# Prefilled ophthalmic syringes

## New possibilities in terminal sterilization

$NO_2$ as new alternative sterilization method to EtO gas supported by new packaging and device designs


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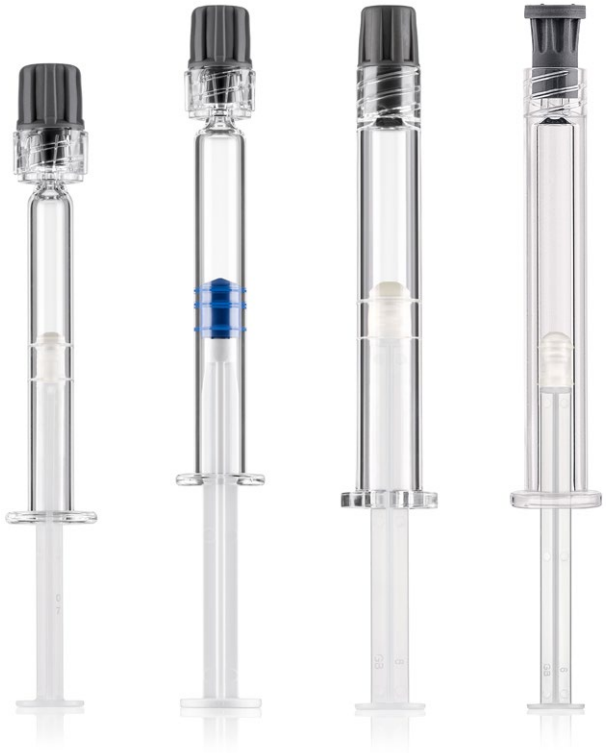


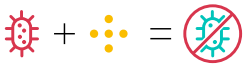
## Background

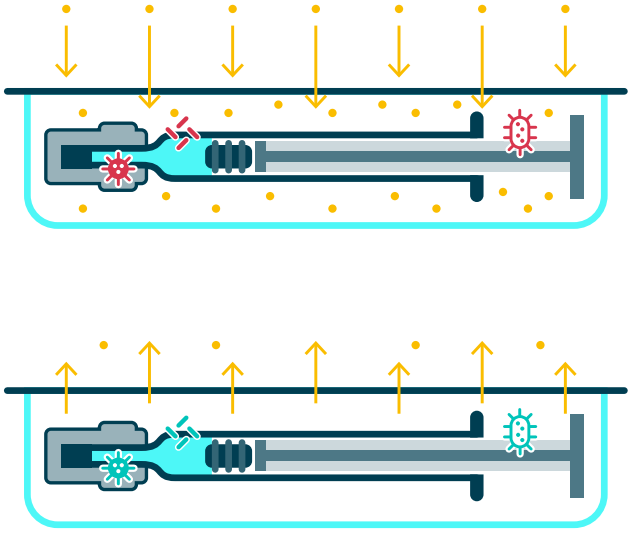
- Ophthalmic prefilled syringes are mainly used for intravitreal injection and require full surface sterilization to prevent serious eye infections
- Elastomer caps of prefillable syringes are gas permeable to achieve full sterilization of the complete surface in 1st sterilization (empty container) between rubber and barrel
- Today sterilization of the surface of the prefilled and blistered syringe is carried out mainly by EtO gas
- Prefilled ophthalmic syringes need to be gas tight to have minimal migration of gas into the container
- This study is carried out to assess the suitability of $NO_2$ sterilization modality with different syringe configurations
- It also aims to identify the best syringe configuration for either sterilization method

blister-packed prefilled syringe

# The principle of surface sterilization

- Gas will sterilize the prefilled syringe surface within the blister
- The Tyvek lid is highly gas permeable
- Gas will de-contaminate the surfaces and is removed after the treatment
- Microorganisms will be inactivated, SAL 10-6 (Sterility Assurance level)





# The principle of surface sterilization

Ingress into prefilled syringe during surface sterilization might be possible through

## Cap

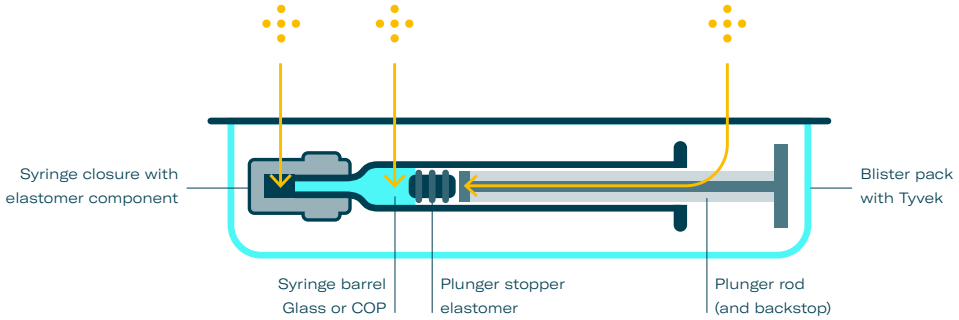
- gas permeability needed for sterilization in 1st cycle (RTF, empty syringe)
- gas tightness required for terminal sterilization

## Syringe barrel

- potentially permeable in case of COP (Cyclic Olefin Polymer)
- glass fully gas tight

## Plunger stopper

- material to be gas tight for terminal gas sterilization and to maintain stability over shelf life
- leakage safe stoppering in Fill & Finish process mandatory



# Questions to be answered

1. Do EtO and $NO_2$ sterilization cycles differ in gas ingress into the different prefilled syringe designs?

2. Is $NO_2$ sterilization suited for surface sterilization of ophthalmic prefilled syringes?

3. Which syringe setup (barrel material, elastomers, cap design, blister) is the best for terminal EtO and $NO_2$ sterilization?

4. Which sterile barrier packaging materials are suitable for both sterilization methods?

$NO_2$ sterilization chamber, Sterigenics

# Design of experiments

1. Base line syringe configuration: intravitreal 0.5 ml, filled with 0.165 µl WFI each

2. Different prefilled syringe combinations of
   – cap designs (TELC®, TWILC®)
   – plunger stoppers (4 different suppliers)
   – blister designs (open, closed)
   – barrel material (Gx® glass, ClearJect® COP)
   were analyzed for differences in gas ingress. The syringes were prepared in different ways to prohibit or allow sterilization gas flow into the filled syringe (sealed tip or sealed back)

3. Syringes for each configuration were either EtO-sterilized (middle range cycle (600 mg/L, 40 °C, shallow vacuum) or $NO_2$-sterilized (21 °C, shallow vacuum)

4. Residuals of EtO (EtO/ECH) and $NO_2$ ($NO_2^-$/$NO_3^-$) were analysed in the labs, samples needed to be pooled accordingly

# Residual limits of sterilization gas

## EtO

As there is an ISO regulatory limit to EtO residuals, the test results found were put into a pass/fail matrix

Note for Guidance on limitations to the use of ethylene oxide in the manufacturing of medicinal products, EMA London 2001

ISO 10993-7:2008 - Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals

## $NO_2$

For $NO_2^-$/$NO_3^-$ there are no values defined for pharma applications yet. Therefore the limits for drinking water, were applied

Guidelines for drinking-water quality - 4th ed. World Health Organization 2011

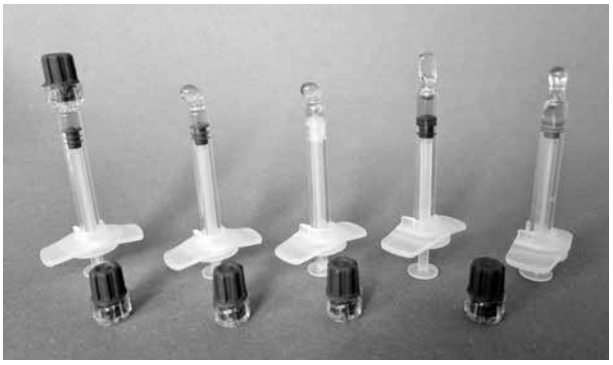
Directive (EU) 2020/2184 of the European Parliament and the Council on the quality of water intended for human consumption

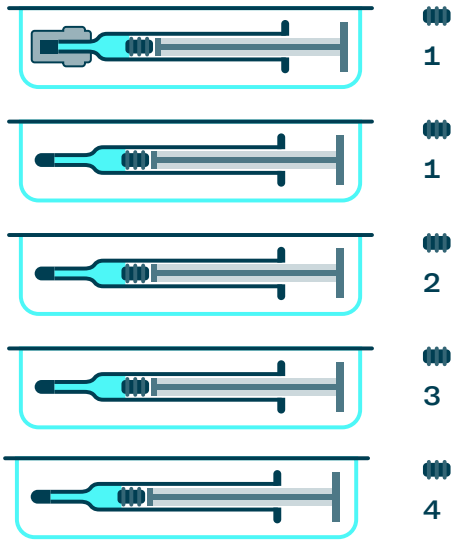
| | | |
|---|---|---|
| **Specification (finished product), allowed:**<br>**Ethylene oxide: 1 µg/g = 1 ppm**<br>**Ethylene chlorhydrine (or any ethylenehydrine): 50 µg/g**<br>**Limit of Quantification LOQ: EtO 0.3 ppm**<br>**values below cannot be detected** | **acceptable: 0.3-1 ppm** | + |
| | **acceptable <0.3 ppm/50 µg/g** | below detection limit |
| | **Not acceptable: >1 ppm** | – |
| **Specification (drinking water) allowed:**<br>**$NO_3^-$: 50 mg/L $NO_2^-$: 0.5 mg/L**<br>**Minimum detection limit MDL = 0.05 mg/L**<br>**values below cannot be detected** | **acceptable: 0.05-50 mg/L** | + |
| | **acceptable <50 mg/L/0.5 mg/L** | below detection limit |
| | **Not acceptable: >50 mg/L** | – |

# A. Comparison of plunger stoppers

**Is there a difference in gas ingress caused by different plunger stopper elastomers?**

- Glass syringes were sealed at the tip to exclude potential ingress through the cap
- Butyl rubbers (coated) are tight towards both EtO and $NO_2$
- Non gas tight novel plunger stoppers need to be scrutinized carefully for acceptable ingress rates
- $NO_2$ is a suitable way for terminal sterilization






| Sterilization | Plunger Stopper | Pass/fail EtO limit | Pass/fail ECH limit |
|---|---|---|---|
| EtO non sealed tip | 1 | – | b. d. l. |
| EtO sealed tip | 4 | – | b. d. l. |
| EtO sealed tip | 1 | + | b. d. l. |
| EtO sealed tip | 2 | + | b. d. l. |

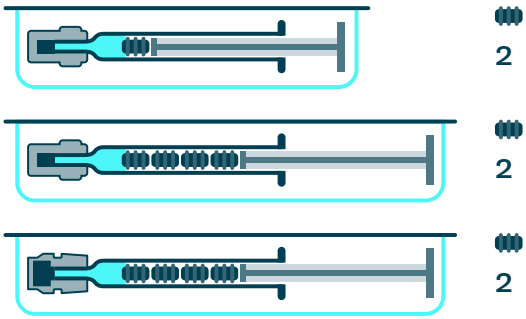
| Sterilization | Plunger Stopper | Pass/fail $NO_2^-$ limit | Pass/fail $NO_3^-$ limit |
|---|---|---|---|
| $NO_2$ non sealed tip | 2 | – | b. d. l. |
| $NO_2$ sealed tip | 3 | – | b. d. l. |
| $NO_2$ sealed tip | 4 | b. d. l. | b. d. l. |
| $NO_2$ sealed tip | 1 | b. d. l. | b. d. l. |
| $NO_2$ sealed tip | 2 | b. d. l. | b. d. l. |

b. d. l. = below detection limit

# B. Comparison of syringe cap designs

**Is there a difference in gas ingress caused by different cap designs?**

- Potential gas ingress through the plunger stoppers was excluded
- Ingress through the gas permeable caps was observed: the caps made from gas permeable rubber are not tight towards EtO or $NO_2$
- Two different cap designs show gradually different EtO and $NO_2$ ingress rates
- Gas permeable caps pose a risk, especially in EtO sterilization, as EtO residuals may migrate in the filled syringe through the cap




| Sterilization | Syringe | Plunger Stopper | Pass/fail EtO limit | Pass/fail ECH limit |
|---|---|---|---|---|
| EtO | Glass sealed end TELC cap | 2 | – | b. d. l. |
| EtO | Glass sealed end TWILC cap | 2 | b. d. l. | b. d. l. |

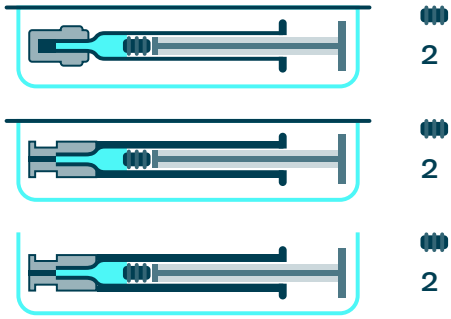
| Sterilization | Syringe | Plunger Stopper | Pass/fail $NO_2^-$ limit | Pass/fail $NO_3^-$ limit |
|---|---|---|---|---|
| $NO_2$ | Glass sealed end TELC cap | 2 | + | b. d. l. |
| $NO_2$ | Glass sealed end TWILC cap | 2 | + | b. d. l. |

b. d. l. = below detection limit

# C. Comparison COP vs. Glass syringe

**1. Is there a difference in gas ingress caused by different barrel materials?**
**2. Is there a difference in gas ingress into COP syringes due to trapping gas in blister?**

- No migration of gas through the COP barrel could be observed
- Gas impermeable cap in COP syringes is advantageous
- COP like glass is gas tight towards EtO and $NO_2$ in the tested sterilization cycles
- A closed blister did not show trapping effects of gas within the blister: closed blisters did not cause higher gas residuals in the liquid




| Sterilization | Blister | Syringe | Plunger Stopper | Pass/fail EtO limit | Pass/fail ECH limit |
|---|---|---|---|---|---|
| EtO | Design 1 | Glass TELC standard | 2 | – | b. d. l. |
| EtO | Design 1 | COP with TC | 2 | b. d. l. | b. d. l. |
| EtO | blister open | COP with TC | 2 | b. d. l. | b. d. l. |

| Sterilization | Blister | Syringe | Plunger Stopper | Pass/fail $NO_2^-$ limit | Pass/fail $NO_3^-$ limit |
|---|---|---|---|---|---|
| $NO_2$ | Design 1 | Glass TELC standard | 2 | + | b. d. l. |
| $NO_2$ | Design 1 | COP with TC | 2 | + | b. d. l. |
| $NO_2$ | blister open | COP with TC | 2 | + | b. d. l. |

b. d. l. = below detection limit

# Conclusion

- $NO_2$ sterilization is a viable alternative to EtO sterilization for ophthalmic prefilled syringes
- Gas may migrate through gas permeable elastomers used for prefilled syringe caps
- EtO and $NO_2$ and their residulas are hard to compare directly, as regulation is different and especially $NO_2$ as sterilizing agent is not strictly regulated for Pharma use
- Gas trapping in blisters did not occur – secondary packaging does not cause higher EtO or $NO_2$ values in the filled syringe
- The sterilization gas did not significantly influence the technical properties of the packaging materials or syringe. Colour change may occur
- Applying gentle sterilization cycles for EtO or $NO_2$ will help to reduce gas ingress into the syringe
- This study was carried out as a joint project by Gerresheimer, Sterigenics and Früh Verpackungstechnik, Raw data can be shared on demand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