STEAM STERILISATION: A NEW OPTION FOR OMPI EZ-FILL VIALS & CARTRIDGES

Pharmaceutical primary packaging for parenteral drugs is increasingly commonly provided in pre-sterilised nest and tub configuration. Nowadays, sterilisation – one of the most critical parts in the production of ready-to-fill glass containers – is applied by their manufacturers mainly through ethylene oxide (EtO). This method has served the market well for many years, but as drugs and delivery devices have advanced, some limitations have become apparent. The rapid rise in biological drug development is expanding the market for new sterilisation technologies that can overcome the limitations of current method and facilitate innovation and progress in the pharmaceutical and biotechnology industries. In this article, Andrea Zambon, Product Manager, EZ-fill Vials & Cartridges at Ompi Pharmaceutical Systems, explains how, in compliance with the European and United States Pharmacopoeias, the company is therefore now offering a totally new option for ready-to-fill glass containers: steam sterilisation for vials and cartridges.

Sterilisation of pharmaceutical primary packaging for parenteral drugs has always been a sensitive topic for pharmaceutical companies. Since the introduction of the first ready-to-fill containers (syringes) in the market during the 1970s, national regulatory bodies have always had a special consideration for this specific phase of the process, in order to guarantee the safety and the health of patients.

The sterilisation method used during the process depends primarily on the nature of containers, closures and packaging material.

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Ethylene oxide (EtO) sterilisation is largely used in the market by ready-to-fill glass containers producers and it became a standard for most of their sterilisation processes.

EtO is basically a gas that operates through alkylation of sulphydryl, amino, carboxylic, phenolic, hydroxyl, phenolic group of structural proteins and enzymes. Its typical treatment conditions are generally characterised by:

- gas concentration between 200 and 1000 mg/L
- temperature 30°C for cold cycle and 60°C for warm cycle
- time between 1.5 and 12 hours
- variable pressure depending on the EtO presence (usually it could be blended with other substances such as nitrogen or carbon dioxide).

Sterilisation method for pharmaceutical primary containers is a highly regulated topic. Even though EtO sterilisation is largely validated and used in the market, according to US/EU Pharmacopeia and GMP guidelines it should only be used when no other method is practicable. This is in order to ensure that any residue of gas or its degradation products in the sterilised product is below the concentration that could give rise to toxic effects during the use of the product. To avoid any doubt about it, during process validation it is always required to show that there is no damaging effect on the product. For example, the parameters and limits of the EtO

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sterilisation cycle (e.g. temperature, pressure, humidity, gas concentration, exposure time, degassing, aeration time and determination of residuals) should be specified and monitored closely. At the same time, the need to monitor the EtO sterilisation process rigidly makes this option more comprehensive than others.

For all these particular reasons, selecting the appropriate process for a given dosage form or component requires a strong knowledge of sterilisation techniques and information concerning any effects on the material that will be sterilised.

EtO sterilisation is frequently selected when the material to be sterilised cannot withstand the high temperatures obtained during steam sterilisation.[1-7]

Besides all the important regulatory aspects, the need for an alternative sterilisation method in addition to EtO is all the more necessary if we look at the rapid rise in biological drug development, where a lot of unstable molecules that can react with the primary containers are under development.

Most of the new drug products being developed today are biologics, such as therapeutic proteins. The percentage sales from biotechnology products (bioengineered vaccines & biologics), within the world's top 100, is set to increase to 46% in 2020, whereas in 2006 it was 21%.[8] Having a new way of approaching drug/container interaction especially for biotech drugs is now a "must have" and not a "nice to have".

Candidates include injectable solutions, peptides and vaccines. Residual agents such as EtO in fact can yield adduct formation for low-dose protein therapeutics. Due to its structure, EtO is counted among the very reactive compounds. The reactivity includes with organic structures within cells and cell nuclei (DNA, RNA and proteins).[9] Formulation development teams in fact should be considering evaluating possible effects of product exposure to trace quantities of EtO.[10]

In order to answer this new and complex scenario, Ompi Pharmaceutical Systems started to develop its specific solution based on steam sterilisation. This process led Ompi, back in 2012, to add first steam sterilised barrels and then pre-capped steam-sterilised cartridges into the portfolio. Nowadays, as part of that continuous desire to enlarge the product offering, the portfolio is about to list brand new Ompi EZ-fill Vials sterilised through steam sterilisation (Figure 1).

Before going into the detail of the Ompi EZ-fill steam sterilisation solution it is useful to provide an overview of the entire

Figure 1: Ompi EZ-fill Vials in nest & tub.

Ompi EZ-fill Vials & Cartridges process. It is described as follows:

- **incoming materials:** all the raw materials for Ompi EZ-fill Vials & Cartridges undergo incoming inspections that are necessary to declare them suitable for ISO7 / ISO5 production. Vials and cartridges are supplied to the Ompi EZ-fill area (ISO8)
- **washing:** vials and cartridges are washed into the validated washing machine by WFI (Water For Injection)
- **siliconisation:** cartridges can be optionally siliconised (baked silicone)
- **heating:** drying and depyrogenation is performed through an oven. Cycle is optimised for each format in order to reduce the exposure time and assure optimal drying
- **capping:** cartridges can optionally (upon customers' requests) be pre-capped with selected rubber formulations
- **packaging:** vials and cartridges enter the ISO7 and ISO5 area and are placed into two main packaging configurations:

1) **Tray:** box made out of a single injection mould preventing glass-to-glass contact between containers during transportation and storage

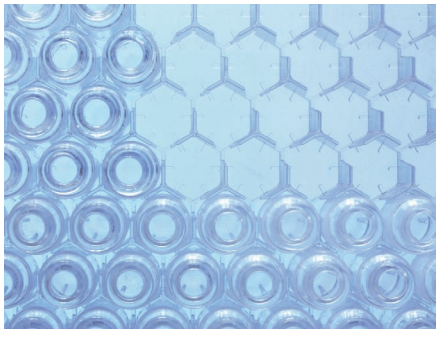

Figure 2: No glass-to-glass contact in Ompi EZ-fill tray packaging.

2) **Nest & Tub:** standard nest & tub configuration as the PFS solution one, preventing glass-to-glass contact (Figure 2).

Both configurations are sealed by a Tyvek® lid and packaged in single or double steribags. Final pallet configuration takes place according to the procedure determined by the specific sterilisation media desired. Key attention is given to the cleanliness of the packaging components as to the production of the glass container itself

- **final sterilisation:** according to desired sterilisation media.

Generally speaking, with steam sterilisation, saturated water vapour is blown inside a dedicated autoclave. This is properly equipped with an external jacket aimed to stabilise the conditions of temperature and pressure inside it across the entire sterilisation cycle.

Steam sterilisation at Ompi Pharmaceutical Systems today is actually performed by a highly specific and well-designed cycle that is the result of a long study on all its critical parameters and their interconnections. The main critical parameters are:

- Temperature
- Pressure
- Time
- Packaging materials & their configuration.

What is interesting, and what Ompi is particularly proud of, is that all these parameters are not simply held constant throughout the entire cycle but they are made to vary in highly specific way in order to get the best result in terms of the quality of the sterilised final product.

Another key point of the whole Ompi steam sterilisation project is that glass pharmaceutical containers intended for steam sterilisation are treated using the same process, honed over 40 years, as the ones

Figure 3: The autoclave used in steam sterilisation is equipped with an external jacket aimed to stabilise the conditions of temperature and pressure inside it across the entire sterilisation cycle. Saturated water vapour is blown inside.

intended for EtO sterilisation. Moreover, this also means that Ompi developed its steam-sterilised solution without changing final packaging configuration from the EtO-sterilised configuration.

In fact, as mentioned above, during the Ompi EZ-fill process, glass pharmaceutical containers are washed, depyrogenised, packed inside Nest & Tub or Tray configuration, bagged in single or double steribags and finally packed in regular Ompi EZ-fill boxes, either in case of EtO sterilisation or in case of Steam sterilisation (see Figure 4).

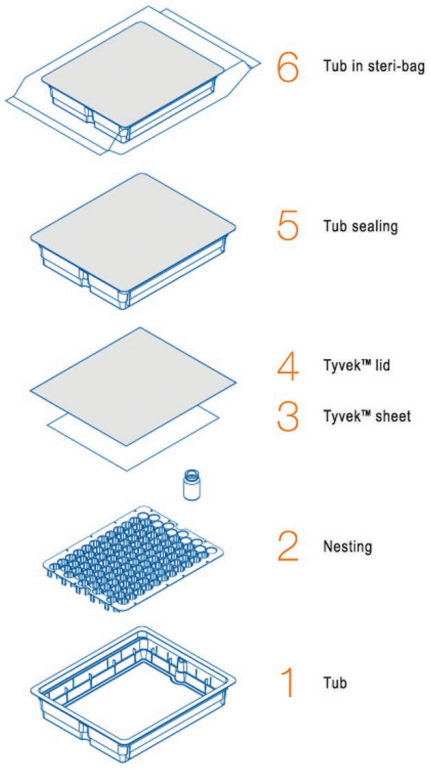

Figure 4: Ompi EZ-fill Vials in nest & tub: configuration explosion.

EtO sterilisation has always been performed outside Ompi facilities by qualified sterilisers. In contrast, steam sterilisation is run internally by means of a dedicated proprietary Ompi autoclave. This said, steam sterilisation is not performed on a full pallet but on bagged nest & tub or tray units. Pallets addressed to customers are then built up after the sterilisation phase.

Ompi meticulously designs packaging configuration and composition together with its specialised suppliers. This is an important phase of the process because these elements have to allow water vapour to reach the inside surfaces of glass containers and sterilise them. In the same time, they are a critical barrier that guarantees sterility across transportation of the final product and storage at the customer.

CONCLUSIONS

Even if EtO is the most commonly adopted sterilisation method in the market by ready-to-fill container producers, an alternative to this type of sterilisation is demanded both by regulation authorities, and drug development trends point only to this demand increasingly strongly. Following these requirements, Ompi developed its own steam sterilisation for cartridges, now extended to vials (Ompi EZ-fill Vials) in order to be even closer to authorities and customers' needs, giving an important alternative for this crucial phase in the production of ready-to-fill glass containers without changing the final packaging configuration.

Beginning October 2015, Ompi is introducing the first validated formats of Ompi EZ-fill Vials with steam sterilisation (from 2R to 8R) that are going to be added to the pre-capped cartridges already offered on the market with this kind of sterilisation. Its aim is to widen its steam-sterilised portfolio in the coming months.

REFERENCES:

1. *European Pharmacopoeia 8.0, Monograph 5.1.1, "Methods of preparation of sterile products". EMEA/CVMP/271/01: "Note for guidance on limitations to the used of ethylene oxide in the manufacture of medicinal products". March 2001.*
2. *European GMP Guide, EudraLex, Vol 4, Annex 1, "Manufacture of sterile medicinal products". November 2008.*
3. *CPMP/QWP/486/95, "Note for guidance on manufacture of the finished dosage form. April 1996.*
4. *CPMP/QWP/054/98, "Decision trees for the selection of sterilisation methods". 2000.*
5. *PIC/S* (Pharmaceutical inspection convention / cooperation scheme), "Guide to good manufacturing practice for medicinal products, Annex 1". March 2014.*
6. *US Pharmacopeia <1211>, "Sterilisation and sterility assurance of compendial articles".*
7. *FDA Guidance for Industry, "Sterile drug products produced by aseptic processing- current good manufacturing practices". September 2004.*
8. *Evaluate Ltd, "EvaluatePharma – World Preview 2015, Outlook to 2020". 2015.*
9. *European Agency for the Evaluation of Medicinal Products, London, 29 March 2001.*
10. *Jameel F, Hersenson S, "Formulation & Process Development Strategies for Manufacturing Biopharmaceuticals". Wiley, 2010.*

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- Washing
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- Nesting, Tub Insertion & Tyvek Sealing
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Vials

Nest & Tub

Tray

Cartridges

Nest & Tub

Syringes

Nest & Tub