Sterigenics®
A Sotera Health company

Gaseous sterilization solutions for Drug substances and prefilled Devices (Ethylene Oxide and Nitrogen Dioxide)

原料药和预灌封注射器的气体灭菌解决方案（环氧乙烷和二氧化氮）

Jessica Yuan

AUG 2024

Introduction of Sotera Health

Sotera Health

Safeguarding Global Health®

Nelson Labs® A Sotera Health company	Nordion® A Sotera Health company	Sterigenics® A Sotera Health company
Expert Lab Testing & Advisory Services	**Reliable Global Supply of Cobalt-60**	**Comprehensive Sterilization Solutions & Expert Advisory Services**
Safeguarding Global Health® – with every test we complete.	**Safeguarding Global Health® – with every Cobalt-60 source we supply.**	**Safeguarding Global Health® – with every product we sterilize.**

袁桂英(Jessica Yuan)

职位：工厂总经理

工作单位：施洁医疗技术(上海)有限公司

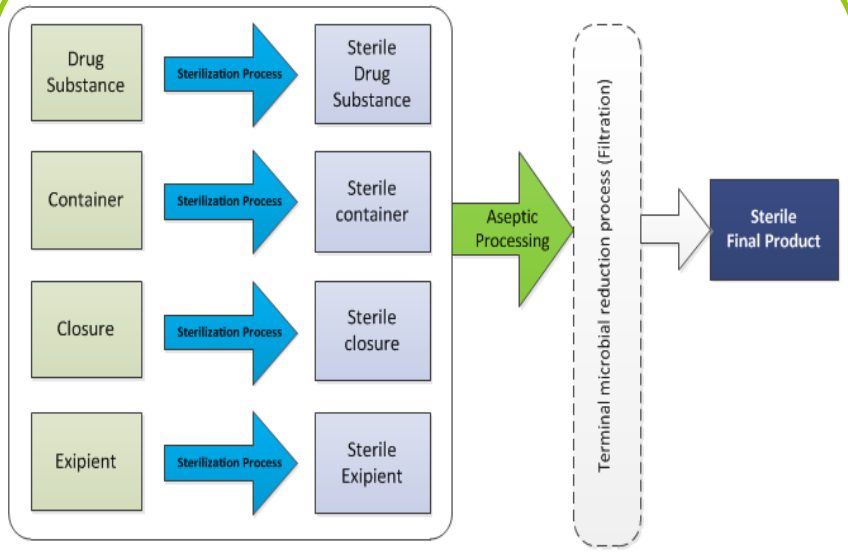
工作经历：

- 2014.10~现在 施洁医疗技术(上海)有限公司 工厂总经理
- 2013.09~2014.09 施洁中国区质量经理
- 2009.12~2013.09 施洁医疗技术(上海)有限公司 质量经理
- 中国医疗器械行业协会医疗器械包装专委会技术工作组 灭菌组组长
- IRCA认可 ISO9001 主任审核员
- 联系电话：18616605050

There are two (2) strategies to produce a sterile drug product:
两种获得无菌药品的策略

Introduction 介绍

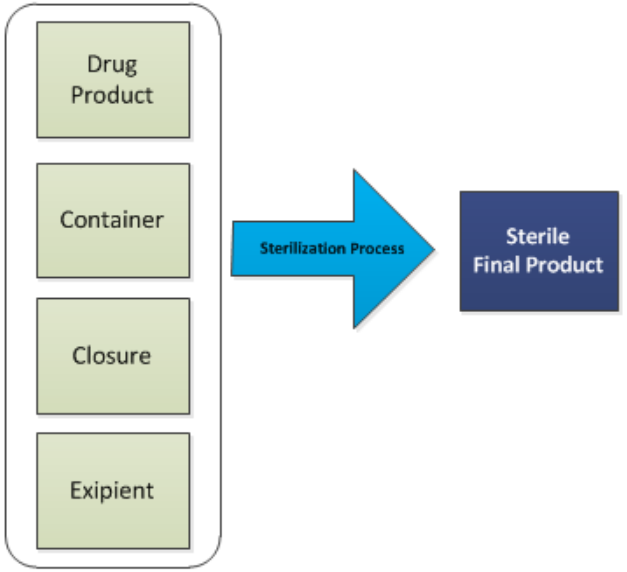
Aseptic Assembly
无菌组装



Maintain sterility of a product that is assembled from components, each of which has been previously sterilized

Sterile

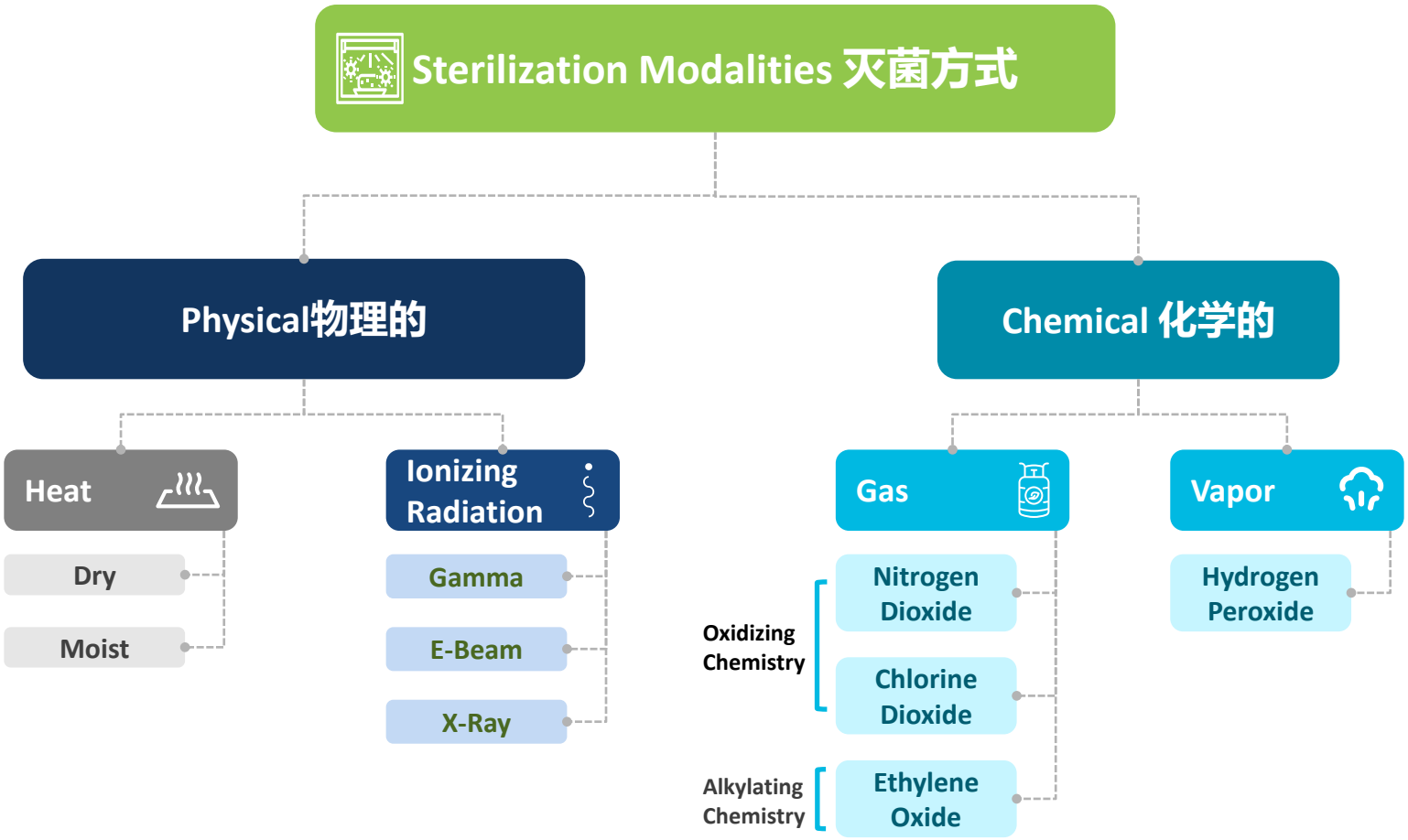
Terminal Sterilization
终端灭菌



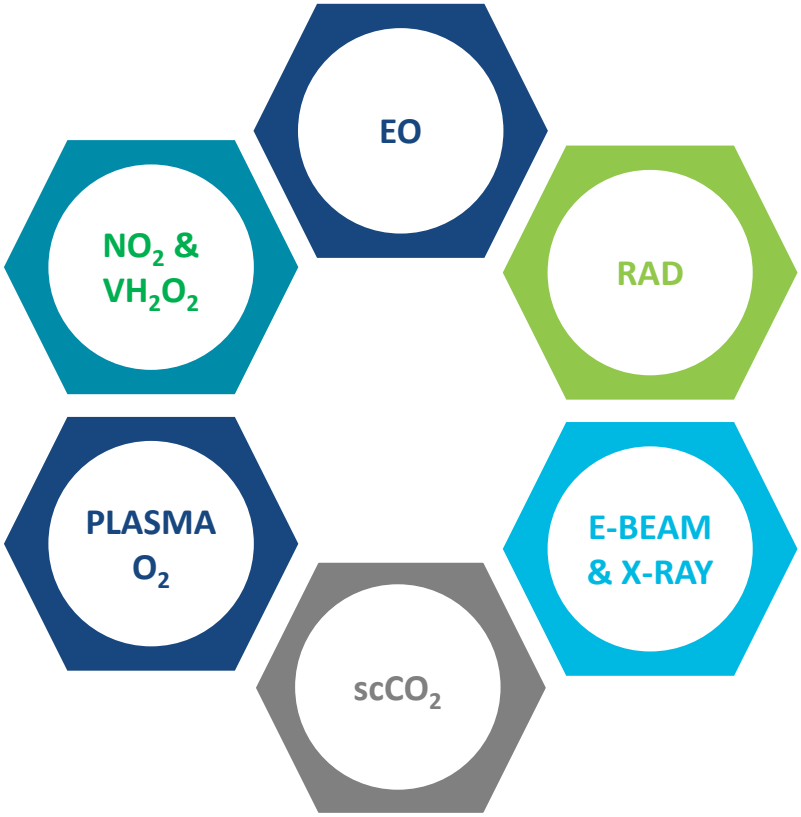
Exposure to a physical or chemical sterilizing agent for a predetermined extent of treatment

Sterilized

Introduction 介绍



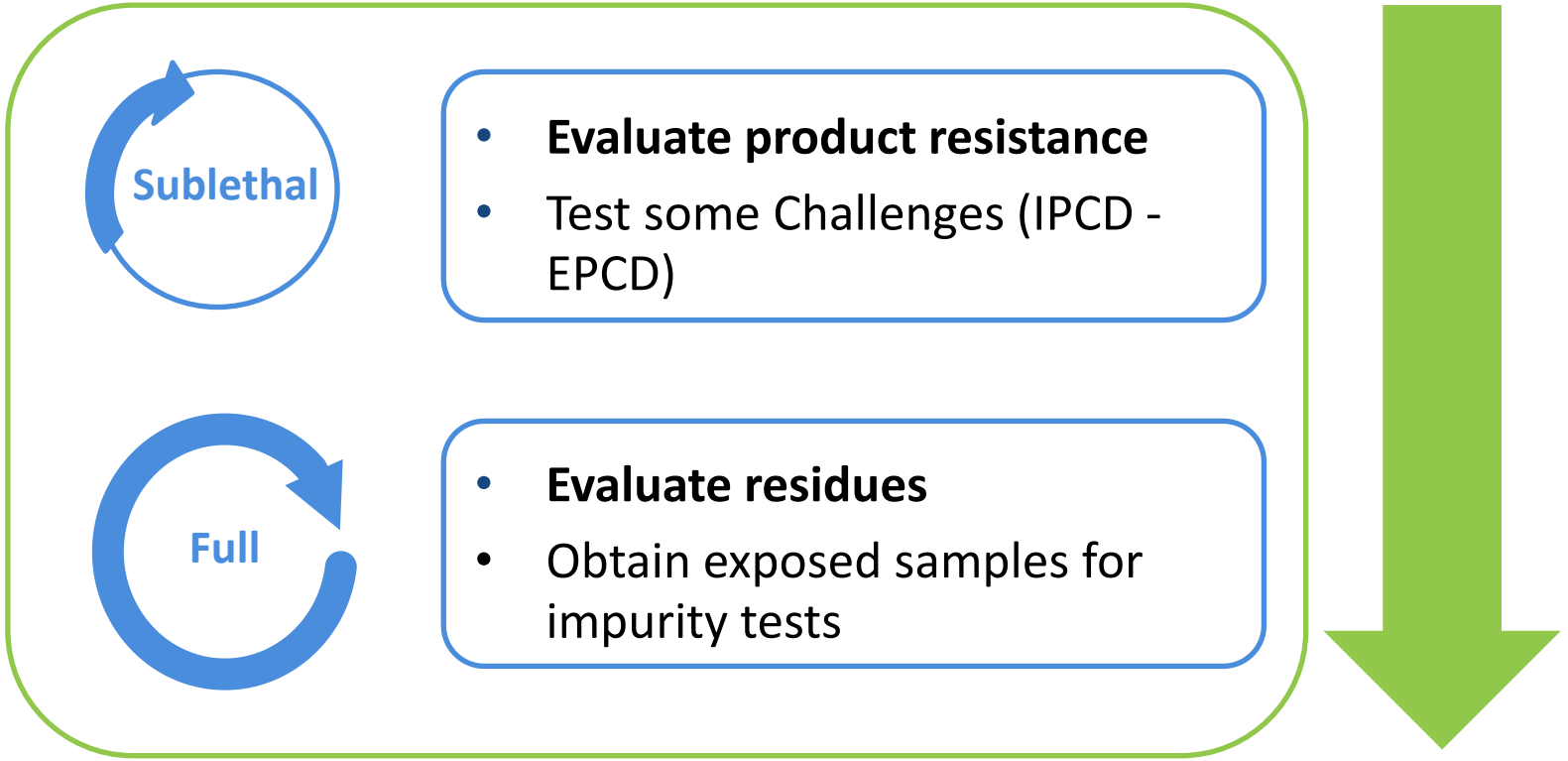
Provide Optimal Sterilization Solutions 提供优化的灭菌解决方案



- Ethylene Oxide
- Nitrogen Dioxide and Vaporized Hydrogen Peroxide
- Gamma Radiation
- Electron Beam and X-Ray
- Supercritical Carbon Dioxide
- Plasma Oxygen

Provide Optimal Sterilization Solutions提供优化的灭菌解决方案

Feasibility testing（可行性研究）：



Final product Design 最终产品设计

Ethylene Oxide Sterilization环氧乙烷灭菌

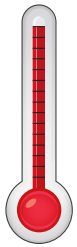
EO is commonly used in Sterilization （环氧乙烷灭菌）

Mainly used to sterilize:

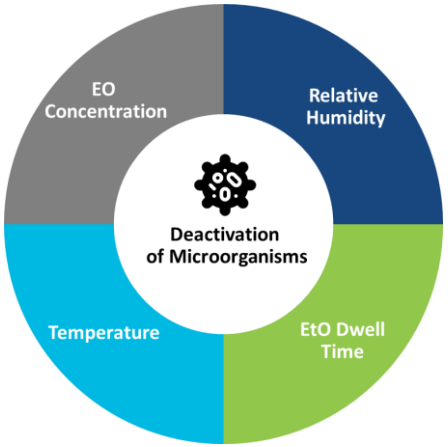
- Heat-sensitive material
- Material sensitive to ionizing radiation
- From Small to High volumes
- Packs with multiple components/complex products

EO Sterilization Process – Critical Parameters (EO 灭菌过程-关键参数)

Typical range 400-700 mg/L

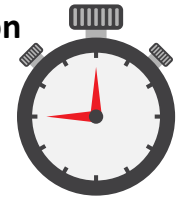


Industrial sterilization
performed in 104-140 °F
(40–60°C) temperature range

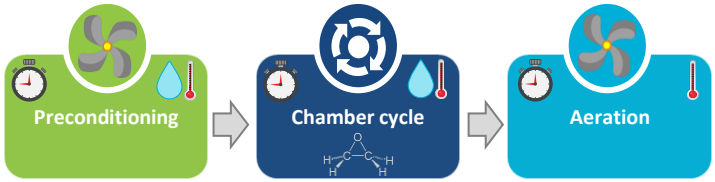


Necessary for **alkylation reaction**
EO is most effective at **RH > 30%**

Microbiological deactivation
is more effective with longer gas dwell phase (typically 3-4 hours)



3-Step Process



Optimize Cycle Development & Creative Processing（优化循环开发）

	Standard	Optimized
Concentration	600 mg/L	300 mg/L
Cycle Design	One pulse EO	N_2 Push
Bioburden	Half Cycle	Cycle Calculation

Complexity of EO is an asset for optimization !

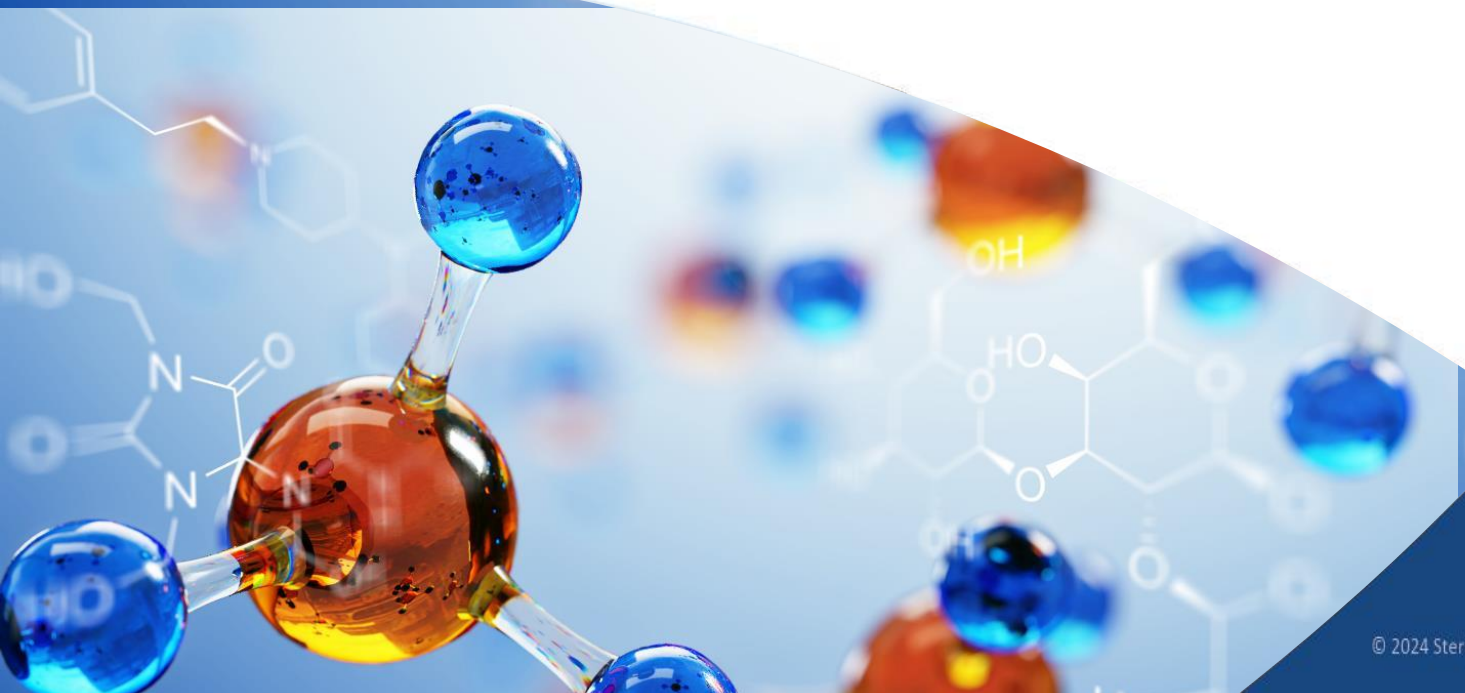
Optimize Cycle Development & Creative Processing（优化循环开发）

Sustainability

Sterilization of Complex/Sensitive Healthcare products

New technologies 新技术

NITROGEN DIOXIDE STERILIZATION



New Technologies（新技术）

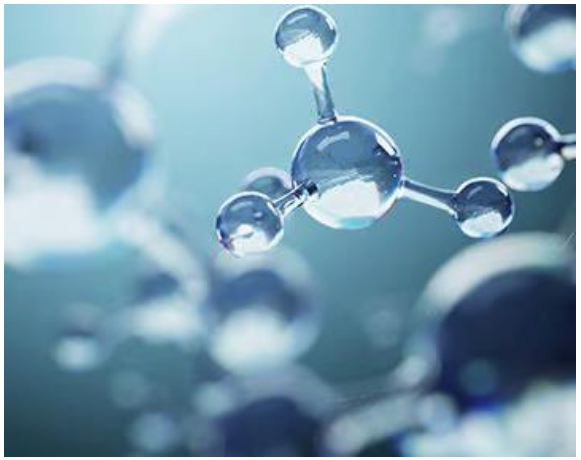
NO2 - An alternate possibility for new complex products?

- Surface sterilization for DP protection
- Low temperature process
- Non-flammable, non-explosive and non-carcinogenic
- Wide variety of compatible materials (if not cellulose based)

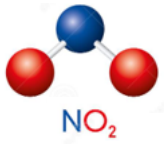
New Technologies（新技术）

NO_2 is a complementary technology

- Supplement Current Modalities
- Right Process for the Product
- Safe and efficient (ES&G)
- **Regulatory landscape** favorable
    - FDA Challenge 1 in Nov 2019
    - NO_2 accepted by EPA (US)
    - EU GMP Process approval (2024)

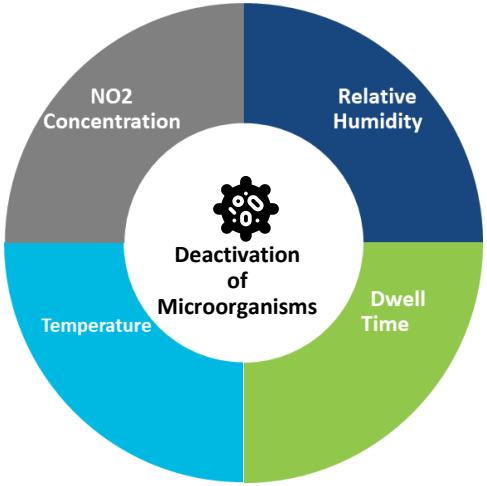


NO2 – Basics（NO2基础）

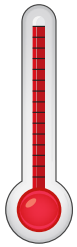


Typical range **10-15 mg/L**

Key Parameters



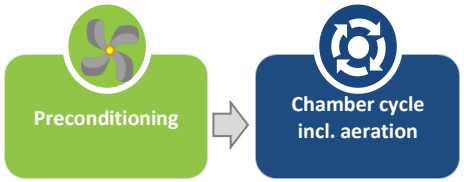
Necessary for **oxidation reaction** effective at **60-80 RH %**



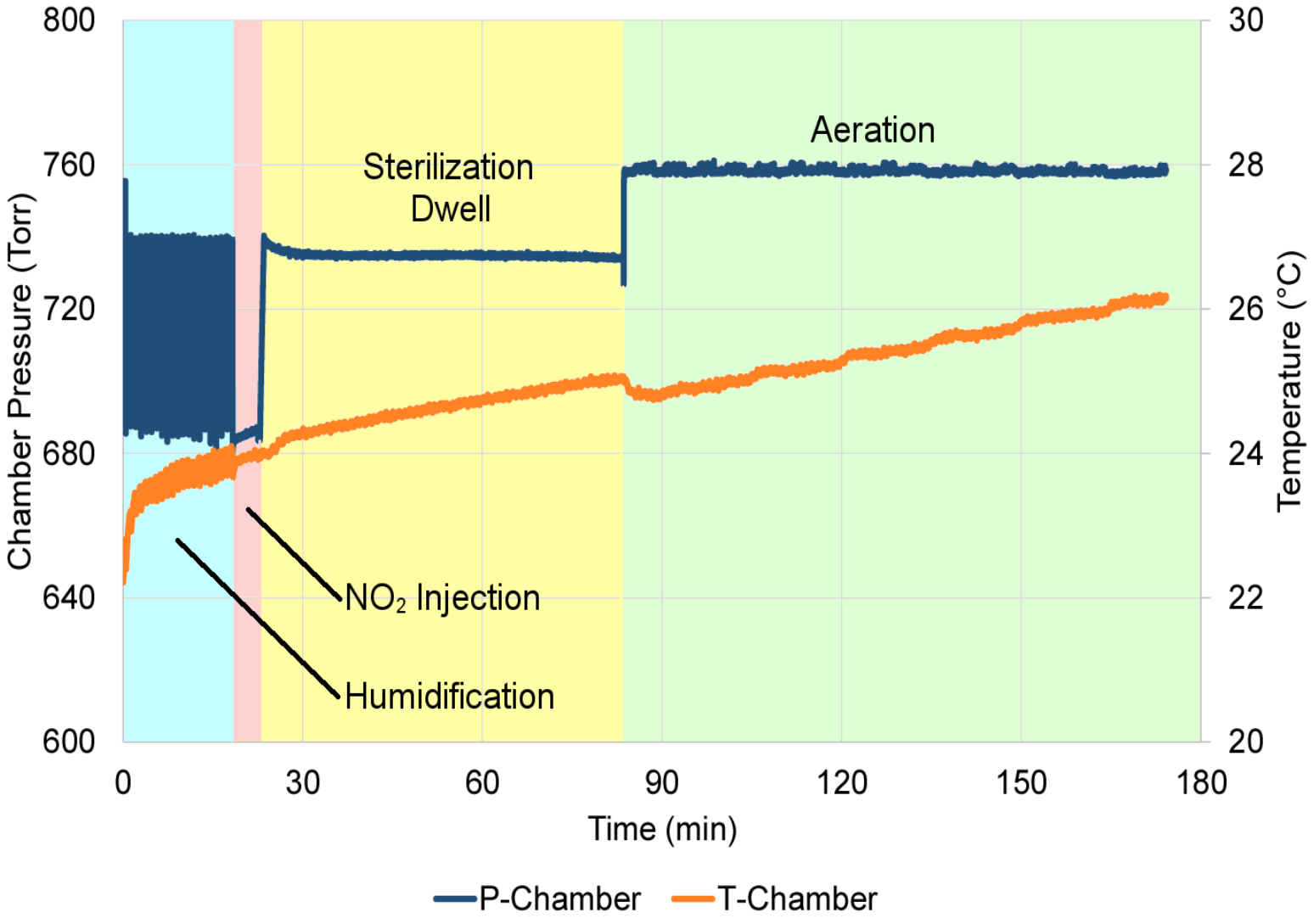
Industrial sterilization
performed in 50-77 °F
(18-21°C) temperature range

Microbiological deactivation
is more effective multiplr pulses (**Total Cycle time = 10-18h**)

2-Step Process



What does the cycle look like(NO2灭菌循环)

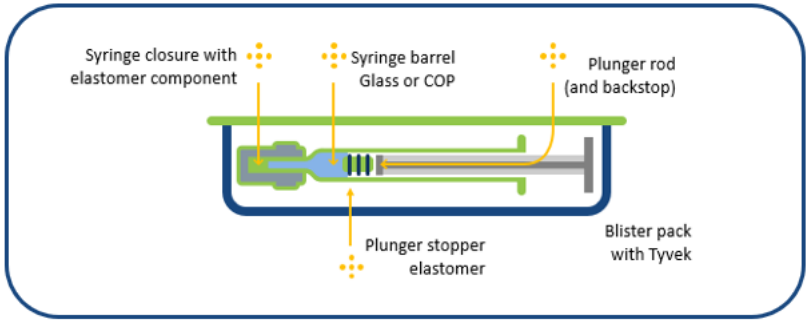


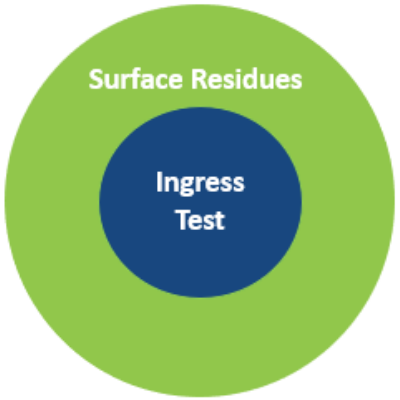
NO_2 Analytical Testing（NO2分析测试）

Gas Residues :

NO_2^-/ NO_3^-

Gas ingress pathways :





- The **hazards** posed by these residuals are considered **low**
- No international standard for NO_2sterilant residuals
- Limits to be justified by customer based on product usage
- Biocompatibility (E&L) testing by customer

NO2 Packaging Compatibility （NO2包装相容性）

NO_2 is compatible with commonly-used sterile barrier packaging materials

- Tyvek® based pouches
- Extrusion Coated / Laminated Films
- Thermoformed Trays (PETG) with Tyvek® lids

NO_2 interacts chemically with cellulosic materials

NO2 Material Compatibility（NO2材料相容性）

- **NO_2 is compatible with many Drug Delivery materials:**
  - Cyclic Olefins (COC, COP)
  - Bromo/Chlorobutyl Rubber
  - Borosilicate Glass
  - PTFE/Teflon
  - Stainless steel
  - Polycarbonate
  - Polypropylene
  - Polyethylene
  - ABS
- **NO_2 may chemically interact with:**
  - Polyacetal (Delrin®)
  - Polyurethanes
  - Nylons

Examples of products sterilized with NO2

Medical Devices

Orthopedic Implants

Electronic Implants

Drug Products

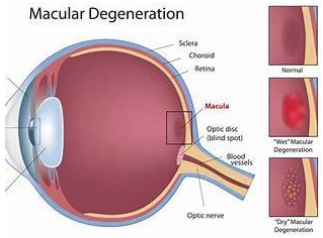
Active Pharmaceutical Ingredients

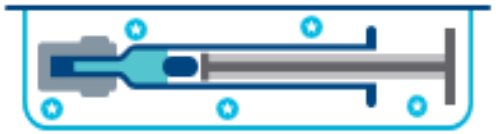
Prefilled syringes (external)

Drug Implants

Pre-filled devices present a unique challenges for sterilization

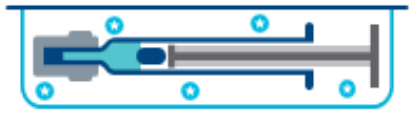
- Temperature-sensitive drugs products (biologics)
- Complex formulation challenges
- Innovative plastic material with coating
- Syringe Plunger movement
- Impurities (ingress, stability)
- Sterilization SAL $\leq 10^{-6}$ at worst-case position
- Regulatory complexity





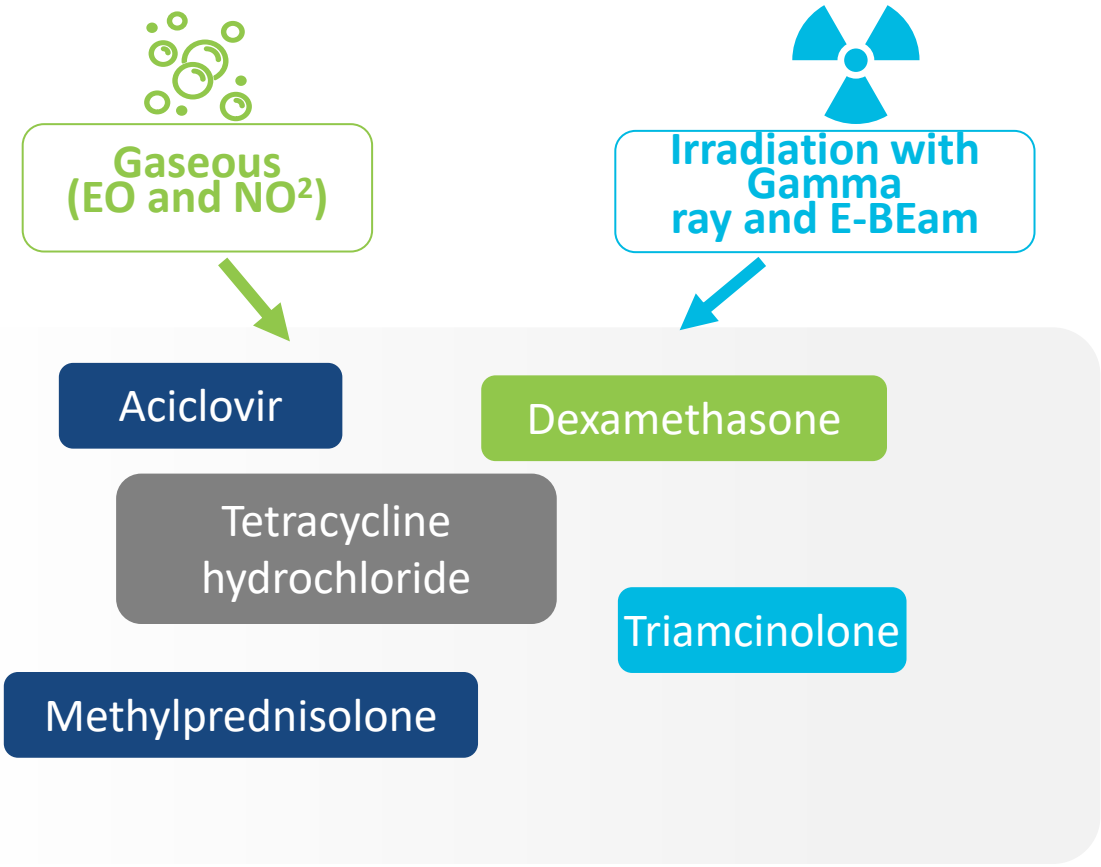
NO_2 versus EO (No2 对比EO)

Pre-filled devices



Characteristic	EO	NO_2
Lethality	high	medium
Diffusion into most polymers/ plastics	high	low
Sterilant concentration (mg/L)	High (200-400mg/L)	Low (10-20 mg/L)
Load Volume	1-32 Pallets	1 Pallet
Processing temperature	40°C	20°C
Processing Time	Long (> 3 days)	Medium (±15h)
Microorganism for BI	B. Atrophaeus (7days incubation)	G. Stearothermophilus (14 days incubation)
Residues	ETO,ECH,(EG)	NO_2,NO_3 – Low hasard

Drug Sustbstance Sterilization



Drug Sustbstance Sterilization

	EO		Gamma	
	Assay	Related substances	Assay	Related substances
Dexamethasone	+	+	+	< x dose
Methylprednisolone	+	+	+	< x dose
Aciclovir	+	+	+	+
Tetracycline.HCl	+	+	+	+
Triamcinolone	+	+	+	+

- *The effect of Gamma and Ethylene Oxide Sterilization on a Selection of Active Pharmaceutical Ingredients for Ophthalmics - Journal of Pharmaceutical Sciences*
- *Sterilization of biopharmaceuticals: Effect of gamma irradiation, e-beam irradiation and nitrogen dioxide on human insulin - ScienceDirect*

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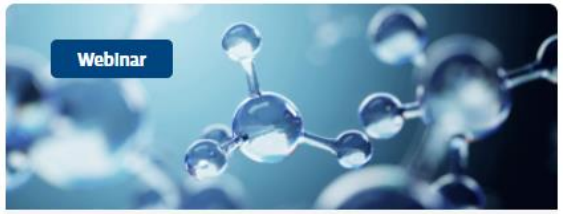
Laboratory Testing

Market Segment



Medical Packaging and the Impact of NO2 Sterilization

by Allen Bickel (Noxilizer), Jeremy Elwell, Nicole Palluck

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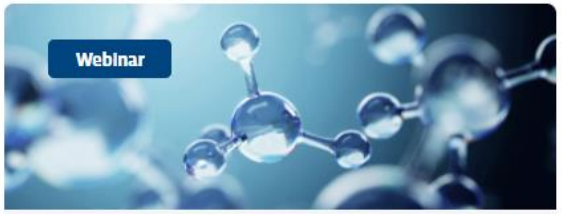

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by Dr. David Opie

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Thank You

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