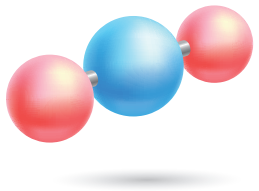
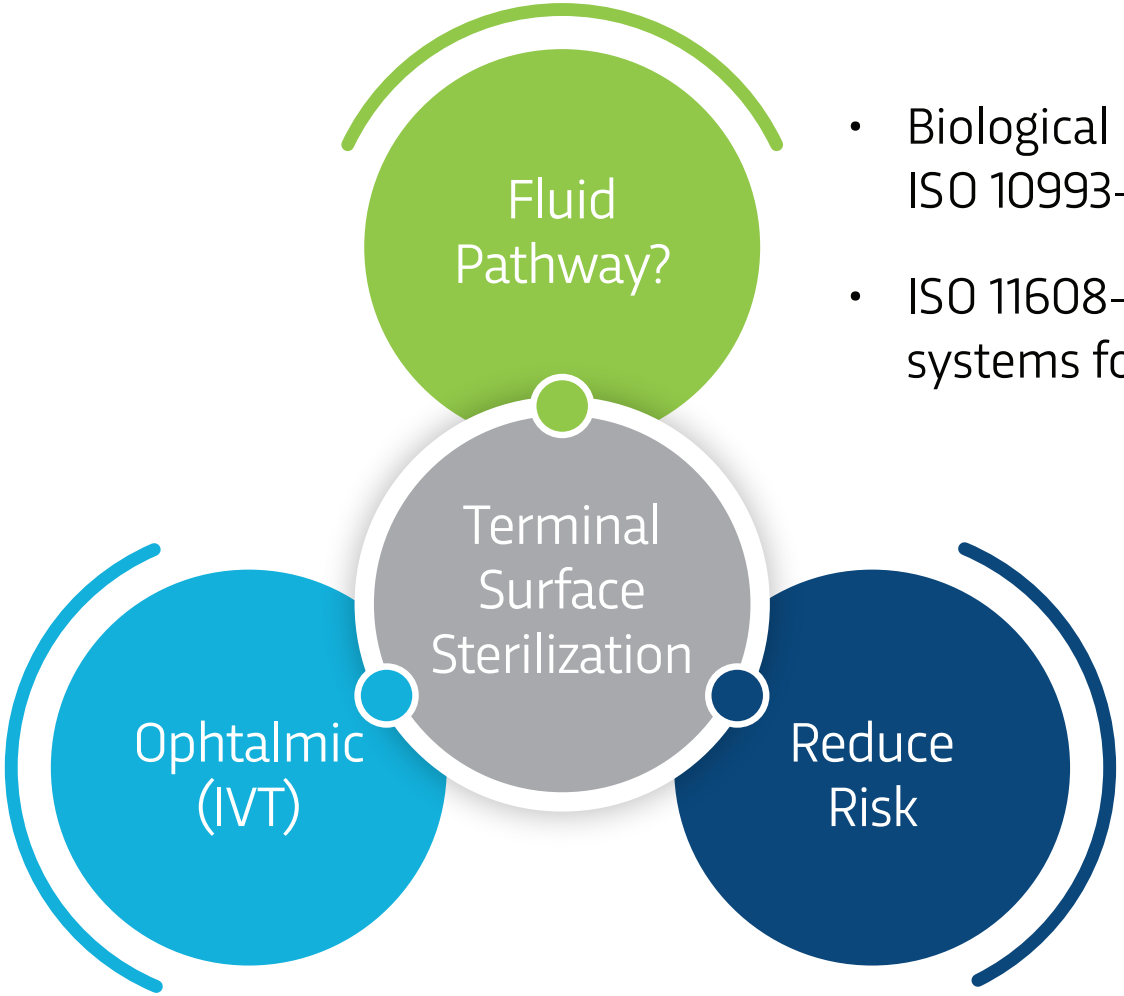
Sterigenics®
A Sotera Health company

Nitrogen Dioxide

State-of-the-art safe and efficient modality to eliminate contamination risks from your pre-filled devices and combination drug products



When is terminal surface sterilization required?

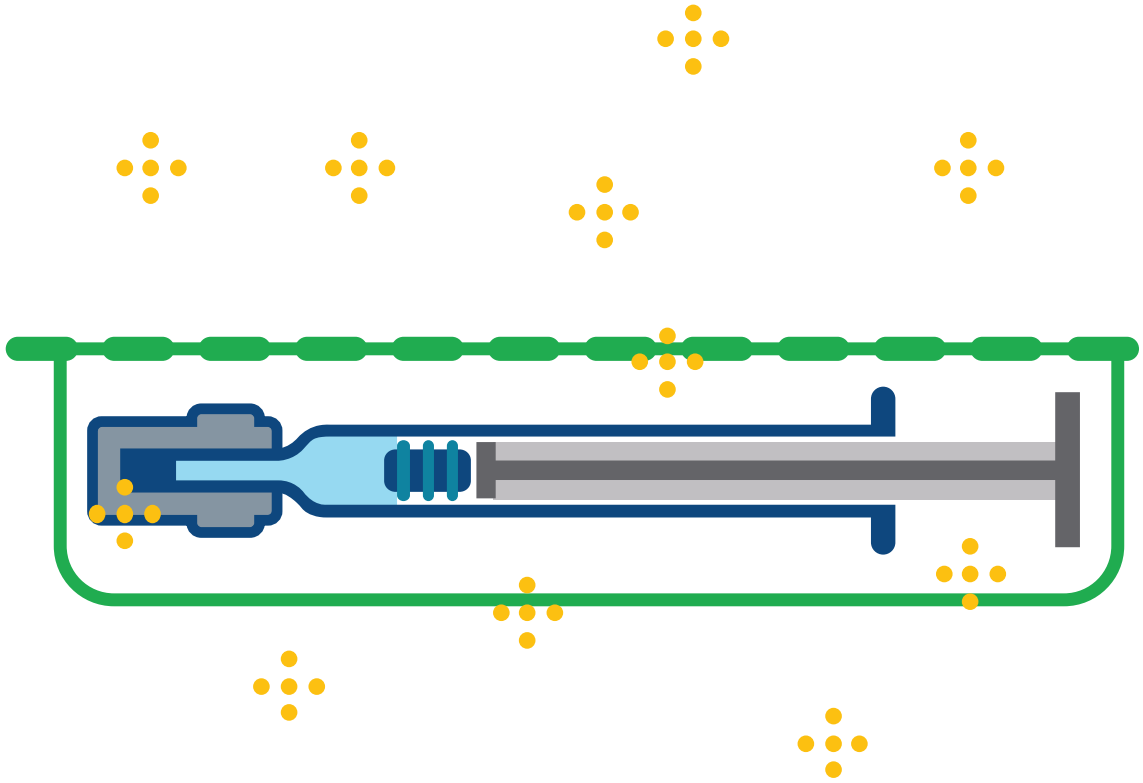


- Biological hazard assessment ISO 10993-1
- ISO 11608-3 needle-based injection systems for medical use

Sterigenics
A Sotera Health company

What is terminal surface sterilization?

This is the sterilization of the surface of the already aseptically filled device, for infection risk mitigation.



Sterigenics
A Sotera Health company

What is terminal surface sterilization?

Pre-filled devices present unique challenges for sterilization.

- Temperature-sensitive drugs products (biologics)
- Innovative plastic material with coating
- Limit piston movement
- Low impurities (ingress, stability)
- Sterility with a SAL $\leq 10^{-6}$
- Regulatory complexity (combination product – EU/US market)

NO_2 is a perfect technology to suit these challenges!

This requires specific process design:

Cold chain management

Adequate sterilization technology

Limit impact on the drug

Sterigenics
A Sotera Health company

Sterigenics is the unique service provider for industrial NO_2 sterilization

Sterigenics
A Sotera Health company

NO_2 sterilization as safe and efficient modality

- Works with most of standard primary packaging material (not cellulosic based)

- Aeration in the chamber

- Ambient temperature
- Preserve product shelf-life

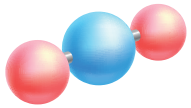
- Bacteria
- Fungi
- Virus

- Low concentration
- Non-explosive
- Non-carcinogenic
- Limited residuals with low hazard

- Protects inner surfaces from exposure to sterilant (PFS for example)

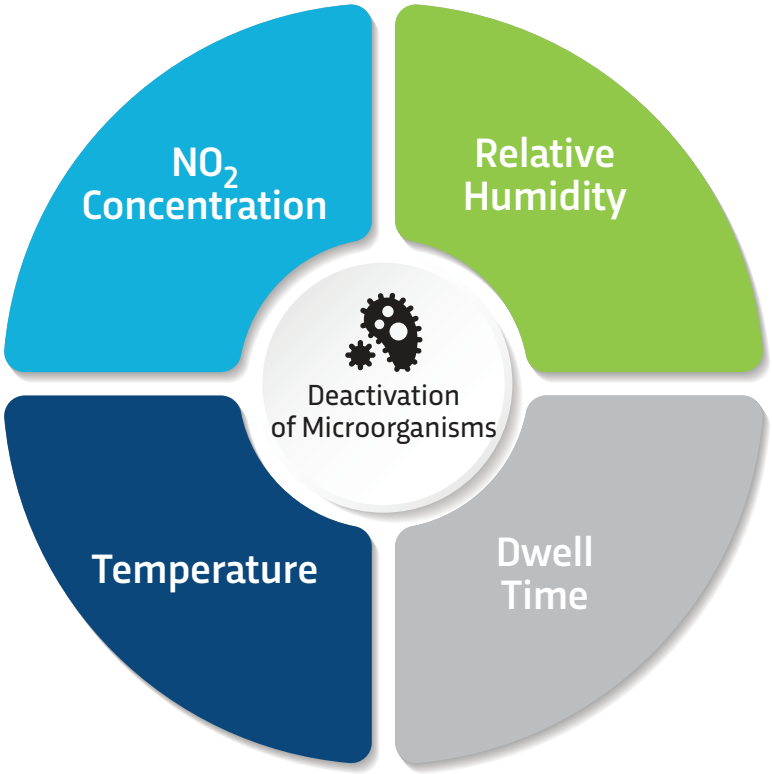
Sterigenics®
A Sotera Health company

NO_2 critical sterilization parameters



NO_2

Typically **10-20 mg/L** per pulse



Typically **60-80 RH%**

Typically performed **<25°C (77°F)**

Microbiological deactivation increasing exposure using multiple pulses (**Total cycle time = 10-16h**)

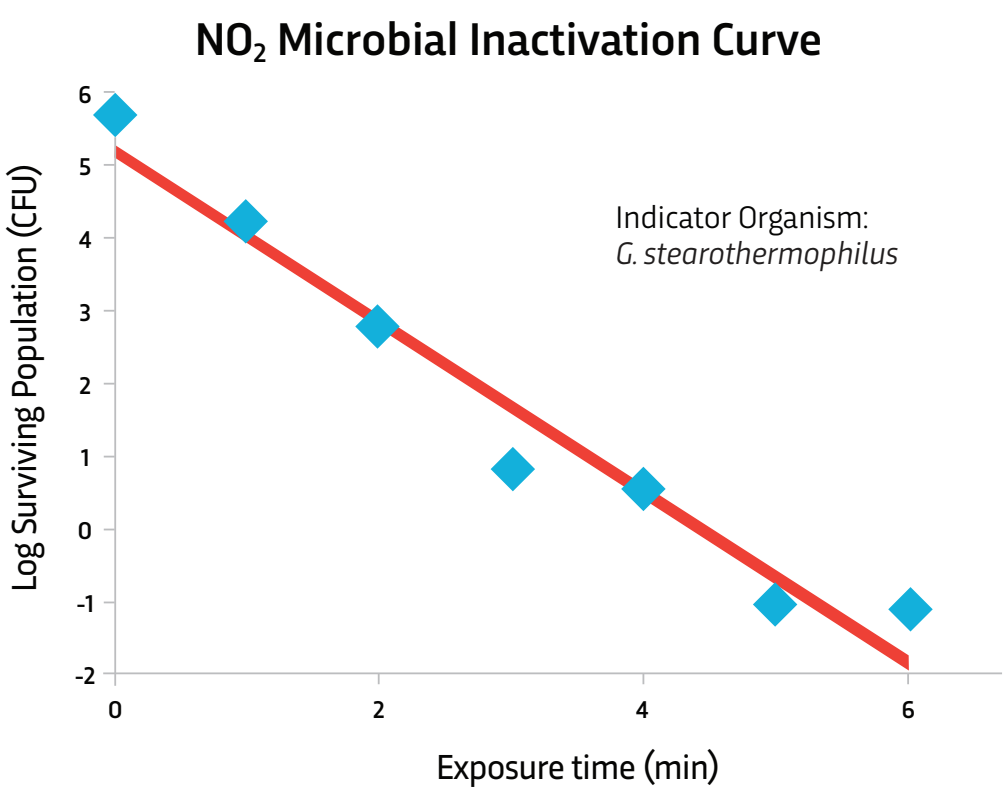
2-Step Process

PRE-TEMPERING (IF USED) → CHAMBER CYCLE

Sterigenics
A Sotera Health company

Demonstrated microbial inactivation

The linear kinetic inactivation allows standard validation approaches (overkill)



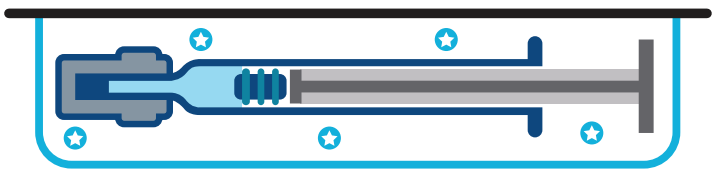
Standard : ISO 14937 - general requirement for sterilization

Source: Block's disinfection, sterilization and preservation, 6th edition, Wolters Kluwer, Gerald McDonnell, Joyce Hansen

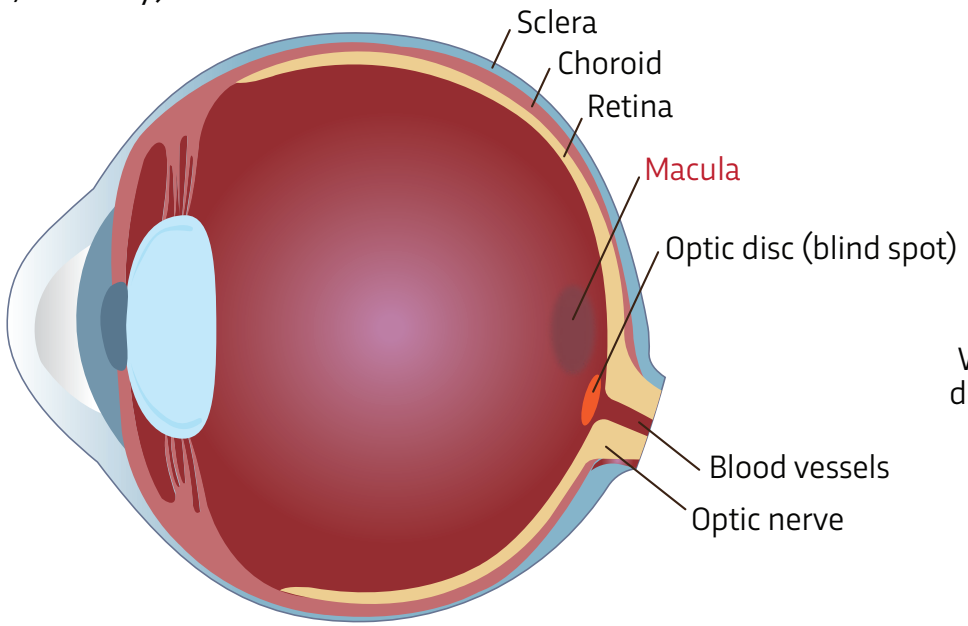
Sterigenics
A Sotera Health company

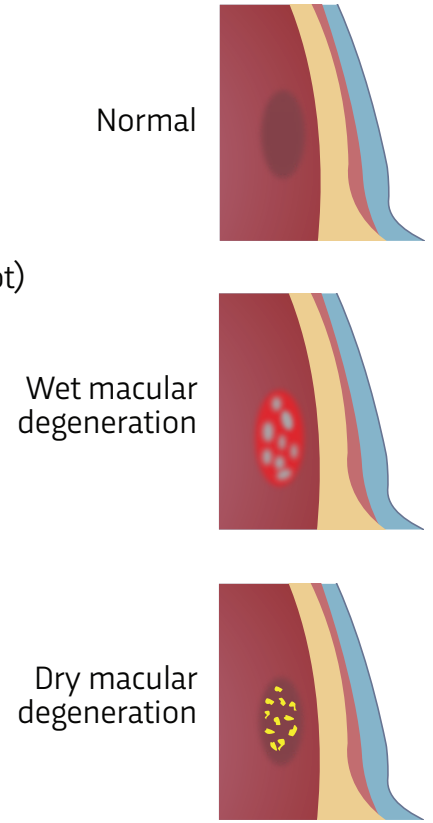
NO_2 case study: Ophtalmic pre-filled devices (IVT)

- Biosimilar - Biologic molecule, sensitive to temperature
- Light sensitive
- Low impurities (ingress, stability)
- Sterile with SAL $\leq 10^{-6}$
- Novel technology (FDA - EU markets)



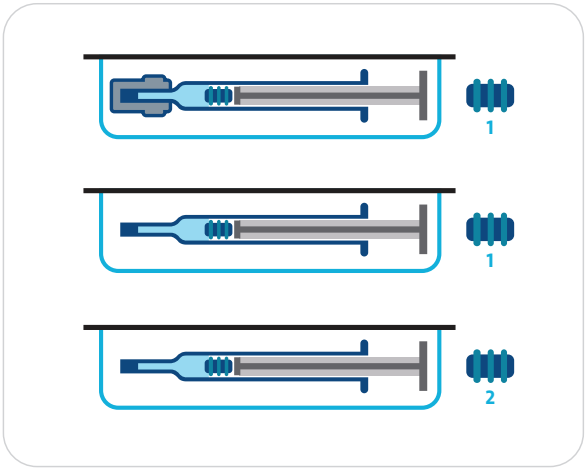
Macular degeneration

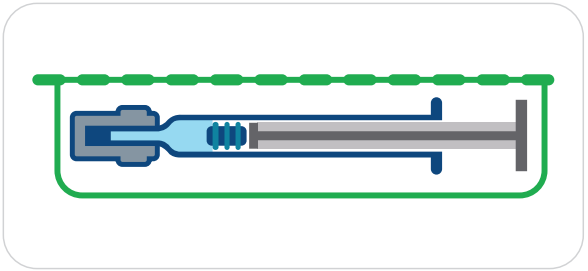


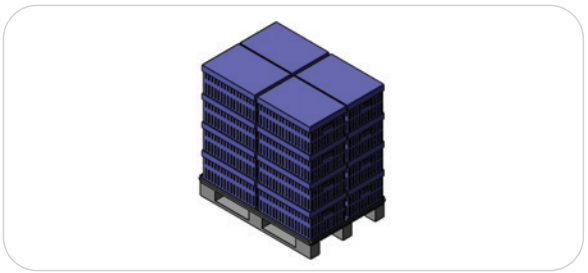


Sterigenics
A Sotera Health company

Case study: Validation study plan





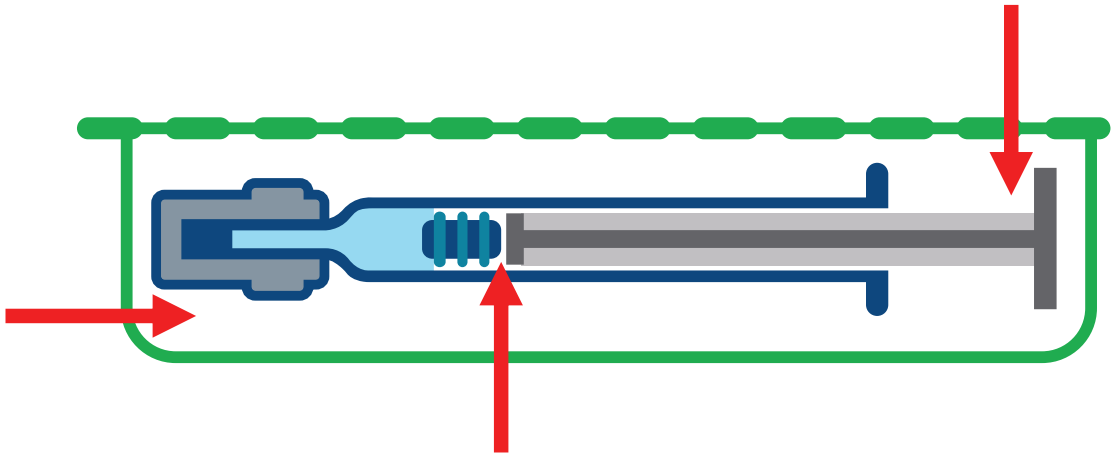


1. **Feasibility tests**
   Evaluate impact of sterilization on different product designs
2. **Product definition**
   Final product design
3. **Process definition**
   - Identify challenging sterilization positions
   - Establish process lethality curve
4. **Process qualification** (mPQ/pPQ)
5. **Product qualification** – Stability

Sterigenics®
A Sotera Health company

Case study: Validation study plan

Identify of the **most difficult to sterilize** position to create a valid Process Challenge Device (PCD)

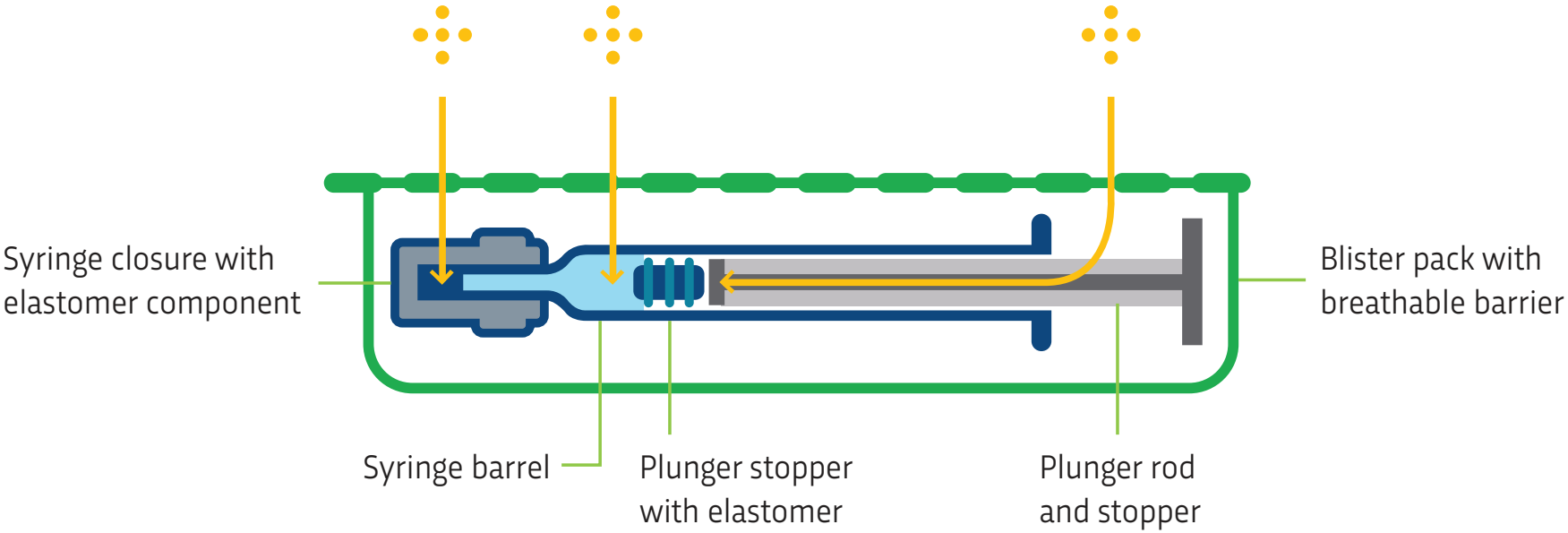


Sterility Result: SAL $\leq 10^{-8}$

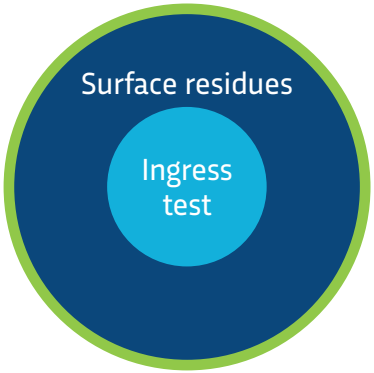
Sterigenics
A Sotera Health company

Case study: Gas residues

Gas ingress possible through the cap, syringe barrel and the plunger stopper



Sterigenics
A Sotera Health company



NO_2^-/NO_3^-

Nelson Labs
A Sotera Health company

- Ion chromatography testing
- Biocompatibility & residue testing performed by Nelson Laboratories

Residue inside the drug product

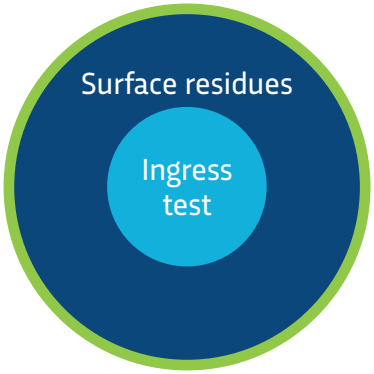
Sample	NO_3^- (mg/L)	NO_2^- (mg/L)
Average 3 cycles (3 samples/cycle)	[0.09]	<MDL
Evaluation*	PASS (≤0.33)	PASS (<MDL)

<MDL: Results below MDL (0.05 mg/L in UPW; equivalent to 0.001 mg/TI)

[ ]: Results between MDL and method quantification limit (MQL, 0.20 mg/L in UPW; equivalent to 0.004 mg/TI)

*Acceptance criteria established by the manufacturer based on product specific toxicological data

Sterigenics
A Sotera Health company



NO_2^-/NO_3^-

Nelson Labs
A Sotera Health company

- Ion chromatography testing
- Biocompatibility & residue testing performed by Nelson Laboratories

Residue on the surface of the syringe

Sample (clinical batch)	NO_3^- (mg/L)	NO_2^- (mg/L)	NO_3^- (mg/device)	NO_2^- (mg/device)
Average 3 PPQ cycles	8.95	<MDL	0.16	<MDL
Evaluation*	PASS (<50)	PASS (<0.5)	PASS	PASS

<MDL: Results below MDL (0.05 mg/L in UPW; equivalent to 0.001 mg/TI)

*Acceptance criteria established by the manufacturer based on Annex 1 (part B) of the EU Dir 2020/2184 on the quality of water intended for human consumption

Sterigenics
A Sotera Health company

Example of process parameters

20 °C	15 mg/L NO_2
500 mBar A pressure	15 minutes dwell time
80 % RH humidity	2 pulses

10 hours total cycle time

Sterigenics
A Sotera Health company

Nitrogen dioxide technology has been endorsed by Authorities

GMP License obtained in Belgium

ISO 13485 Certification by BSI

FDA dossier pre-approved

Sterigenics
A Sotera Health company

Connect with us to get your project started

Annick Gillet
Technical Director EO Pharma, Sterigenics
sterigenics.com

Sterigenics®
A Sotera Health company