Sterility Assurance: Industry Viewpoint with Emphasis on Optimizing Ethylene Oxide Sterilization

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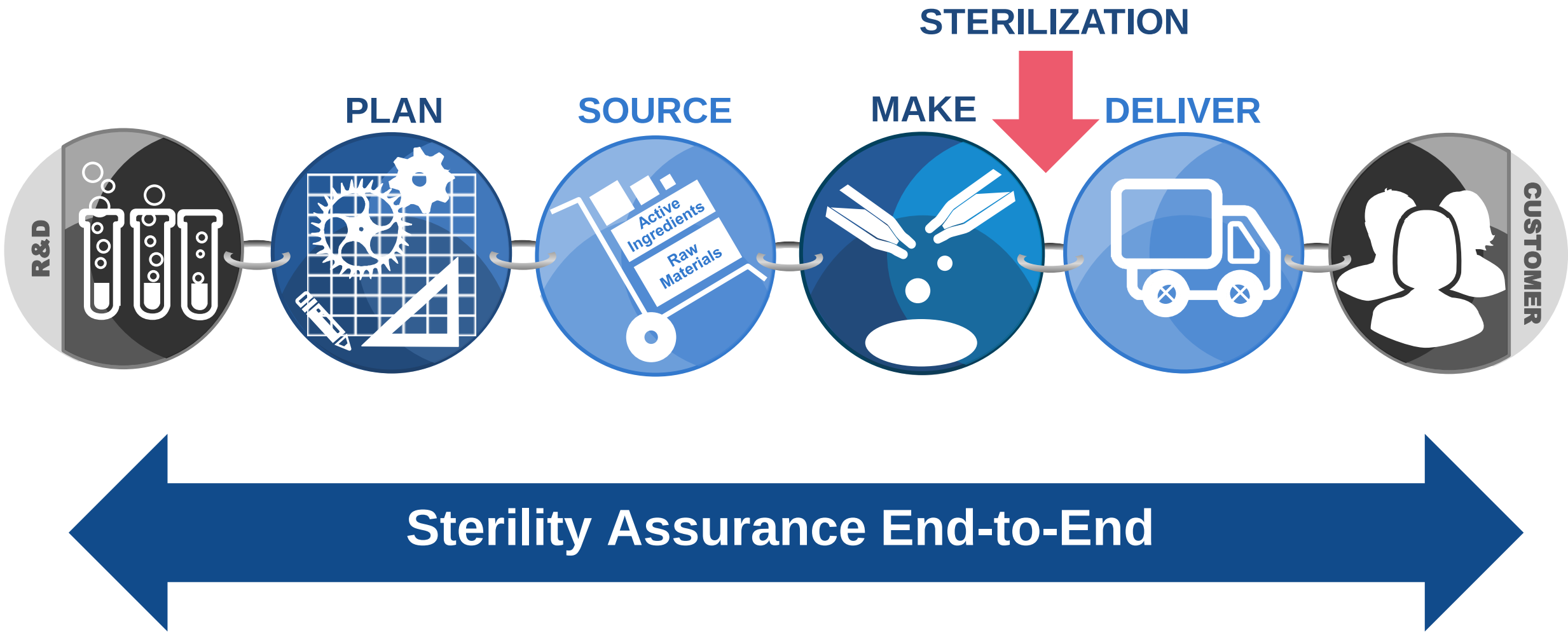
Presentation Key Points

- Sterilization starts and ends with the patient
  - Impacts manufacturing and distribution of devices across entire supply chain
- Sterilization is not just about eradicating microorganisms
  - Involves making sure it does not impact functionality or performance of devices across life cycle
- Ethylene Oxide (EO) sterilization is a highly controlled process
  - Used for sterilizing ~50% of medical devices worldwide
- New approaches may allow us to reduce amount of EO gas in industrial process

Utilizing the End-to-End (E2E)
R&D Phase



E2E Sterility Assurance
R&D Phase

Product Design

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Material Compatibility (Product and Packaging)

2 Broad Categories of Sterilization Modalities

- Traditional – well-understood with developed standards
  - Ethylene Oxide
  - Moist / Dry Heat
  - Radiation – Gamma / E-Beam / X-ray
- Non-traditional – requires greater testing
  - Hydrogen Peroxide
  - NO_2 (Noxilizer™)
  - PAA (Revox™)
  - Chlorine Dioxide

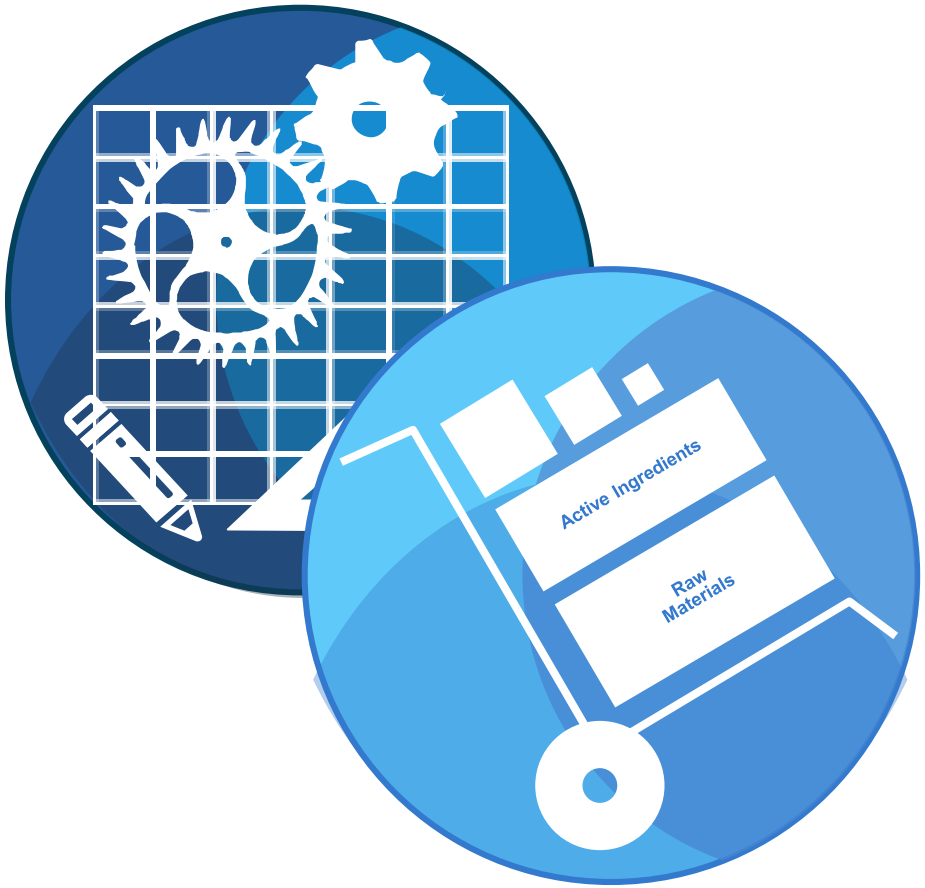
Choosing Modality
1st Question is Material Compatibility

Material	Radiation	Ethylene Oxide	Moist Heat	Dry Heat	VHP	Nitrogen Dioxide	ClO_2	PAA
Polycarbonate	Good - Excellent	Excellent	Not recommended	Up to 170°C	Excellent	Compatible	Compatible	Compatible
Polypropylene	Poor	Fair	Poor	Up to 135°C no stacking	Excellent	Compatible	Compatible	Compatible
Stainless steel	Excellent	Excellent	Excellent	Compatible	Excellent	Compatible	Compatible	Compatible
Nylon	Moderate	Very good	Very good	Marginal (120°C, unless heat stabilized up to 130°C	Fair	Incompatible	Compatible	Compatible
ABS	Good	Excellent	Poor	No Data	Excellent	No data	Compatible	Compatible
Polyurethane	Excellent	Good - Poor	Not recommended	Varies on grade	Excellent	Incompatible	May Discolor	Compatible
Polyethylene	Excellent	Excellent	Not recommended	Marginal up to 120°C	Excellent	Compatible	Compatible	Compatible
Polysulfide's	Excellent	Excellent	Excellent	Up to 160°C	Excellent	Compatible	No Data	Compatible
Polyvinylchloride	Good	Excellent	Poor - Fair	Marginal up to 120°C	Excellent	Compatible	Compatible	Compatible
Common Sterile Pckg. Non-woven polyprop; Tyvek ® Mylar ®	Compatible	Compatible	Compatible	Marginal	Compatible	Compatible	Compatible	Compatible
Cellulosic material Paper / Cardboard	Compatible	Compatible	Compatible	Incompatible	Incompatible	Incompatible	Absorbs but Compatible	Incompatible

E2E Sterility Assurance
R&D Phase

- Product Design
- Material Compatibility (Product & Packaging)
- Validation Methodology
- Sterilization Modality

E2E STERILITY ASSURANCE: Plan & Source Phase

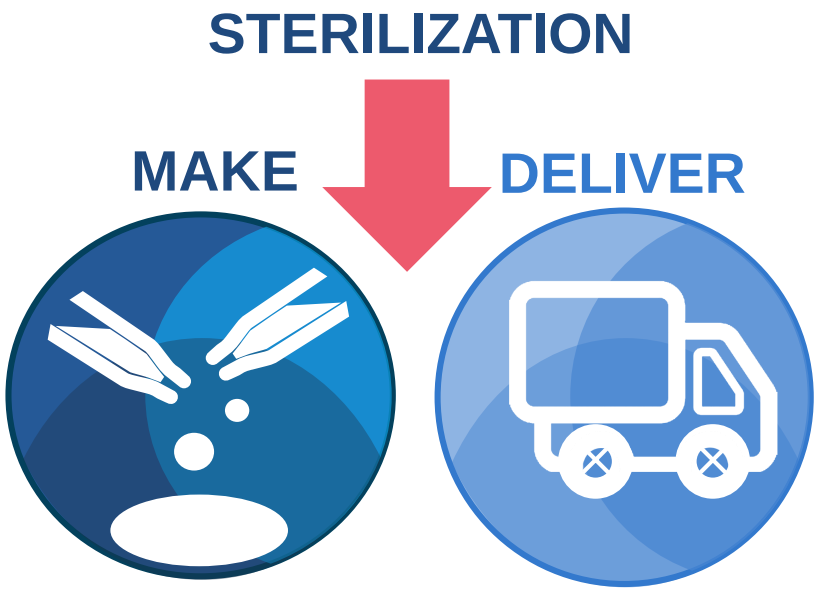


- Plan
  - Identify where and how product will be produced and sterilized
- Source
  - Identify supplier of raw materials
  - Ensure raw material meets design specification and produced to ensure low bioburden

E2E STERILITY ASSURANCE:
Make Phase (i.e., Manufacturing)

- Environmental monitoring
- Sterile barrier (packaging)
- Change control
- Oversight for sterilization execution (e.g. terminal sterilization or aseptic processing)
- Sterilization validation maintenance

E2E STERILITY ASSURANCE: Sterilization Phase

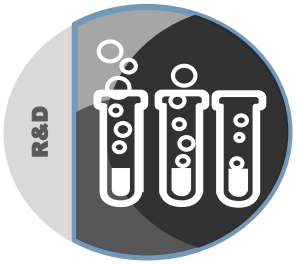


- Receipt and shipment of products
- Inventory control
- Delivery of validated process
- Verification of process
- Quality review and approval process
- Release of product

E2E STERILITY ASSURANCE: Deliver Phase

- Assurance of sterile barrier (over shelf life)
- Environmental controls
  - Temperature
  - Humidity

EO – Same E2E Approach



- New Product Development / Life Cycle Management
  - Cycle Development
  - Cycle validation
  - Appropriateness of PCD
  - Material and Packaging Compatibility

PLAN

- Assessment of EO Sterilization facility

SOURCE

- Sterilization Evaluation
  - Raw materials
  - Process components
  - Manufacturing aids

MAKE

- Sterilization Execution
  - Internal / external
- Monitoring of sterilization process
- Follow ISO 10993-7

DELIVER

- EO Residual Management

- Standards for patient safety

Benefits Unique to EO

Mode	Variables	Advantages	Typical Use	Capacity
Ethylene oxide (EO)	▪ Temperature ▪ Humidity ▪ Time ▪ Gas concentration	▪ Low temperature ▪ High penetration ▪ Adaptable process ▪ Compatibility ▪ Variable sized chambers (single cubic feet to 30+ pallets)	▪ Temperature-sensitive products ▪ Adhesive dressings ▪ Tubing sets	▪ Multiple locations ▪ Global ▪ In-house ▪ Contract ▪ Low spare capacity

EO Sterilization Process is Highly Controlled

1. Pre-conditioning

Pre-conditioning Chambers

2. EO Processing

Sterilization Chambers

3. Aeration

Aeration Chambers

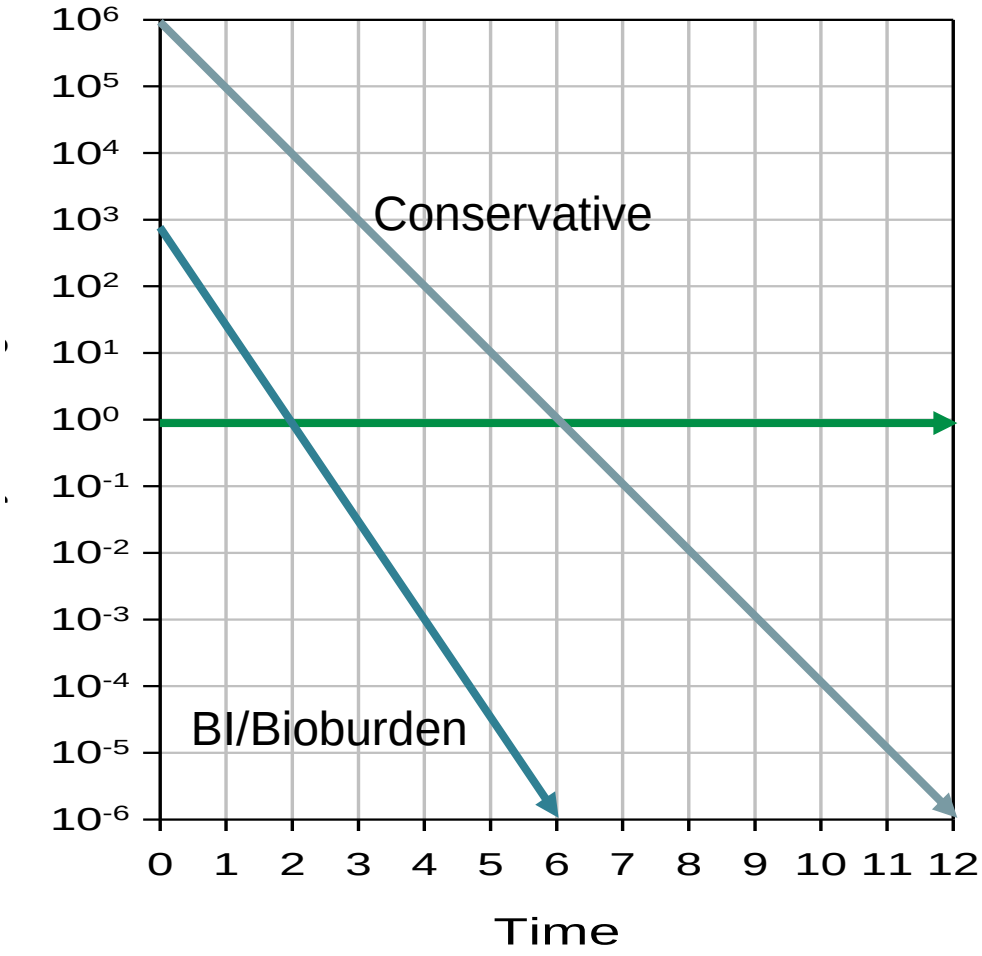
How Better Utilize EO

Modify Product Packaging

- Reduce paper materials in packaging and eliminate paper IFUs
  - Reduce amount of EO used and decrease EO residuals
- EO is absorbed in paper
- Move to electronic IFU
  - Same information with significantly less EO residuals

Optimized Process

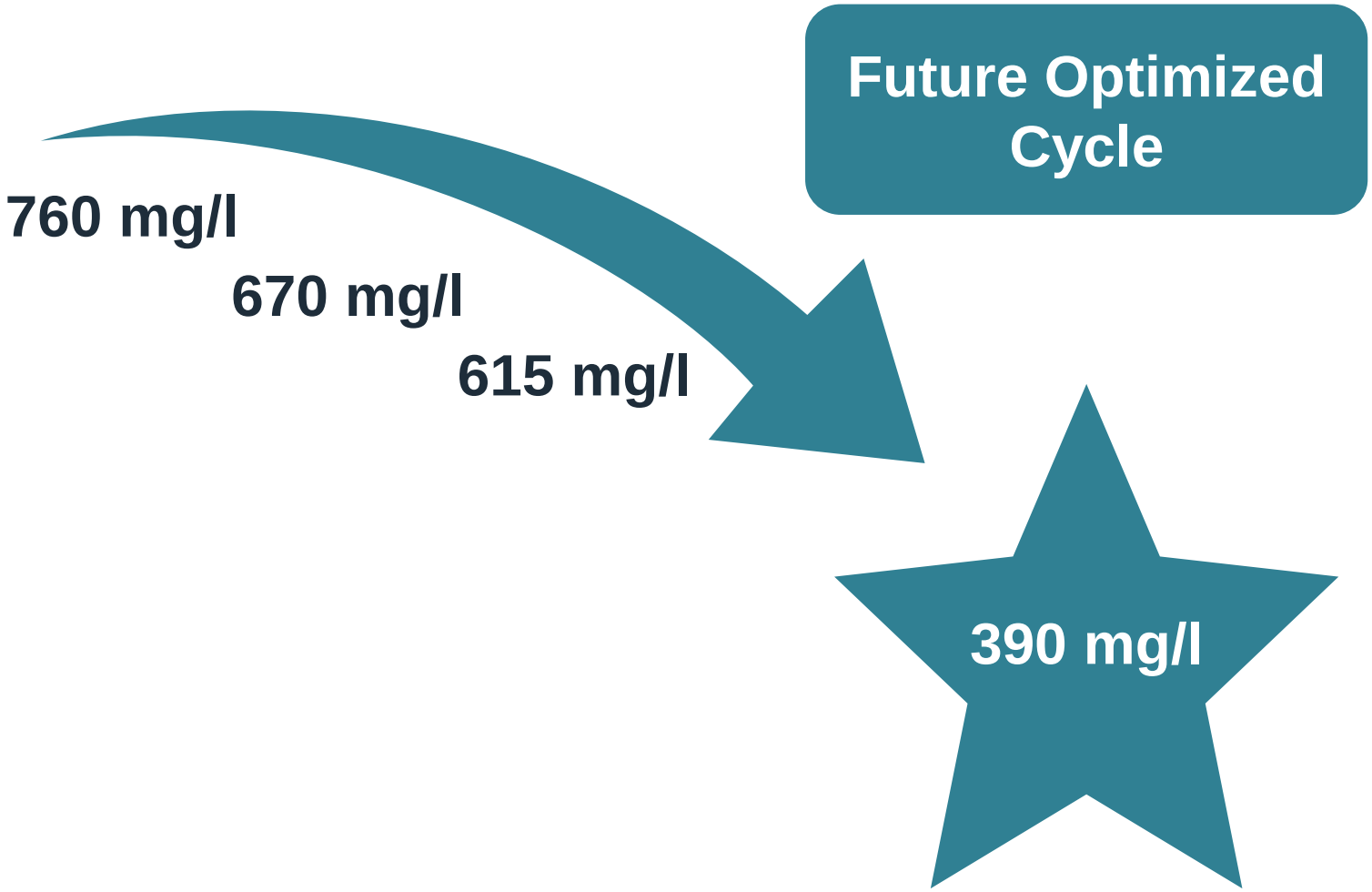
- Conservative approach
  - High degree of confidence but requires large amounts of EO and higher emissions
- Optimized Cycles (BI/Bioburden)
  - Recognized by ANSI/AAMI
  - Shorter exposure times and lower EO levels
  - More complex
  - Will require time, validation and regulatory approval



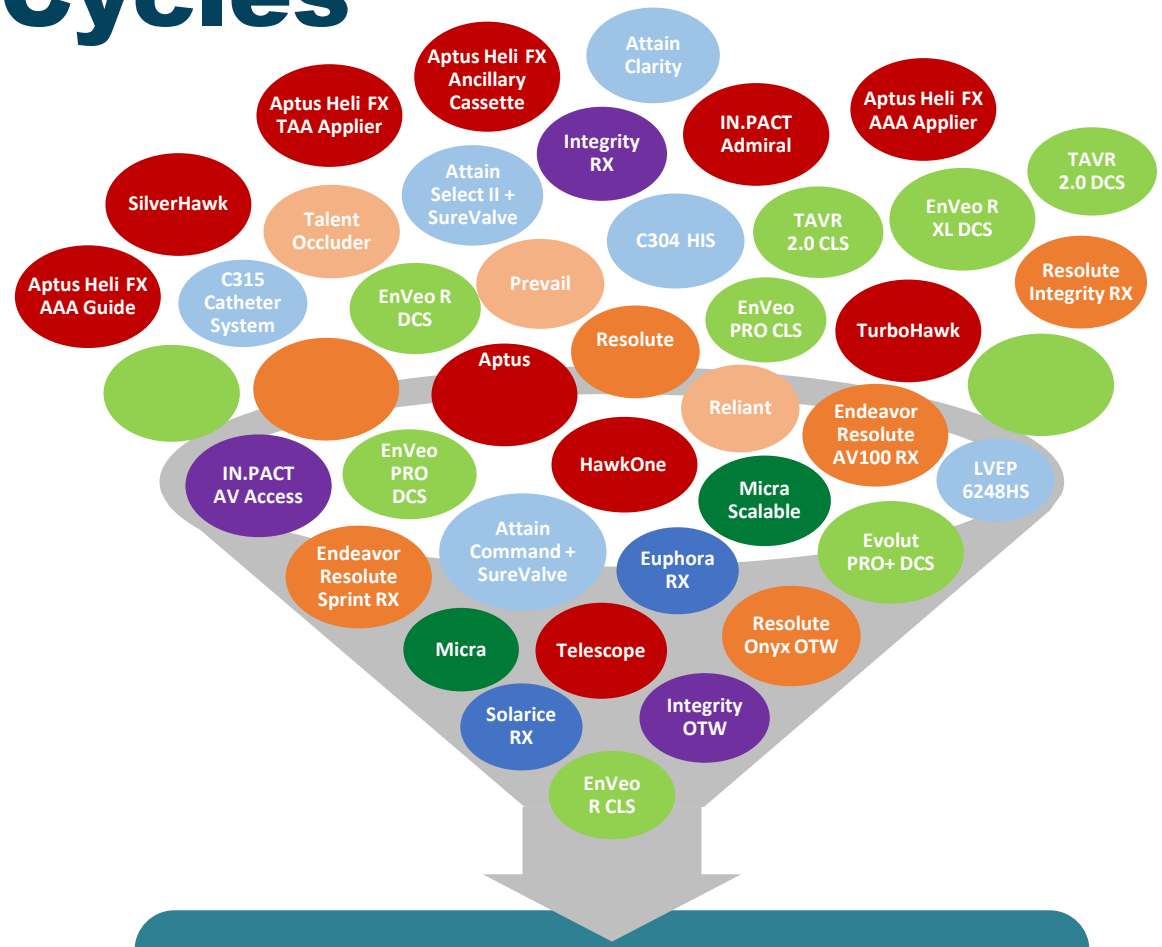
Reduce Exposure Time

Equivalent Exposure Times	Resultant SAL
230 minutes (original production run data based on 120 minutes exposure timer setting)	$10^{-12.7}$
205 minutes (25 minutes less in exposure)	$10^{-10.6}$
195 minutes (35 minutes less in exposure)	$10^{-9.8}$
155 minutes (75 minutes less in exposure)	$10^{-6.5}$

Reduce Gas Concentration



Consolidate Number of Cycles into Optimized Cycles



Optimized

1 consolidated low-EO cycle (390 mg/L)

Multiple products

Currently validated cycles

- Cycle #1
- Cycle #2
- Cycle #3
- Cycle #5
- Cycle #7
- Cycle #8
- Cycle #10
- Cycle PC-A

Summary

- EO sterilization processes are complex and lengthy
  - Each function in sterilization E2E approach is critical and can impact sterilization process and patient
- Sterilization involves more than eradicating microorganisms
  - Make sure functionality or performance is not impaired
- Few products sterilized by EO can move to other modalities
- Changes to sterilization processes are difficult and take time
  - Validation and testing over life-cycle of product
  - Non-traditional methods do not have nationally recognized standards
- Potential approaches to better utilize EO but all will require time