# Hydrogen Peroxide Gas-Plasma Sterilization

## Advantages & benefits of a proven method for device sterilization


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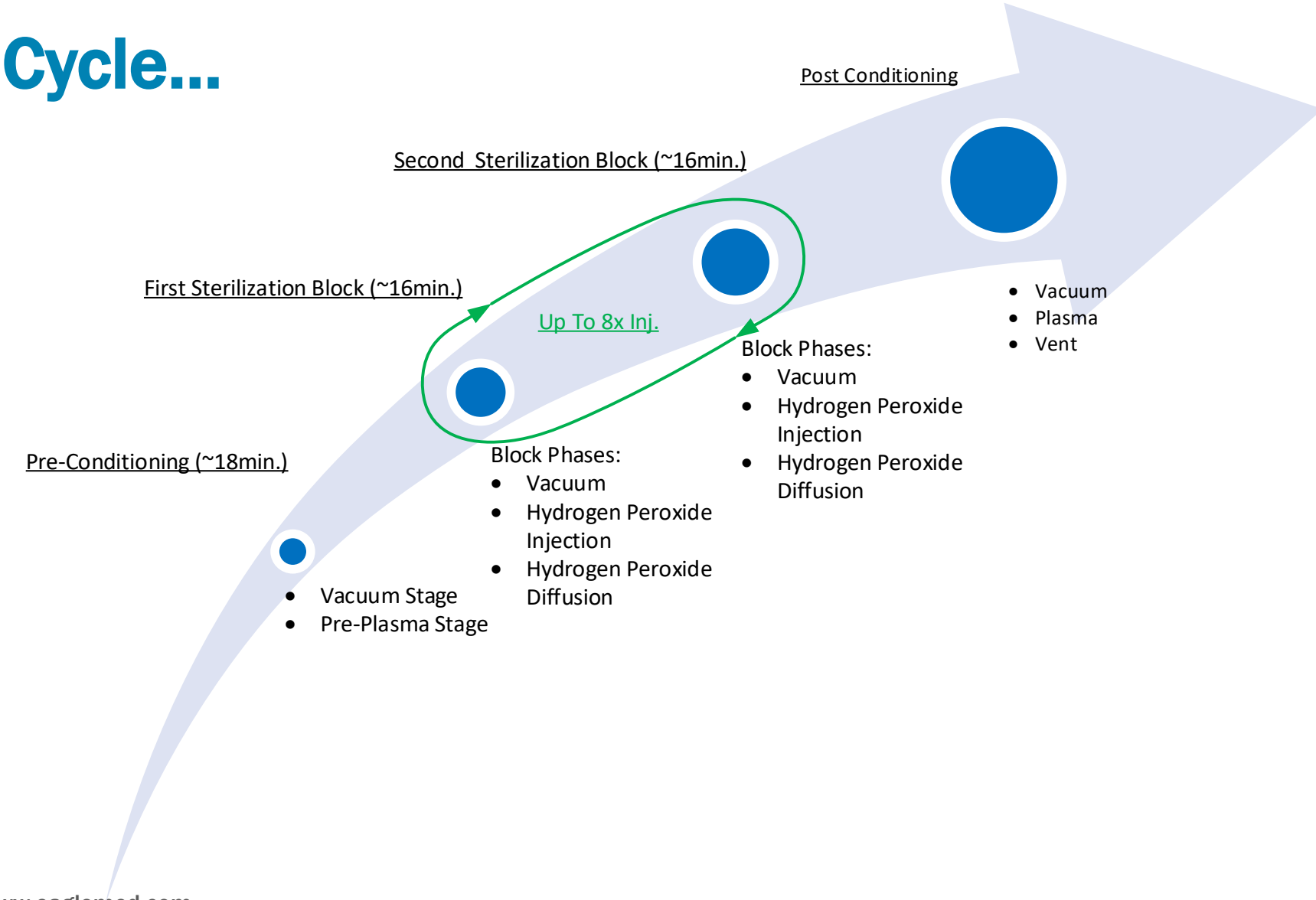
# What is Hydrogen Peroxide Gas-Plasma (HPGP) Sterilization?

- HPGP is a *low-temperature* hydrogen peroxide gas plasma technology, designed to sterilize a wide range of instruments without instrument damage associated with other established sterilization methods.

| Sterilization of New Devices | |
|---|---|
| Orthopedic Implants, | Rigid Scopes, |
| Pre-Filled Syringes, | Cameras, |
| Accessory Cables, | Electronics, |
| Batteries, | Ablation Devices |
| Intraocular Implants | Screws, Pins |
| Among Many Others | |

# The Basic HPGP Cycle…

- Employs the cidal / oxidative properties of vapor Hydrogen Peroxide ($H_2O_2$) to penetrate and kill resident bioburden.
- Applies repetitive injections as determined through Cycle Validation, and
- Plasma formation to dramatically reduce $H_2O_2$ residuals and cycle times for sterilization loads.

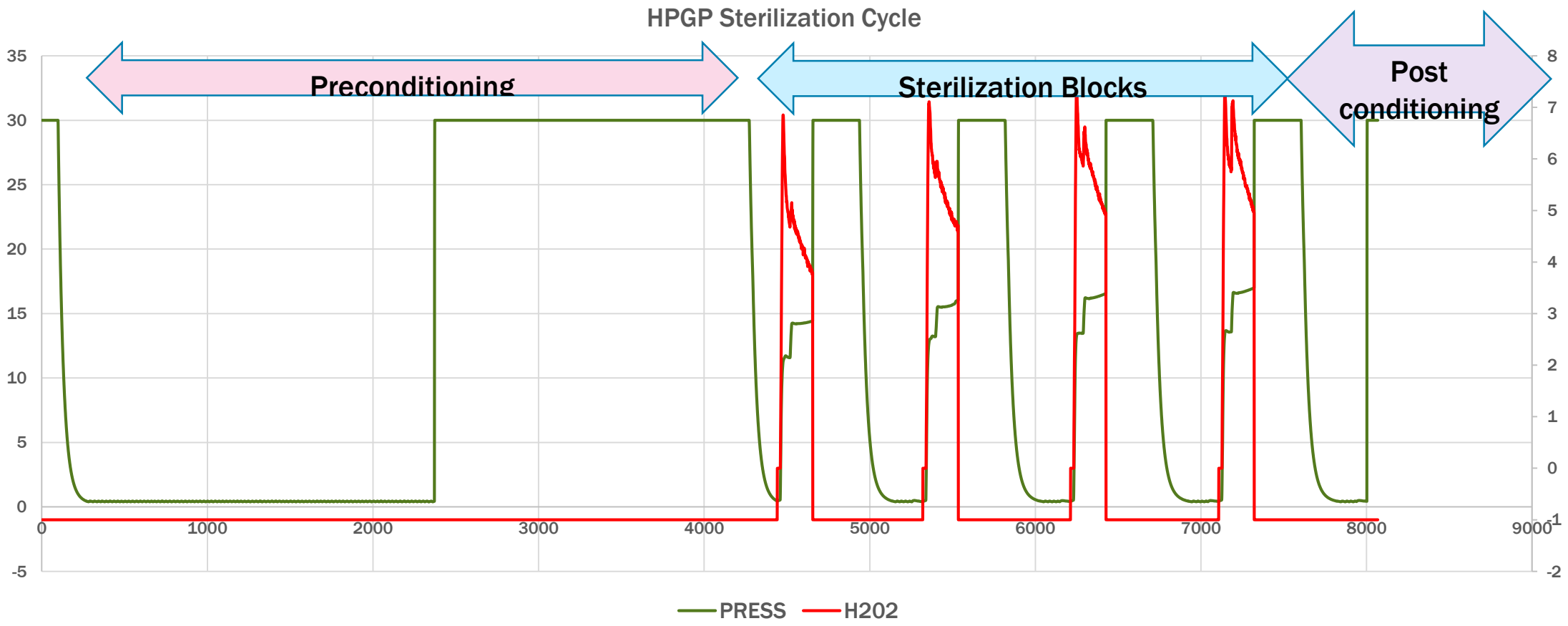


# HPGP Sterilization process

- Three phases constitute a sterilization block; the system can be programed to perform many blocks without equipment limitations. The number of blocks are a function of obtaining the adequate Sterilization Assurance Level (SAL) $10^{-6.}$ in half cycle conditions.
- Additional Plasma and Vent Phases are utilized to condition the load
  - Plasma Phase: Plasma is introduced to break down the $H_2O_2$ into free radicals, afterward these active radicals recombine into $H_2O$ and $O_2$.
  - Vent Phase where the chamber in "vented" allowing clean filtered air into the chamber.
- Pre and post conditioning are also part of the cycle to prepare the load, devices, before and after the sterilization cycle.
  - Pre Conditioning consists in warming the load to optimum temperature condition ~40ºC(normally 30 to 60 minutes).
  - Post Conditioning Phase consists in removing H2O2 residual via Vacuum, Plasma and Vent Phase (normally less than 15 minutes)

# HPGP Sterilization process (cont.)



# A Historical Overview of HPGP, An Established Technique:

- Originally began in the food processing industry, Cir. 1975 as diluted fluid sometimes combined with UV-irradiation, or as a vapor without plasma activation[1, 2]
  - Among the first U.S. Patents for HPG (#4,169,123) was awarded to the Moore-Perk Corporation of Indianapolis, Indiana on September 25, 1979.
- Johnson and Johnson applied the Plasma Innovation to HP-Vapor in 1987 and first Field tested the device in the late 1980's. J&J was awarded Patent #4,943,414, on July 24, 1990.
  - More rapidly and effective removal of $H_20_2$ residuals than vapor only systems
- By the early 2000's HPGP was becoming an accepted form of sterilization and by 2016, achieved FDA acceptance as a "established" sterilization method under Guidance Document;
  - "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile", Category-B.

1. Toledo, R. T. 1975. Chemical sterilants for aseptic packaging. Food Technol. 29(5):102-112.;
2. Antibacterial Effects of Hydrogen Peroxide and Methods for Its Detection and Quantitation, Benjamin j. Juven* and Merle D. Pierson Department of Food Science and Technology, Virginia Polytechnic Institute and State University, Blacksburg, Virginia, US *Journal of Food Protection, Vol.* 59, *No.* 11, 1996,

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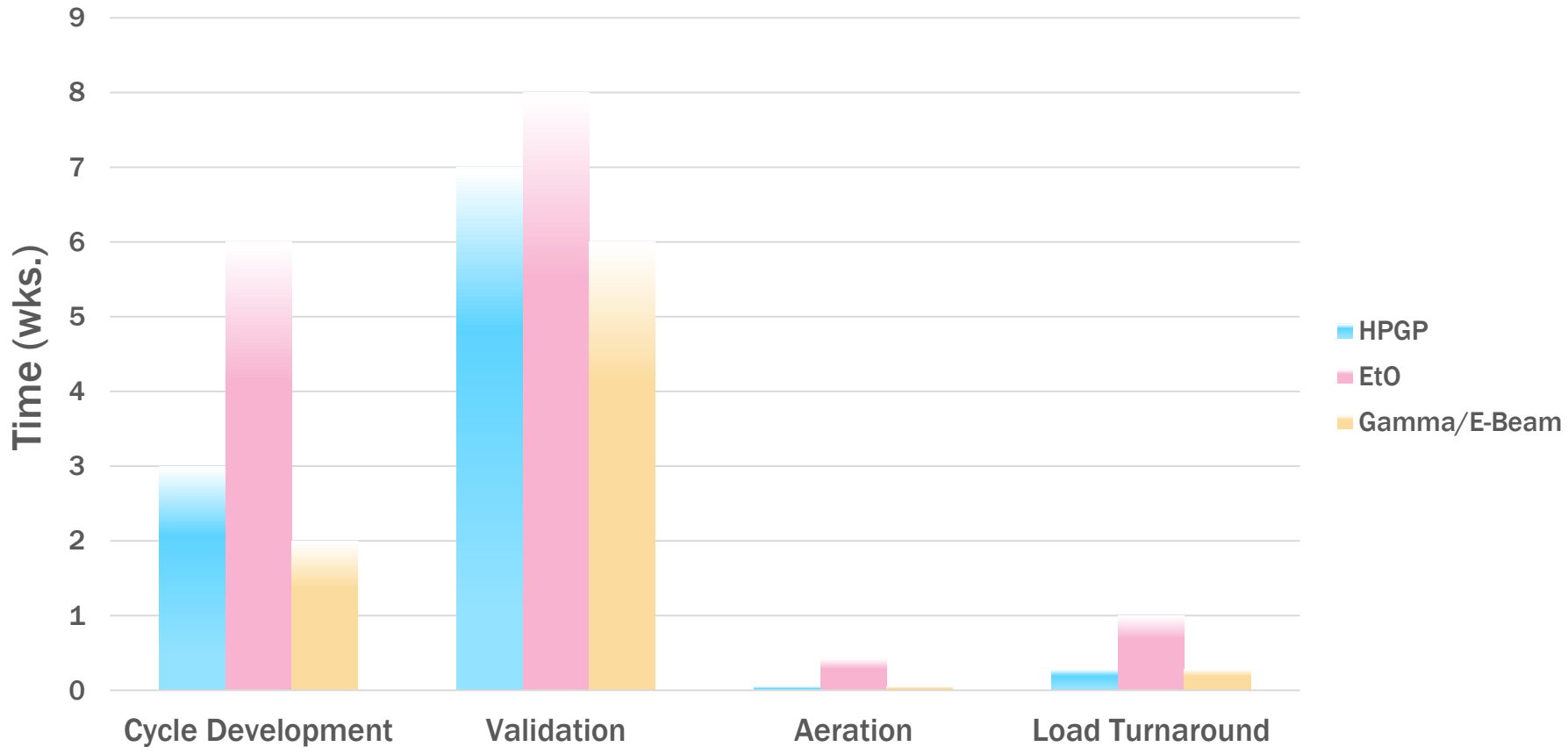
# Why Consider HPGP as Your *Primary* Sterilization Method? Risk vs. Reward(s)

| Method | Risks | User/Oper. | Environment | Device Mat'ls. | Patient |
|---|---|---|---|---|---|
| HPGP | Hazardous Residuals | Very Low | None | Low | None |
| | High Temperatures | Low | Low | Low | N/A |
| | Cycle Times | Short | N/A | Low | N/A |
| | Validation Time | 8-10wks. | N/A | N/A | N/A |
| | Validation Cost | $25k-$35k | N/A | High | N/A |
| EtO Gas | Hazardous Residuals | High | High | Med | High |
| | High Temperatures | Low | Low | Low | Low |
| | Cycle Times | Long | N/A | Med/Long | N/A |
| | Validation Time | 12-16wks. | N/A | N/A | N/A |
| | Validation Cost | $50k-$70k | N/A | High | N/A |

# Comparative Benefits HPGP vs. EtO, Under An Established Sterilization Method…

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# Literature on Comparative Processing Time[2]

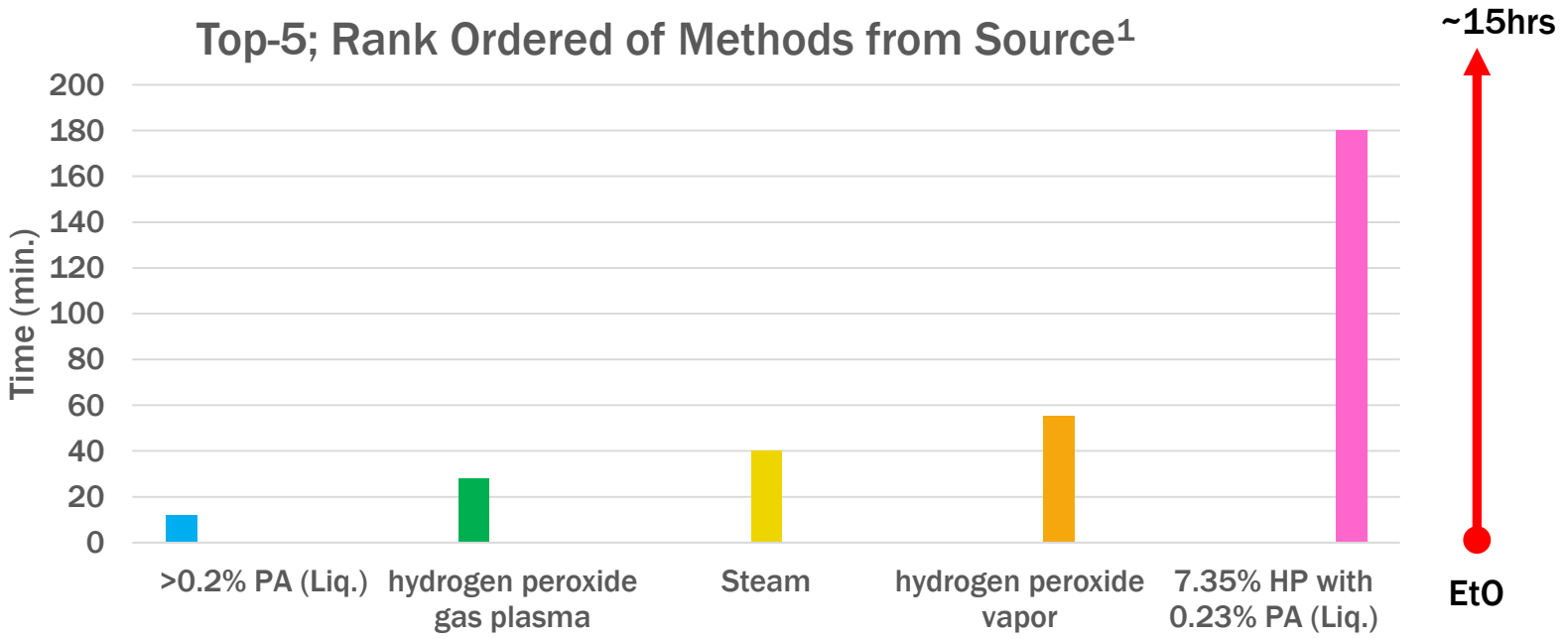





**Table 1**
Methods for disinfection and sterilization of patient care items and environmental surfaces*

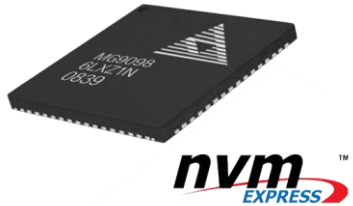
| Process | Level of microbial inactivation | Method | Examples (with processing times) | Health care application (examples) |
|---|---|---|---|---|
| Sterilization | Destroys all microorganisms, including bacterial spores | High temperature<br>Low temperature<br>Liquid immersion | Steam (~40 min), dry heat (1-6 hr depending on temperature)<br>Ethylene oxide gas (~15 hr), hydrogen peroxide gas plasma (28-52 min), ozone (~4 hr), hydrogen peroxide vapor (55 min)<br>Chemical sterilants†: >2% glut (~10 hr); 1.12% glut with 1.93% phenol (12 hr); 7.35% HP with 0.23% PA (3 hr); 8.3% HP with 7.0% PA (5 hr); 7.5% HP (6 hr); 1.0% HP with 0.08% PA (8 hr); ≥0.2% PA (12 min at 50°C-56°C) | Heat-tolerant critical (surgical instruments) and semicritical patient care items<br>Heat-sensitive critical and semicritical patient care items<br>Heat-sensitive critical and semicritical patient care items that can be immersed |

1. Disinfection and sterilization: An overview, William A. Rutala PhD, MPHa,b,*, David J. Weber MD, MPH, American Journal of Infection Control 41 (2013) S2-S5.
2. For Health-Care industry.

# HPGP Usage Today

- More than 20,000 sterilizer installed and operating world wide in Health Care facilities
- In the Industrial setting used in :
  - Orthopedic
  - Intra Ocular Lenses, IOL
  - Pre-Filled Syringes
  - Facial Implants
  - Laser Instruments
  - Neuro Stimulator, Pace Maker
  - Ablation Devices
  - Life Science, Packaging
  - Electronics, transponder with batteries
  - Cochlear Implant
  - Umbilical Clamps
  - GMP lab instrumentation

# Key Advantages of $H_2O_2$ Gas Plasma



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**Less harsh than other forms of sterilization**

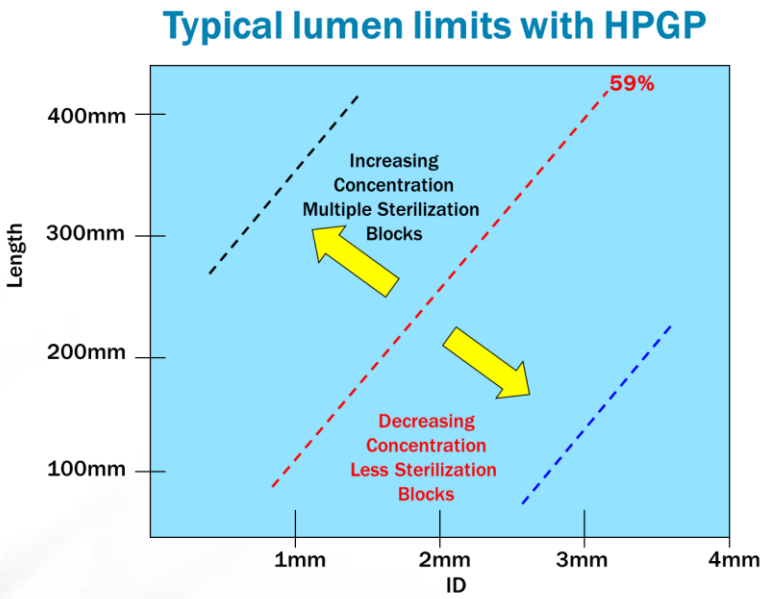
- **Non-Volatile Memory, electronics friendly**
  - Enables “Smart” / “Calibratable” Disposables;
  - Either you pay for hardened electronics OR
  - Use a compatible sterilization technology
- **Low-temperature, Low humidity process**
- **Li-Ion battery compatibility**
  - Enables “wireless” hand-held battery operated devices.
- **Pre-filled syringe and ampule compatible**
  (non-penetrating of enclosure walls & stopper)
- **UHMW Polymer Device Compatibility**

# Device Types That Are Amenable To $H_2O_2$ Sterilization

- Potential for software driven electromedical devices with:
  - Calibration at connection
  - Auto-ID, Startup Programming for disposables
  - Self-Powered rechargeable / disposable battery operated types
- Future Sterilization Applications:
  - Additively manufactured custom devices (3-D printed, DMLS, FDM, SLS)
- Eagle Medical recommends for instances where customers have any questions regarding residuals of post-sterilized devices, using the Nelson toxicology specialists for complete analysis.

# Some Limitations of the HPGP Process

- NOT Compatible with:
  - **Liquids**
  - **Powders**
  - **Cellulosic materials**
  - **Long-lumens**
    **(~0.25m or longer, no dead-ends)**




# Devices Compatibility

| Most Compatible | | Least Compatible |
|---|---|---|
| Orthopedic Implants (UHMWPE and Metals) | Drug Delivery Systems | Long Catheters, Venous and arterial |
| Pre-filled syringes and containers | Bone Screws (PLA) | Bone Allograft (natural) |
| IOL(Silicone, PMMA) | IOL (Acrylics) | Custom IV sets |
| Biopsy Devices | Mechanical heart valves | Collagen |
| Neuro Stimulator | Arthroscopic devices | Aortic Stents |
| Electronics, Batteries, Cables | Hydrogels (dehydrated) | Filters |
| Electro Physiology Catheters | | IV catheters |
| Soft Tissue Patches (synthetic, PP, PTFE) | | Bioabsorbable Polymer |
| Fiber Optics Lasers | | |
| Doppler Probes | | |
| Spinal Fixation Devices | | |
| Endoscopic instruments | | |
| Silicone Implants | | |

# Material Compatibility

| Most Compatible | | Least Compatible |
|---|---|---|
| *PLASTIC and ELASTOMERTER* | | *PLASTIC and ELASTOMERTER/other* |
| UHMWPE/HDPE/LDPE/PE | Polymethylmethacrylate (PMMA) | Cellulosic (Cotton/linen/wood products) |
| Polypropylene (PP) | Polyacetal | Protein (wool/silk/human skin) |
| Silicone, Medical Grade | Polylactic acid (PLA) | But acrylates |
| Polytetrafluoroethylene (PTFE, Teflon) | Acrylic/Acrylic adhesives | Collagen (depending on application) |
| Thermoplastic elastomer (TPE/Hytrel) | Polyurethane | Bioabsorbable polymer (Other than PLA, Polyglycolide PGA |
| Polyvinylchloride (PVC) | Sintered Glass (>Surface Area) | Natural Rubber (neoprene, santoprene) |
| Polycarbonate (PC) | Polyesters | Copper Large quantities) |
| Polysulfide (PSF) | Nylons | Brass (large quantities) |
| Polyethylene terephthalate glycol copolymer (PETG) | Hydrogels (dehydrated) | |
| Polystyrene (PS) | Carbon Fibr resin | |
| Polyetherether Ketone (PEEK) | Collagen (hemostat sponges) | |
| Polyetherimide | | |
| ABS | | |
| Butyl Rubber | | |

# Material Compatibility (cont.)

| Most Compatible |
| --- |
| ***Adhesives*** |
| Epoxies (2-Part) |
| UV Curable Acrylics and Urethanes |
| Cyanoacrylates |
| ***Metals/Non-Metals*** |
| Ceramics |
| Glass |
| Stainless Steel (303,304,316) |
| Aluminum |
| Cobalt Chrome |
| Titanium |

# A Brief Survey of HPGP Materials & Residuals

- Materials Where Residuals are Typically NOT an Issue:
  - Polyethylene
  - Polypropylene
  - UHMW – PE
  - UHMW – PP
  - Stainless Steels (303, 304, 316, etc.)
  - Titanium and Ti-Alloys
  - ABS, ABS-Alloys (Polycarbonate)
  - Polycarbonate
  - LCPs
  - Ceramics
  - PEEK

- Materials Where Residuals *May* Need Careful Attention[1]:
  - Polystyrene,
  - Polyurethane
  - Poly(methylmethacrylate) (PMMA)
  - Poly(2-hydroxyethylmethacrylate) (HEMA), fluorosilicone acrylate
  - Silicone
  - Mixtures of polyurethane and silicone

1. demonstrated strong cytotoxicity after standard aeration; Petr Kačer, Jiří Švrček, Kamila Syslová, Jiří Václavík, Dušan Pavlík, Jaroslav Červený and Marek Kuzma (2012), Vapor Phase Hydrogen Peroxide – Method for Decontamination of Surfaces and Working Areas from Organic Pollutants, Organic Pollutants Ten Years After the Stockholm Convention - Environmental and Analytical Update, Dr. Tomasz Puzyn (Ed.), ISBN: 978-953-307-917-2, InTech.

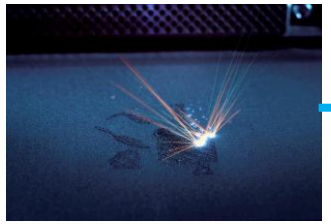
# New Frontiers in Device Mfg. & Sterilization

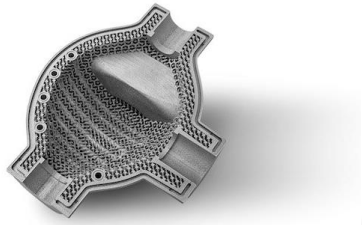
**Now esoteric and one-of-a-kind designs are viable**

- For animal or human trials
- To meet this need materials now have an $H_2O_2$ option.

**Do you Have Issues with:**

- Blended polymers?
- 3-D printed parts in metal ceramic or polymer?
- Adhesives with irradiation interactions or embrittlement?
- Irradiation color shifting?
- These effects are NOT likely as part of an $H_2O_2$ approach at SAL $10^{-6}$ sterility assurance.





- 3D-Printed DMLS / SLM Parts

# The Business case for Hydrogen Peroxide Gas Plasma

- Cost Effectiveness Vs. Ethylene Oxide & E-Beam/$\gamma$

| Sterilization Category | HPGP[5] | EtO[5] | E-Beam / Gamma[6] |
|---|---|---|---|
| Cost / Load ($ U.S.) | $800 | $1,000 | $1,200 |
| Cost to Validate ($U.S.) | $30,000 | $60,000 | $15,000 |
| Sterility Maint. Costs ($U.S.) | $5,000 | $8,000 | $24,000 |
| Net Difference vs. HPGP[1] | N/A | $33,200 | $4,400 |
| Typ. Load Turnaround Time (days) | 2-3 | 7-10 | 3-5 |

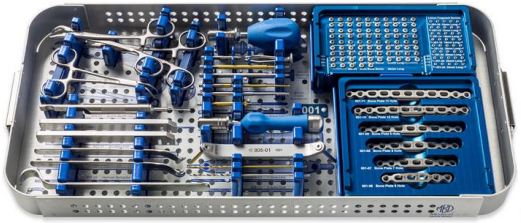
Notes:

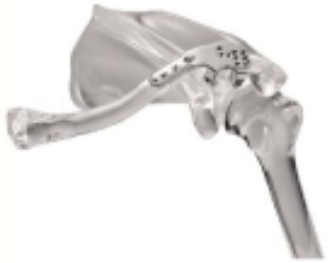
1. Year-1 analysis, your costs may vary, dependent on the total annual throughput and density of tote packaging.
2. $H_2O_2$ Approx. $600 - $800/cycle, (assumes 100% density of an ~1$m^3$ chamber)
3. Irradiation “lot-charge” / cycle $1,200min., (assumes a 1$m^3$ tote)
4. EtO “lot-charge” / cycle, $800 - $1,200 (assumption is a 1$m^3$ tote using a 3M type machine)
5. HPGP & EtO Sterility maintenance costs are annual.
6. Irradiation Sterility maintenance costs are quarterly.

# The Logical Choice for Today's Complex Devices

- ✓ Comparable cost-effectiveness with most current packaging solutions
- ✓ Compatible with EtO based materials & designs
- ✓ Turnkey transition by outsourced provider to HPGP technology
  - ✓ Governed by ISO14937
- ✓ FDA has recognized $H_2O_2$ gas plasma as a "Established" sterilization method.
- ✓ Provides low heat sterility cycles with no off-gassing concerns present with EtO.





# When Speed to Market Matters Most… NPI

- New Product Introduction (NPI) Accelerator
  - Shortens the Sterilization Validation Timeline
    - (Speed to Submission)
  - Shortens the Clinical Trial turn-time for product delivery
    - (Speed through Clinicals)
  - Competitive Costs for Multiple Short-Run “Batch” Deliveries of Product
    - (Speed through Iterations)
- Provides an Economical Sterilization Means in Scale-up

# Cycle Development (OQ)

- Cycle Development is specific to device and packaging combination
- BIs are set in the most difficult to inactivate location and throughout the load
- Device load configuration and packaging are fixed, identified and documented Packaging materials suitable for EtO are also suitable for HPGP
- All BIs must be inactivated under half cycle condition
- BIs usage must be the most resistant organism for the sterilization process
- Temperature profiling for homogeneous distribution
- Min Max pressure studies for max and min load conditions.

# Against Most Resistant Organism

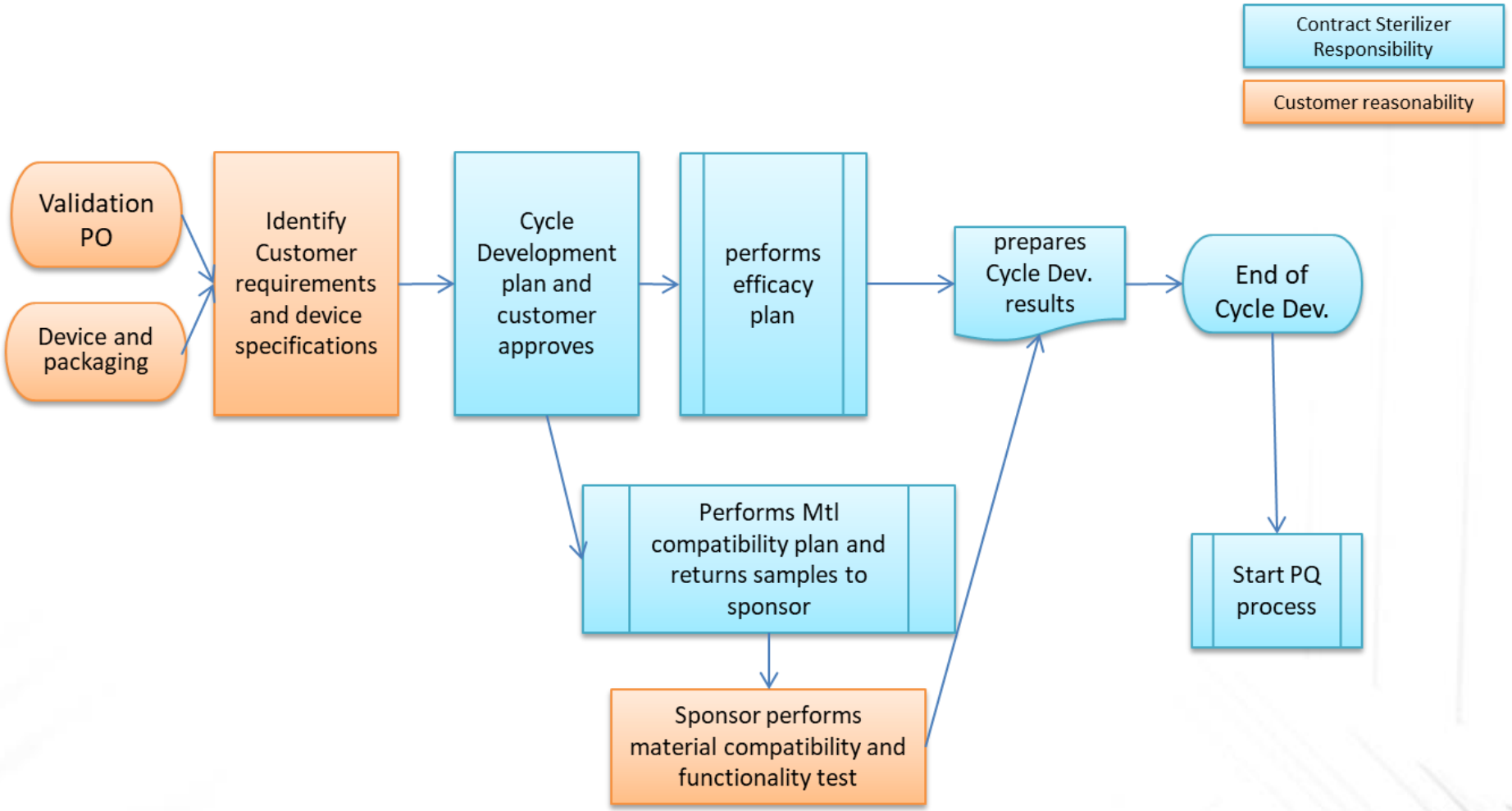
- Geobacillus stearothermophilus has been determined to be the most resistant organism to sterilization by the STERRAD® System (3, 4). This was demonstrated during the early development of the STERRAD System. Several independent researchers have independently demonstrated the resistance of G. stearothermophilus to hydrogen peroxide-based sterilization. Block's textbook on sterilization and disinfection lists B. stearothermophilus as the most resistant organism to sterilization by vapor phase hydrogen peroxide (2). The study by Kokubo et al (1) demonstrated that environmental isolates of several Bacillus species were much less resistant to sterilization by vapor phase hydrogen peroxide than commercially-prepared B. stearothermophilus spores. The European Pharmacopeaia lists B. stearothermophilus as the organism most resistant to sterilization by hydrogen peroxide. Work performed in Dr. Irving Pflug's laboratory demonstrates that vaporphase hydrogen peroxide is an effective means of destroying B. stearothermophilus spores. The D-value of B. stearothermophilus to hydrogen peroxide vapor at 6 mg/L is 1-2 seconds. When the concentration is cut in half (3 mg/L) the D-value is 12-15 seconds. Work performed by ASP demonstrates that the D-value in a STERRAD 100 System sized chamber at 1.5 mg H2O2 /L is 2-3 minutes. All these determinations were performed on non-absorptive substrates such as glass fiber or stainless steel.

**Ref: STERRAD® 200 Sterilizer Technical Dossier[1]**

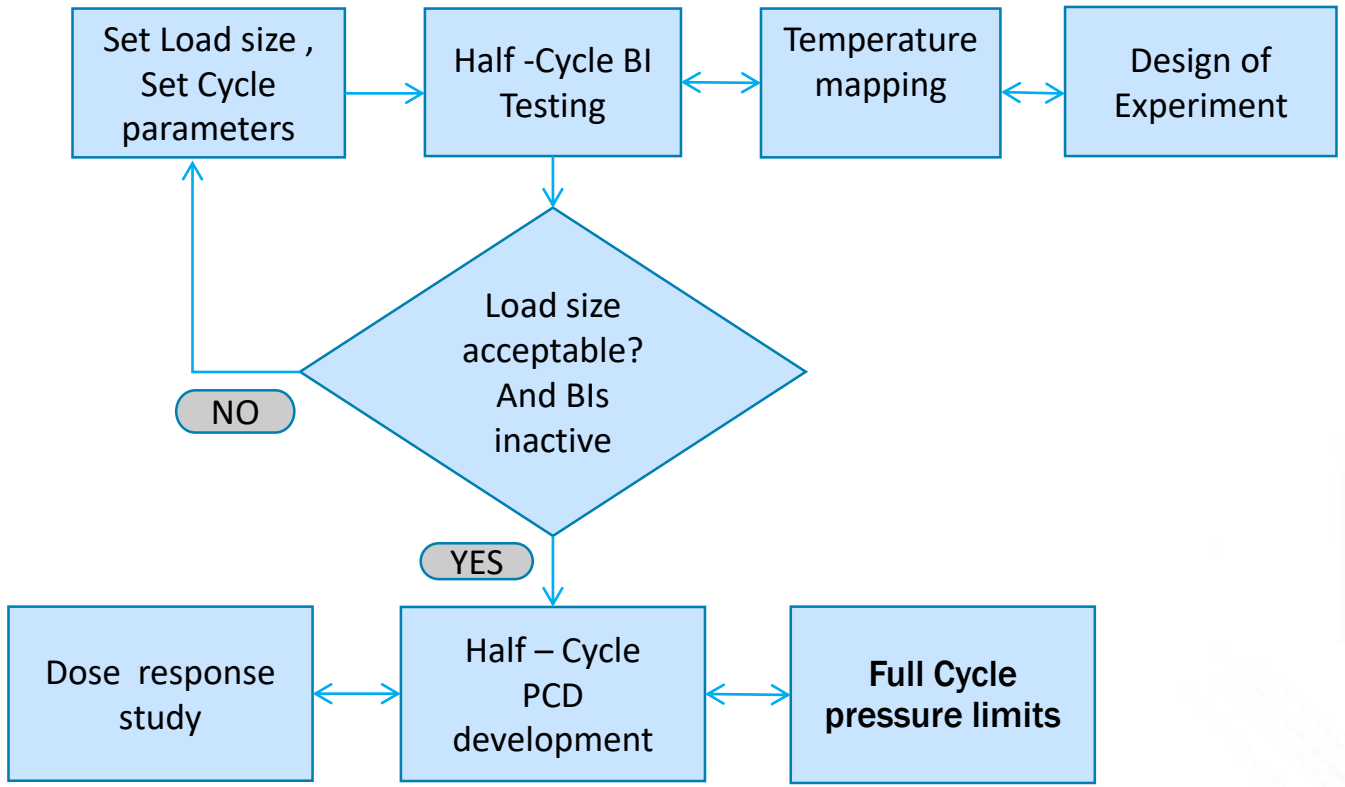
Notes:

1. STERRAD is a registered trademark of Advanced Sterilization Products.

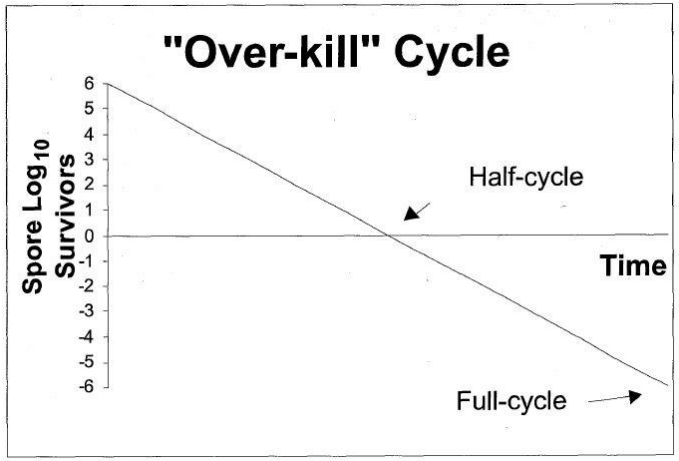
# Cycle Development Flow-Chart



# Cycle Development Process



# PQ Sterilization Validation

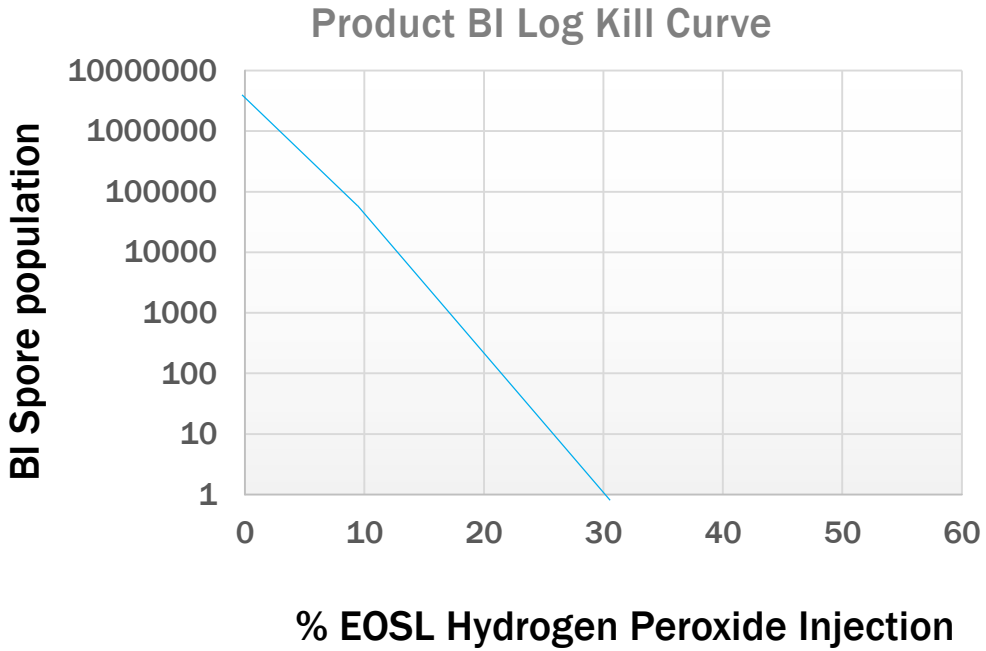



## Inactivation Kinetics in HPGP

### Test Conditions

- **STERRAD 200 Sterilizer**

1. Maximum Pkgd. Product Load
2. Half-cycle Conditions
3. Fractional Injections of Peroxide e.g. 10% to 70% of $H_2O_2$
4. Process Challenge Device gets qualified for use.
5. Three (3) reg. ½-Cycle with PCDs
6. Three (3) Full cycles with Temp-map and PCDs



# Where Are These Sterilization Services?

EagleMedical
PACKAGING, STERILIZATION, INC.

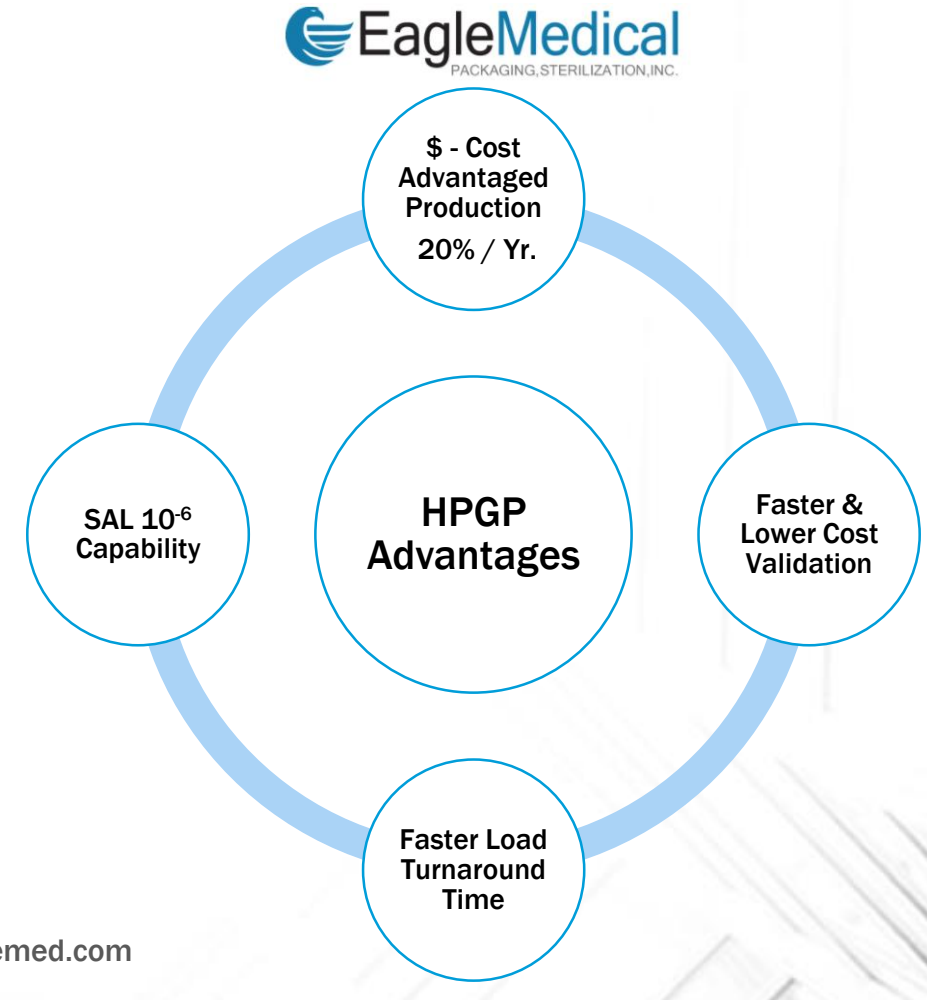
| HPGP, Validated Running Units | HPGP, Pipeline of Units in FAT/PV | Cleanroom Capacity |
|---|---|---|
| 7 – 200 GMP Sterilizers | 6 – 200 GMP Sterilizers | 2,000 $Ft^2$+ (Class-7) |

- Additional HPGP 200 Sterilizers available for GMP capacity expansion.

- "Last Operation" Processes to Med-Device Manufacturers
  - Cleaning / Disinfection
  - Kitting / Assembly / Primary Packaging
  - Sterilization
  - Secondary packaging operations
  - Fulfillment
  - ISO13485 & 14937 Certified
  - FDA Registered

# In Summary, HPGP Should Be At The Top of Your List For Sterilization Methods

- Reasons to look to HPGP as your FIRST choice in Sterilization
  - Sterility Assurance Capability
    - FDA Accepted “Established” Method
  - Where Speed/Time to Market are Paramount
    - NPI
    - Re-Validation / Introduction(s)
    - Clinicals
  - Where Delicate Device Construction or Electronics are Needed
    - Li-Ion Batteries, NVM, Etc.



# Thank you for Listening