Association

When projecting a syringe, it is crucial to focus on the following challenging issues:



How to treat PFSs?

With a counterpressure sterilization cycle

```
PHASE LISTS
n.   phase
 1 PREPARE AUTOCLAVE FOA
 2 HEATING WITH P=P(T)
 3 STERILIZATION WITH P=P(T)
 4 PRESSURIZE CHAMBER BY AIR
 5 CONTROLLED RATE COOLING
 6 COOLING EXTENSION
 7 WATER DRAIN
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Another challenge:
Syringes in Tyvek™ /plastic containers

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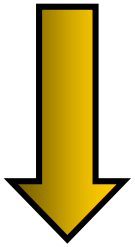
Variable Volume Container + Porous Load



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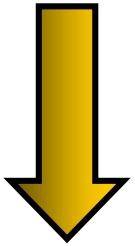


SECONDARY PACKAGING

The resulting cycle will be a summary of two different standard cycles

- Initial vacuum-steam pulses

- Sterilization and cooling in counterpressure with an air-over-steam sterilization.

Customer Requirement: Dry load

A pre-heating phase will be effective for minimizing condense creation.

Load drying will be performed injecting hot air into the chamber.

The air “steals” humidity from the load; water vehicled by air impacts on plates surface and condense.

The system performs load driying and cooling.

The product

Having a **heat-sensitive** product is frequent.
The risk, during a thermal process, is changing its chemical features.

Its molecule might break, affecting therapeutic efficiency or creating toxic compounds.

Related effects:
- Viscosity is reduced
- Colour changes

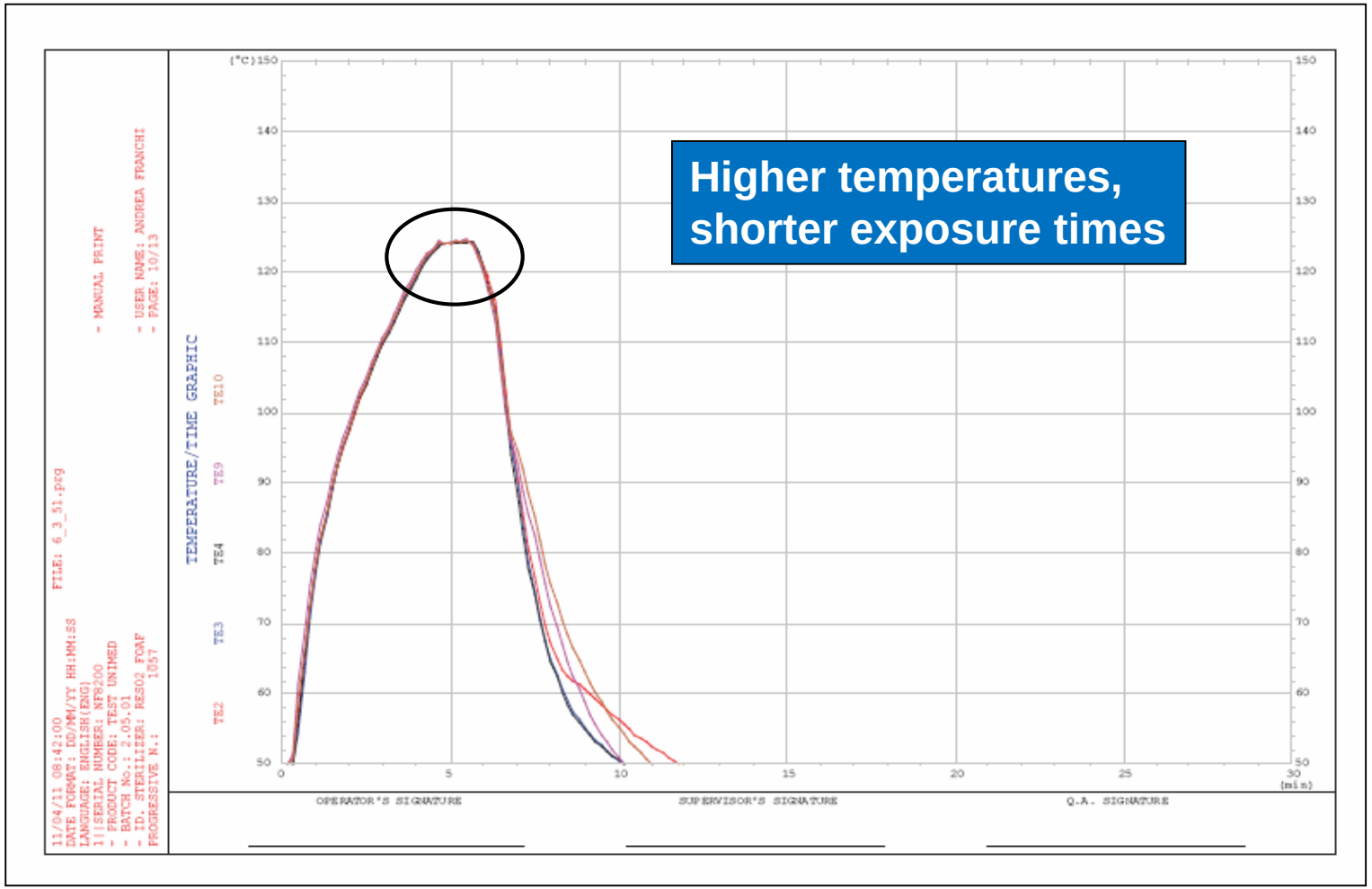
The product

For treating it, usually, we adopt a standard strategy for heat sensitive loads.

- Rapid heating/cooling of the load
- We increase sterilization temperature and decrease the holding time

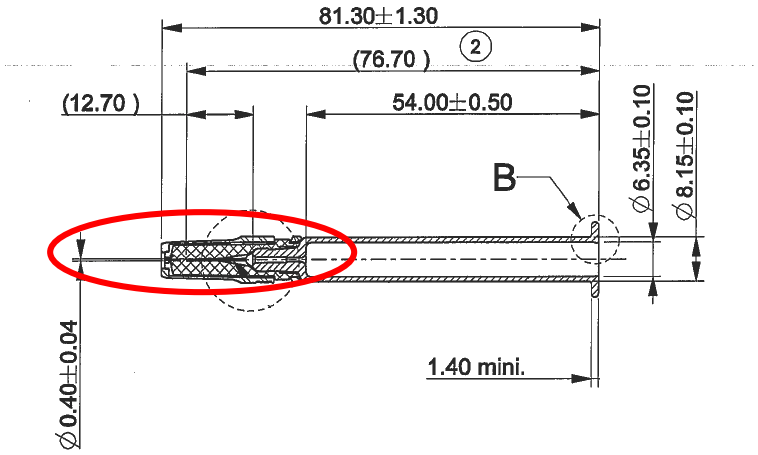
Our customer has to reduce the microbial charge of the product: the lower is the microbial charge the lower is thermal dose for obtaining the desired SAL.

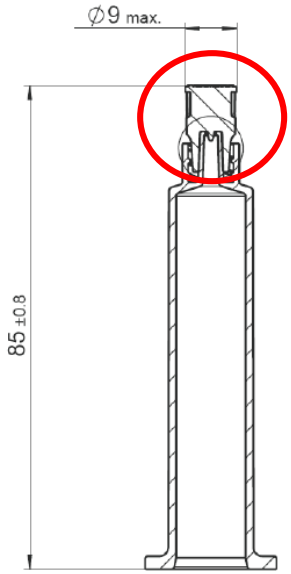
Cycle for heat sensitive materials



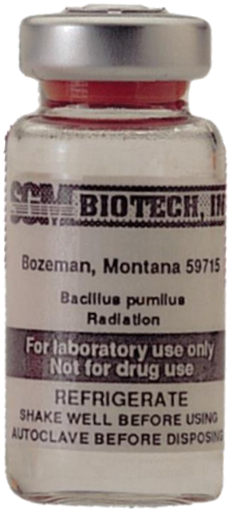
Microbiological challenges

From a microbiological standpoint, the most critical parts are the plunger, the stopper or the needle, if present.





The piece of advice is the inoculation
G. Stearothermophilus spores;
they are highly resistant to the steam process.



"Direct inoculation"

Microbiological issue: the needle

We inoculated the internal and the external parts of the needle

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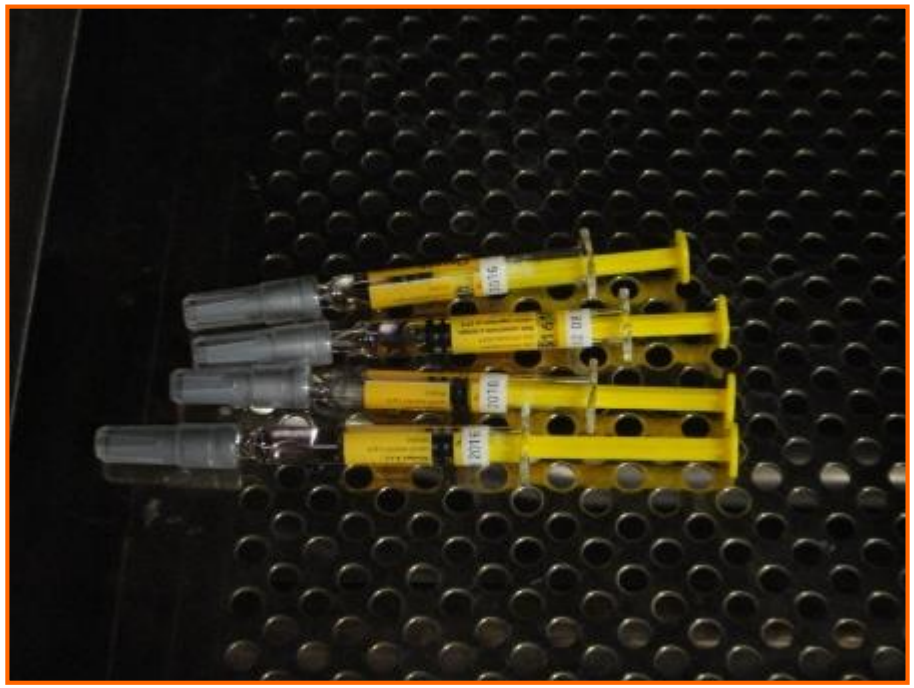

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Method for performing tests of sterility according to 11737-2

6 Methods for performing tests of sterility

6.1 There are two general methods for performing tests of sterility. These are:

a) direct immersion of product in growth medium or addition of growth medium in product, followed by incubation;

b) removal of microorganisms from product and transfer of removed microorganisms to growth medium followed by incubation.

CONCLUSION

A well made equipment,

a well developed sterilizing process,

a well made validation,

are important criteria for satisfying customer's needs and providing the final user with a "safe product".

Thank you.

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