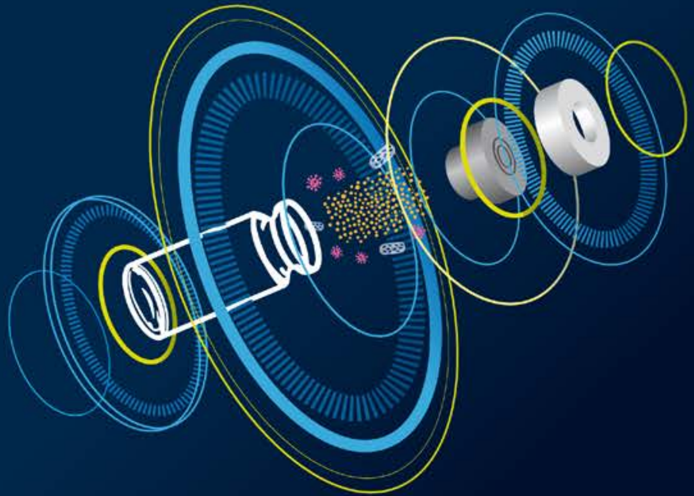
Alternative Sterilization Techniques for Elastomeric Components for Primary Packaging

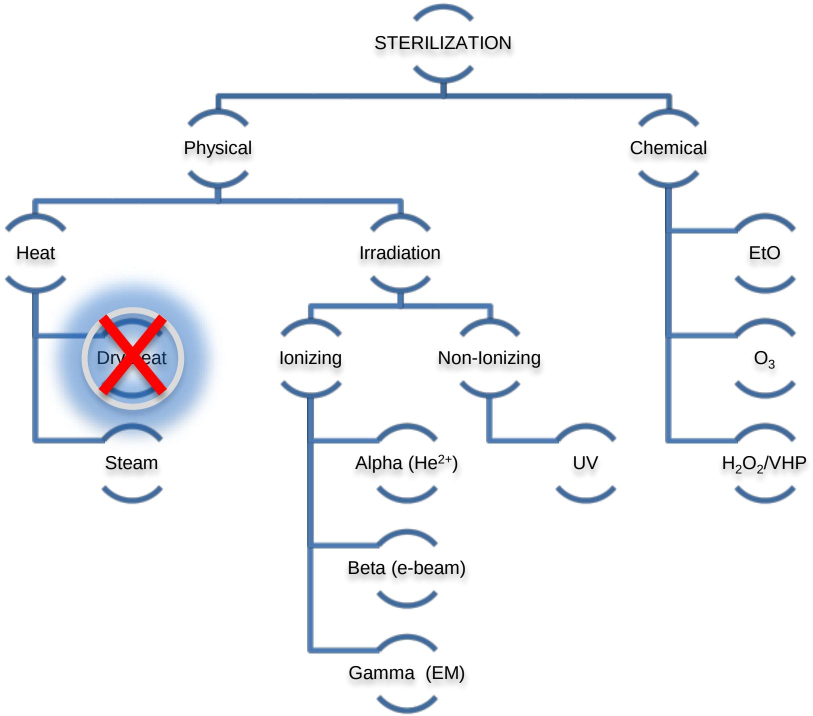


Bram Jongen,
Datwyler
March 20, 2019, Venice/IT

Topics for Today

- Overview most popular sterilization techniques for elastomers currently used in the industry
- Impact of X-ray sterilization on physical and functional properties compared to gamma irradiation
- Impact of ClO_2 on chemical and functional properties of different rubber formulations

Overview sterilization techniques for elastomers



Dry heat:

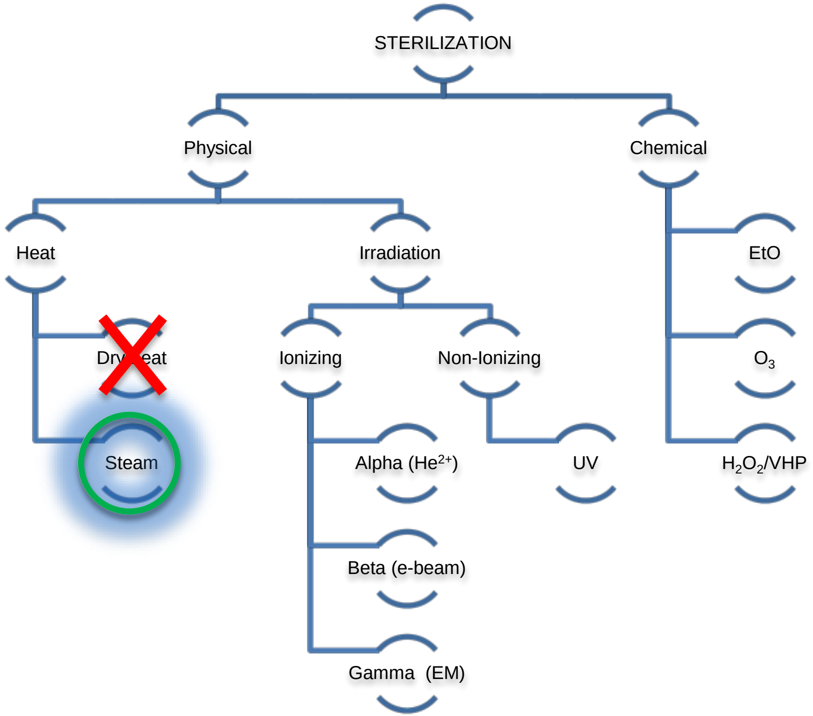
Typical 2h @ 160°C or 6-9min @ 190°C

Rubber:

(-) Rubber further cures at these temperatures

→ chemical and physical properties are negatively affected

Overview sterilization techniques for elastomers



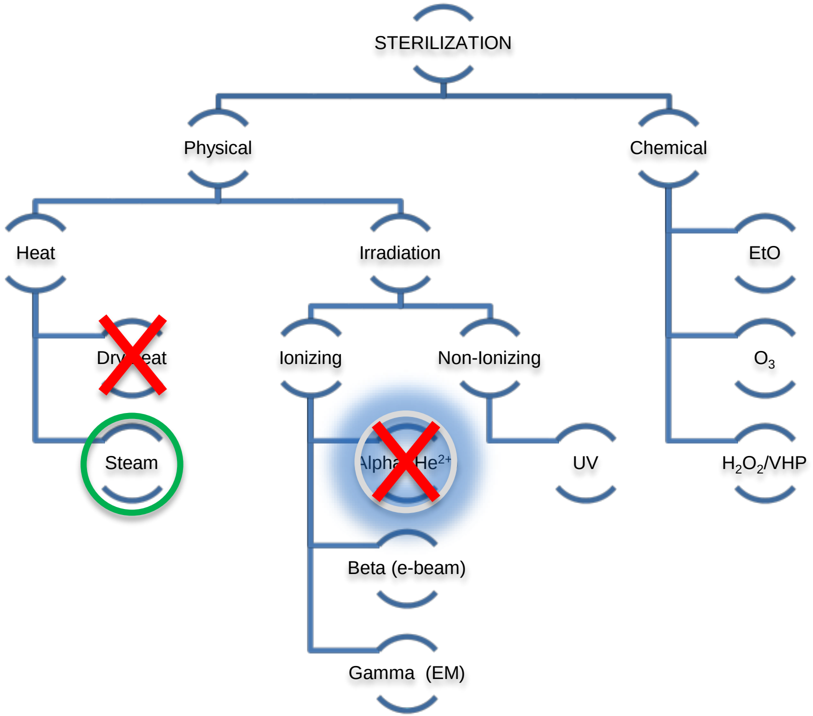
Steam:

"autoclavation" - Typical 30min @ 121°C
Material to sterilize must be physically accessible to steam
Well-known and accepted method

Rubber:

(+) No measurable effect on chemical/physical properties
(-) Subsequent drying step may affect rubber (~dry heat)
(-) Moisture content of rubber

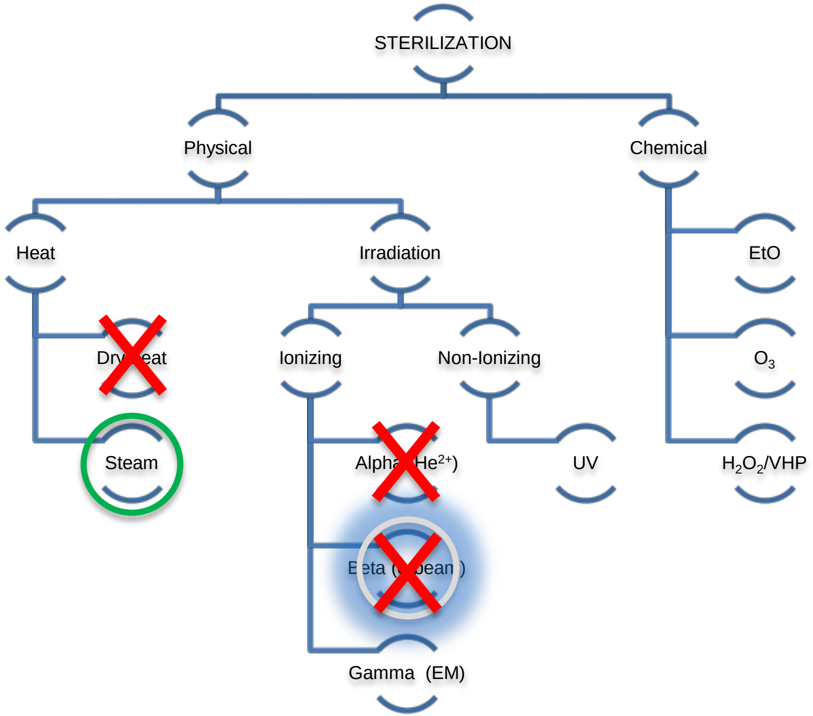
Overview sterilization techniques for elastomers



Alpha Irradiation:

Not suitable because of the very low penetration depth

Overview sterilization techniques for elastomers



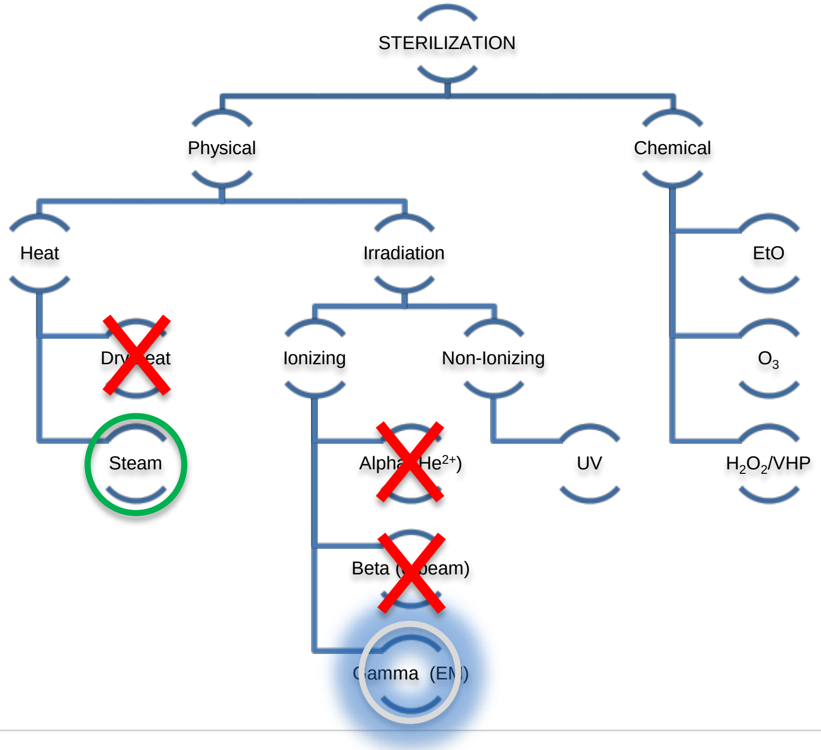
Beta Irradiation:

"e-beam" - intermediate penetrability

Only used for low density products, single product irradiation or bulk packing with low density (e.g. trays, empty bottles)

Bulk packaging of rubber closures is very dense (specific gravity : 1.2-1.4 g/cm³), so not suitable for bulk sterilization

Overview sterilization techniques for elastomers



Gamma Irradiation:

"ElectroMagnetic waves" – high penetrability

Can be used for (dense) bulk sterilisation, even full pallet configurations

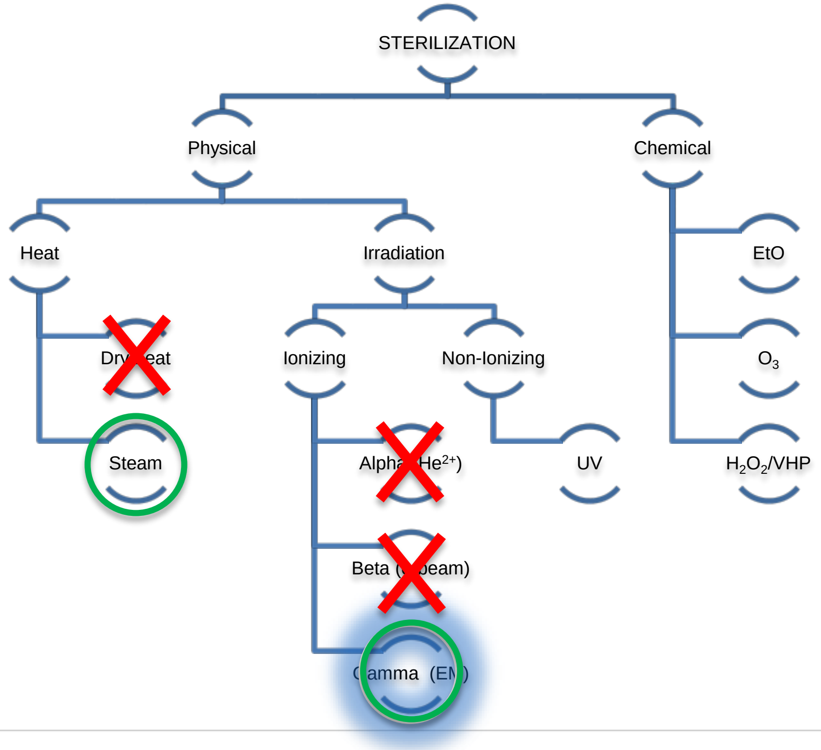
Increased popularity :

- Effective, reliable, clean
- Cost effective
- No residuals, no radioactivity, low temperature impact

ISO 11137 is solid guidance

Effect of irradiation is cumulative
Irradiation dose gradient!

Overview sterilization techniques for elastomers



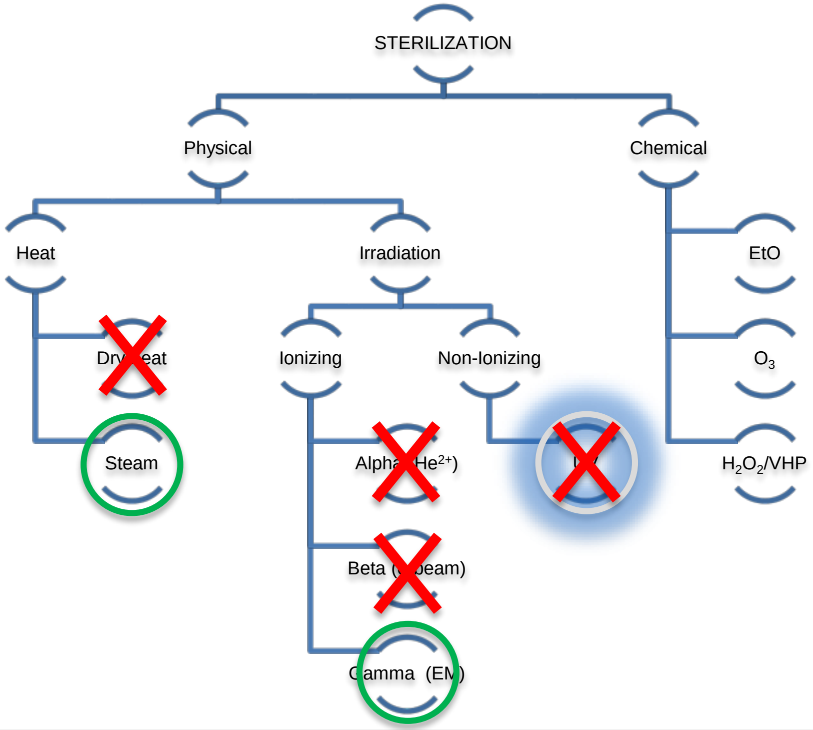
Gamma Irradiation:

"ElectroMagnetic waves" – high penetrability

Rubber:

- Chemical properties are hardly changed
- Physical/Functional properties may alter, depending on compound choice
    - Fragmentation
    - Stickiness
    - Hardness
    - Gliding behavior

Overview sterilization techniques for elastomers

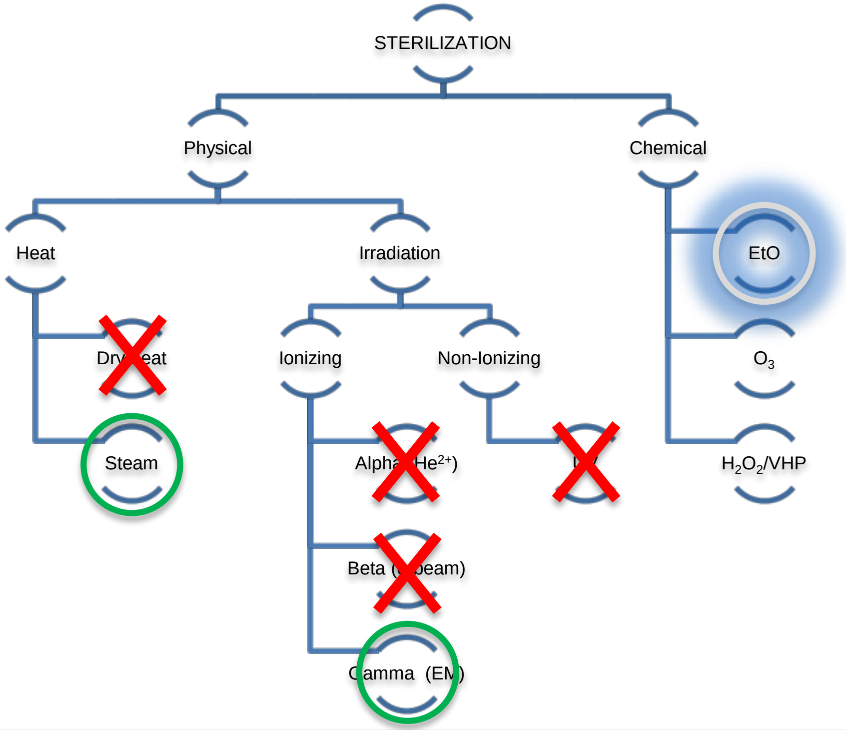


UV:

Not suitable for bulk sterilization due to very limited penetrability.

May be used to sterilize surfaces.

Overview sterilization techniques for elastomers



Ethylene Oxide:

Ethylene oxide is widely used and sterilizes around 50% of all disposable medical devices!

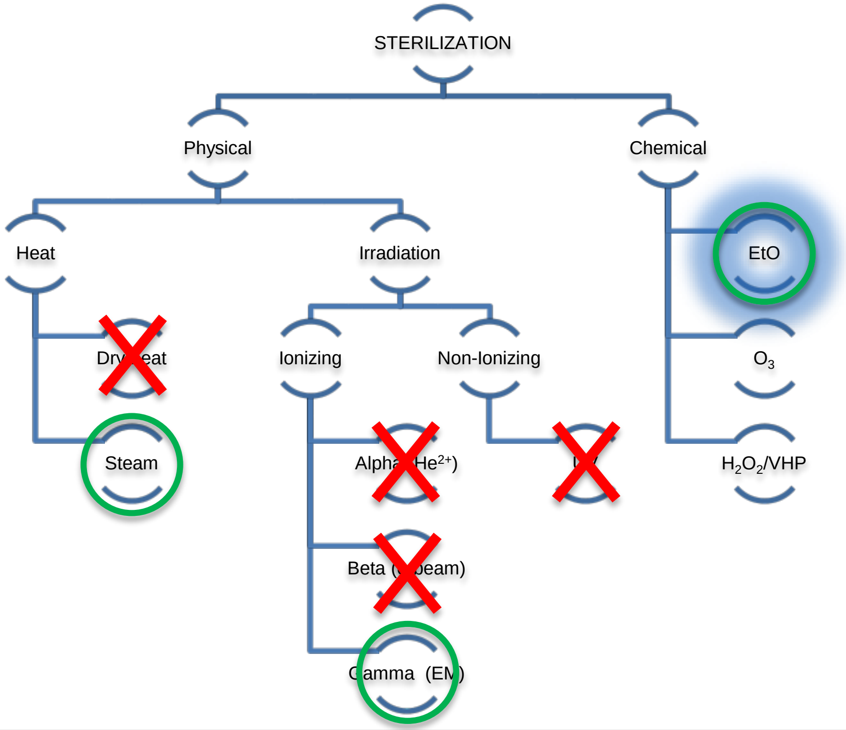
Effectiveness depends on many variables (p,t, gas conc., T, RH) → monitoring is complex

Requires time for aeration after sterilization to remove toxic residues (Ethylene ChloroHydrin, Ethylene Glycol)

Penetrates through paper, cloth, and some thin plastic films

Sterilization of fully packaged goods (e.g. blisters)

Overview sterilization techniques for elastomers



Ethylene Oxide:

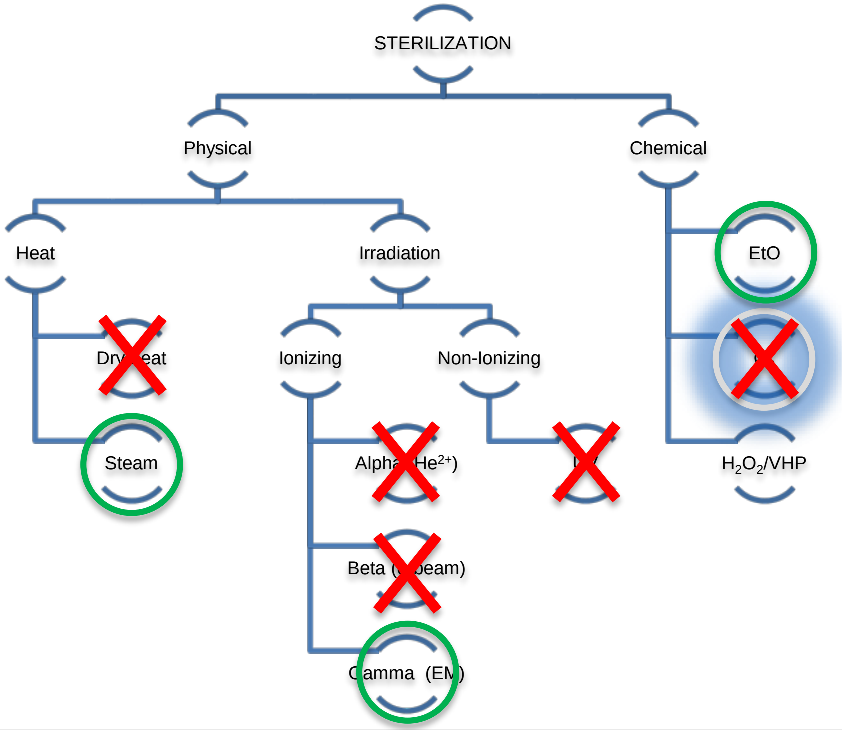
Rubber:

- Not used anymore for bulk sterilisation
- Absorption of EtO (EtO-residues) in rubber Extra precautions needed.

- Used in specific applications (w.glass):
  - Disposable syringes
  - Prefillable syringes (Needle Shields/Tip Caps)

  → dedicated rubber types with high EtO-permeability

Overview sterilization techniques for elastomers

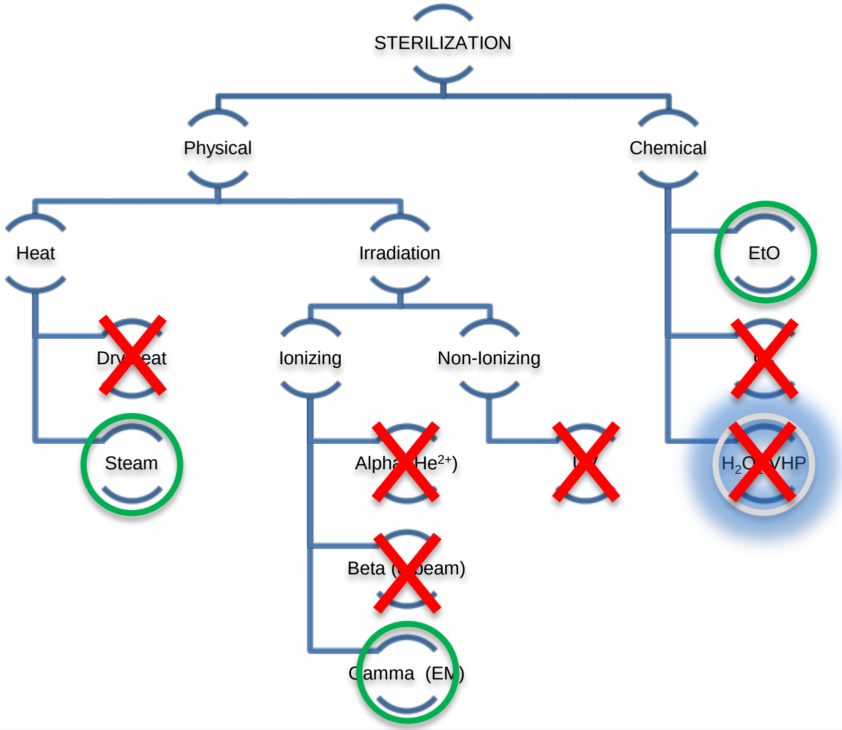


Ozone:

Very reactive, unstable and toxic
Strong oxidizing power

Rubber:
Oxidation may occur

Overview sterilization techniques for elastomers



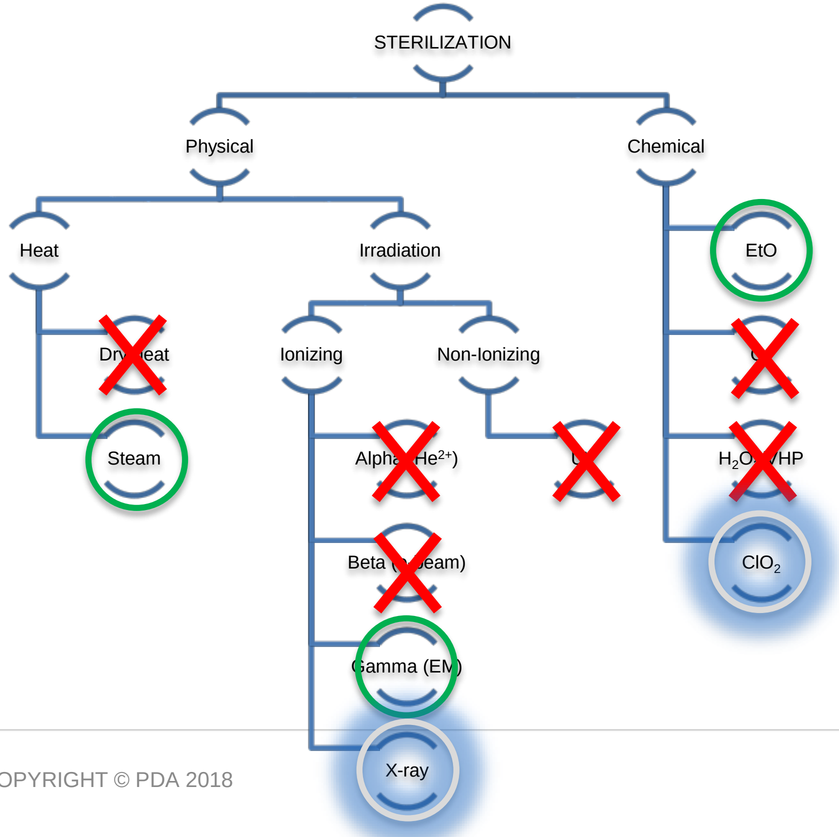
H_2O_2/VHP:

Strong oxidizing power
Material compatibility, a lower capability for penetration and operator health risks

Used in Cleanroom or to sterilize surfaces

Rubber:
No suitable for bulk sterilization

Overview sterilization techniques for elastomers



X-Ray:

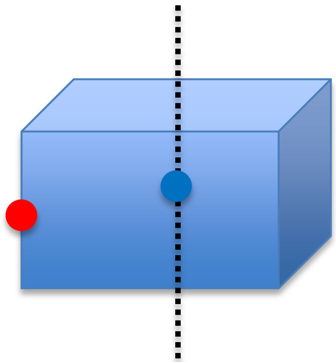
Electromagnetic Waves
Very similar to Gamma
FDA recognized
No need of ^{60}Co or ^{137}Cs
Simple on/off machine
Photons generated via electricity
~Alternative to gamma

ClO_2:

Similar to EtO (oxidizing effect)
No toxic side residues
FDA recognized
~Alternative to EtO

X-Ray Sterilization

- Advantages:
  - Penetration slighter better than gamma rays
    - Easy full pallet sterilization
  - Dose Uniformity Ratio (DUR)
    - Coldest and Hottest spot closer together → less overdose needed
  - Short exposure time
    - Less adverse effects on polymer
  - Processing flexibility
    - Incremental dosing: e.g. 10 passes of 2.5kGy = 25kGy
  - On/Off equipment
    - Works on electricity, not with radioactive material

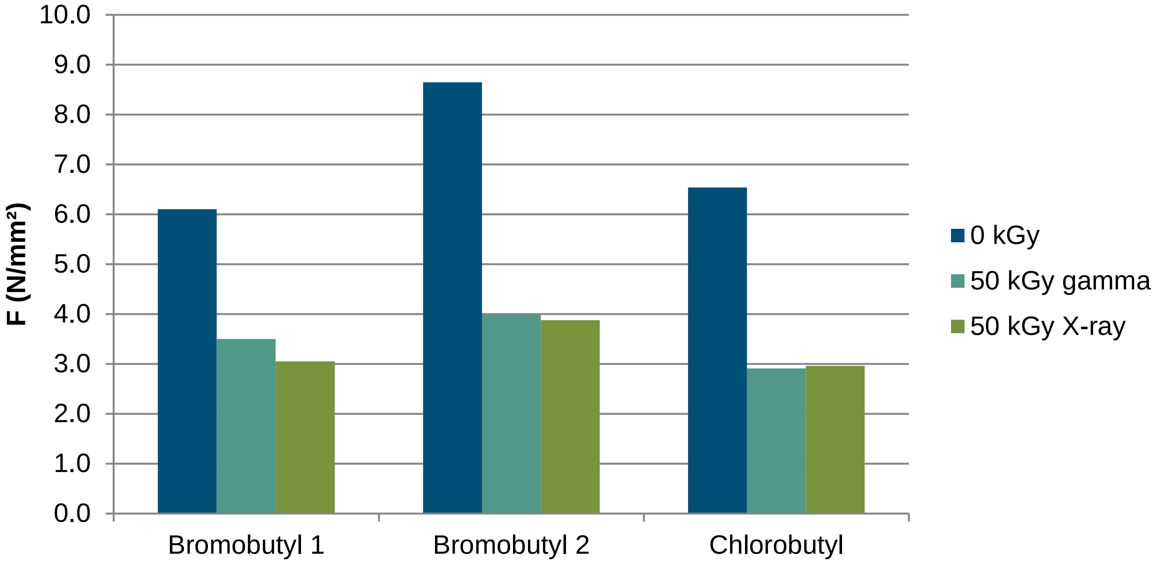


X-Ray Sterilization

- X-Ray sterilization as alternative to Gamma sterilization : how does it affect rubber?
- The following slides show comparative data for selected physical/functional properties that are known to be influenced
  - Tensile strength
  - Hardness
  - Fragmentation
  - Break Loose and Gliding force

X-Ray Sterilization

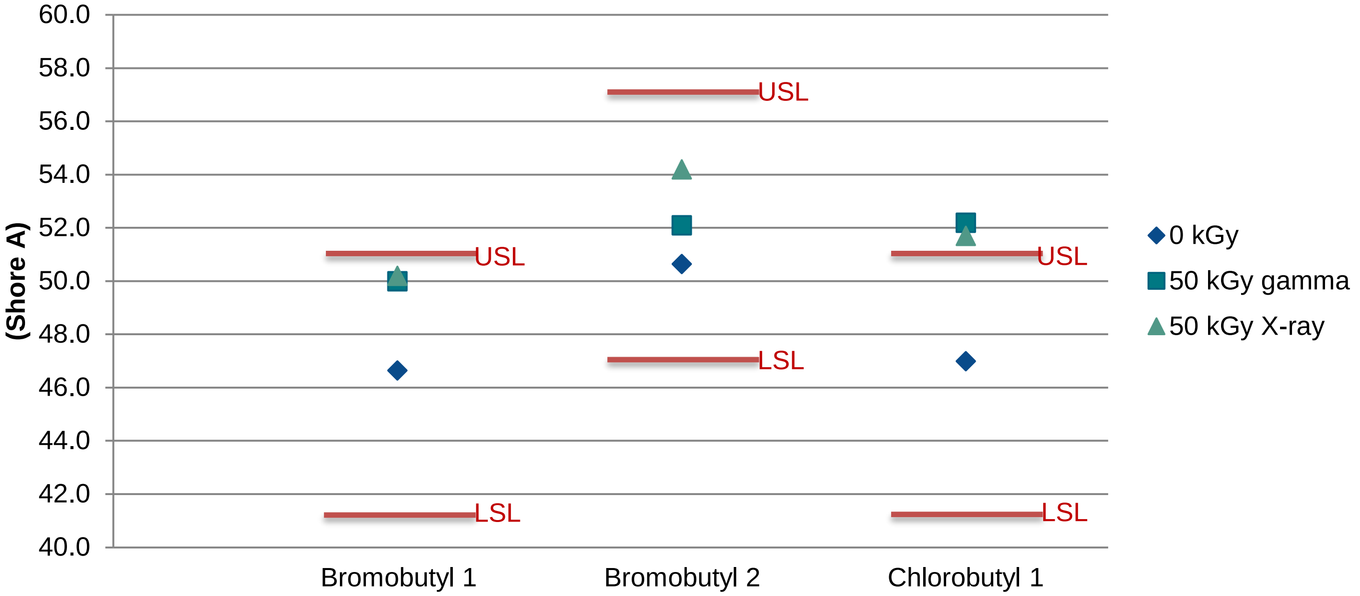
Tensile Strength



- Methodology :
  - 3 different rubber formulations
  - Sterilized X-ray and Gamma
  - Tensile strength measured on test pieces as per Internal method. 200mm/min, ISO 37 Dumb-bell 2

X-Ray Sterilization

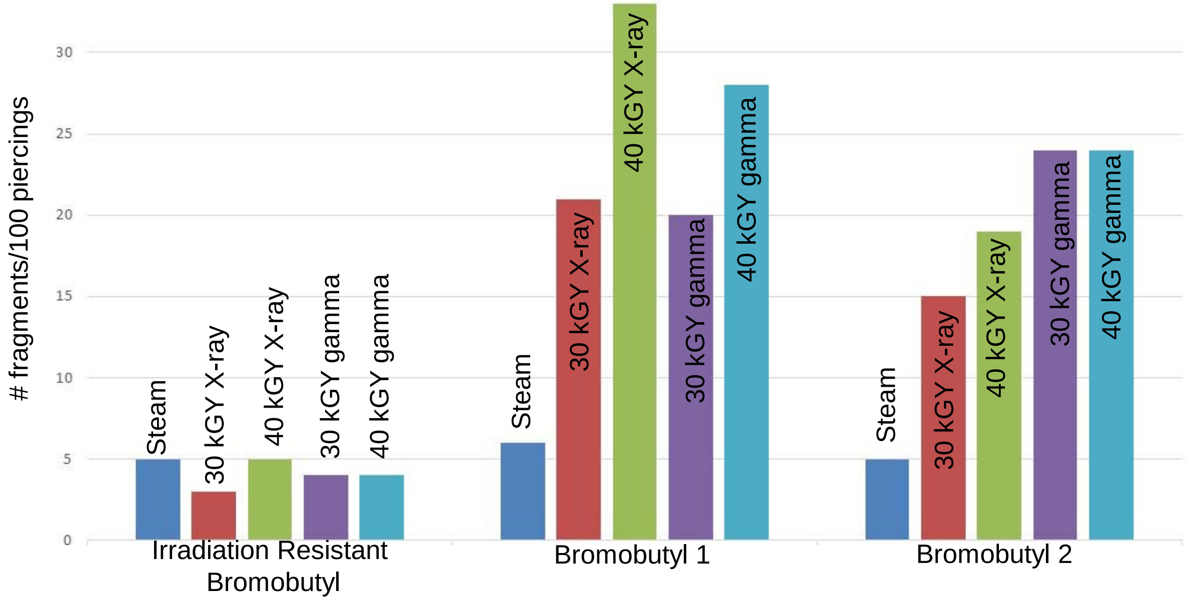
Hardness



- Methodology :
  - 3 different rubber formulations
  - Sterilized X-ray and Gamma
  - Hardness measured on test pieces as per ISO 7619-1

X-Ray Sterilization

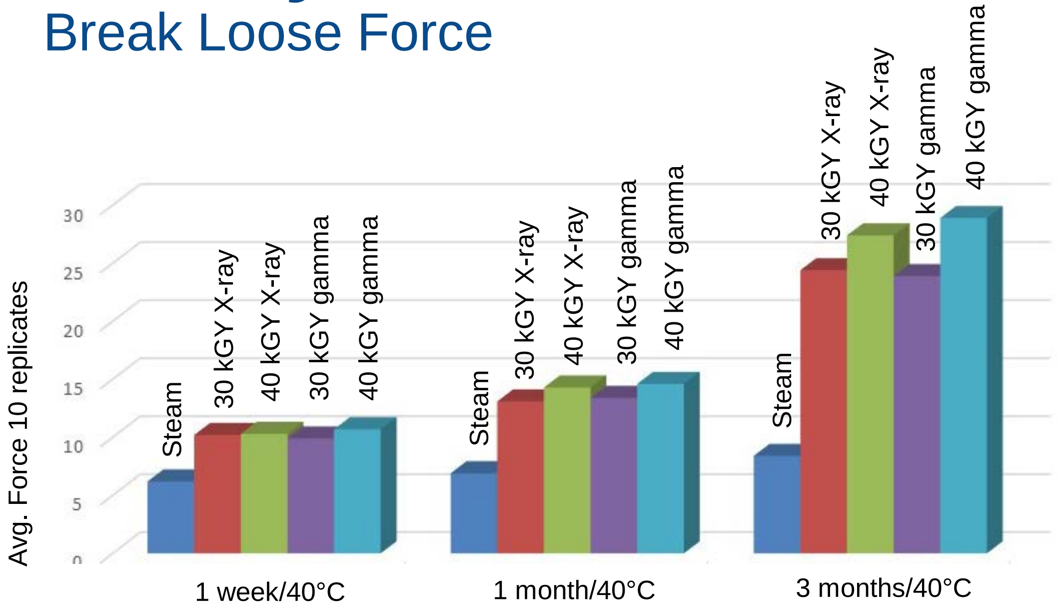
Fragmentation according Pharm.Jap.



- Methodology :
  - 3 different rubber formulations
  - Sterilized X-ray and Gamma
  - Fragmentation using 1.2mm (18G) needles, 5x per stopper, 20 stoppers in total

X-Ray Sterilization

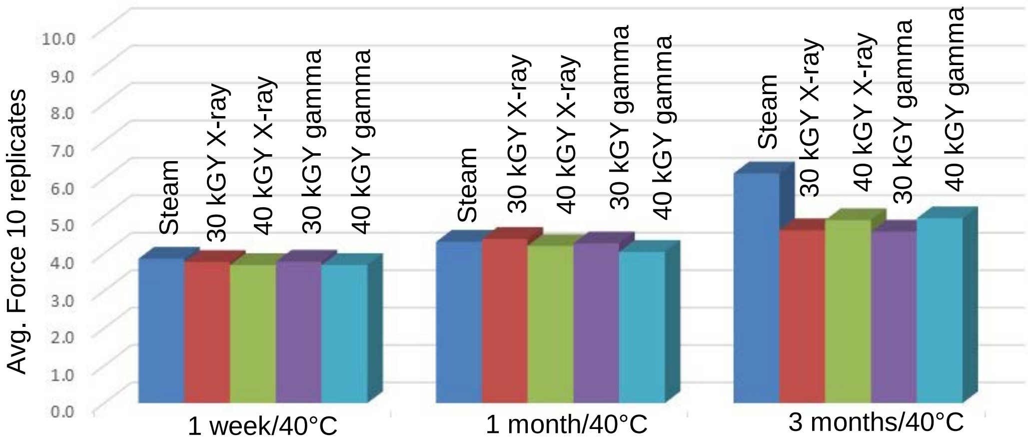
Break Loose Force



- Methodology :
  - Bromobutyl coated
  - Sterilized X-ray and Gamma
  - 1-3mL ISO design, water filled
  - Break Loose Force Tested on Zwick tensile bench

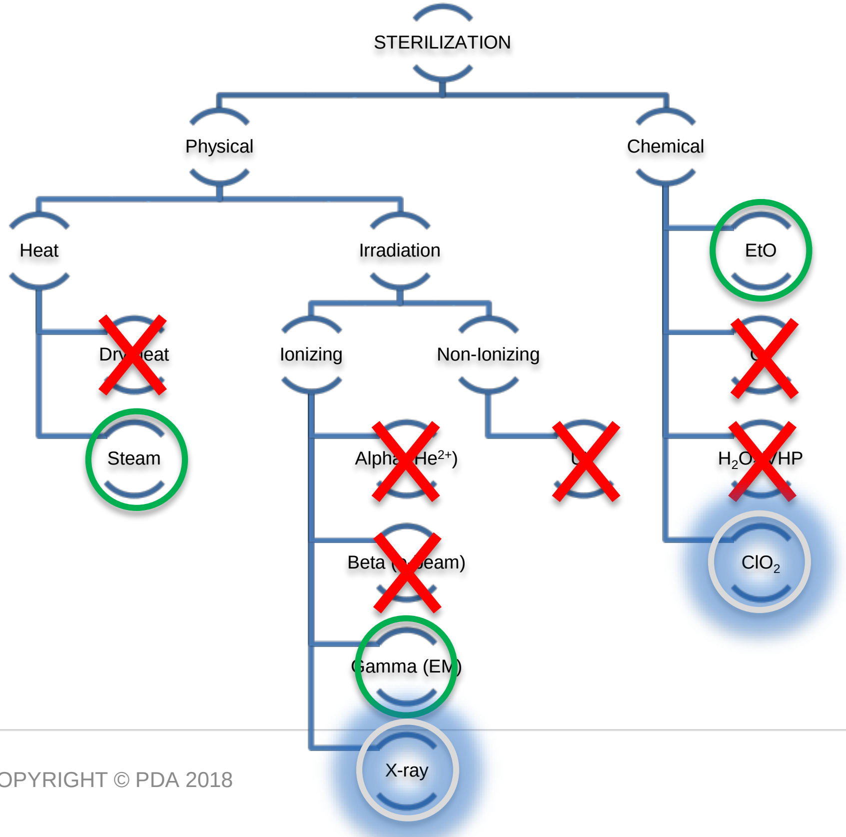
X-Ray Sterilization

Glide Force

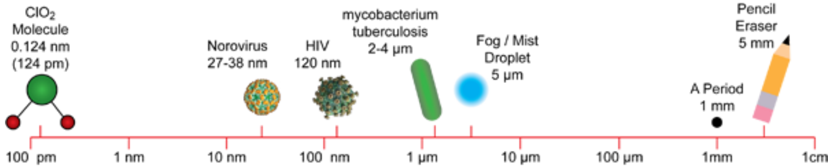


- Methodology :
  - Bromobutyl coated
  - Sterilized X-ray and Gamma
  - 1-3mL ISO design, water filled
  - Average Glide Force tested on Zwick tensile bench

Overview sterilization techniques for elastomers



ClO_2 Sterilization



Source: www.clordisys.com

- Sterilization mechanism : Oxidation and thus breaking up cells and inactivate them
- Advantages:
  - Good penetrability (through poreus surfaces, cracks and crevices and can even penetrate through organic matter) thanks to small molecular size
  - Gas, not a vapor → easier to control/develop and validate
  - No residual harmful chemicals

ClO_2 Sterilization

- ClO_2 as alternative to EtO sterilization : How does it affect rubber?
- The following slides show comparative data for selected chemical/functional properties that are known to be influenced:
  - Fragmentation – Resealability – Penetrability
  - Chemical cleanliness
  - WFI compatibility of rubber
  - Extractables study

ClO_2 Sterilization

Fragmentation – Resealability – Penetrability

Material	ClO_2 exposure (ppm-hrs)	# fragments /48 piercings ≤5 visible fragments*	# leaking /10 vials No leaks*	Piercing force (N) ≤10 N*
Needle Shield SBR	0	1	0	3.2
	720 (std dose)	3	0	3.3
	14400	3	0	3.7
Irradiation resistant Bromobutyl	0	0	0	3.6
	720	1	0	3.4
	3600	2	0	3.4
	14400	1	0	3.6
Irradiation resistant Bromobutyl COATED	0	2	0	3.0
	720	3	0	3.1
	3600	1	0	3.2
	14400	1	0	3.1

- Methodology :
  - 3 different rubber formulations
  - Sterilized with different ClO_2 doses
  - Tested as per USP <381>, Pharm.Eur. 3.2.9. – functional part

ClO_2 Sterilization

Chemical cleanliness - Needle Shield SBR

Needle Shield SBR	ClO_2 (ppm-hrs) /EtO	Turb. ≤ 6	Color	Alkal. ≤0.3	Abs. ≤0.2	Red. Subst. ≤3.0	Heavy metals ≤2	Zn ≤5.0	Amm ≤2	Res. Evap. ≤2.0	Vol. Sulph.
ClO_2	0	2.76	Pass	0.07	0.06	0.58	<2	0.11	<2	0.50	<0.02
	720 (std)	0.23	Pass	0.07	0.10	0.99	<2	0.61	<2	0.00	<0.02
	14400	0.04	Pass	0.32	0.34	3.35	<2	0.80	<2	1.00	<0.02
EtO	before	2.70	Pass	0.03	0.04	0.63	<2	0.39	<2	0.00	<0.02
	after	5.20	Pass	0.03	0.29	2.86	<2	0.53	<2	0.00	<0.02

- Methodology :
  - 3 different rubber formulations
  - Sterilized with different ClO_2 doses
  - Tested as per USP <381>, Pharm.Eur. 3.2.9. – chemical part
  - Compared with EtO resp. Gamma irradiated references

ClO_2 Sterilization

Chemical cleanliness - Irradiation resistant Bromobutyl

Irradiation resistant Bromobutyl	ClO_2 (ppm-hrs) / ɣ (kGy)	Turb. ≤ 6	Color	Alkal. ≤0.3	Abs. ≤0.2	Red. Subst. ≤3.0	Heavy metals ≤2	Zn ≤5.0	Amm ≤2	Res. Evap. ≤2.0	Vol. Sulph.
ClO_2	0	0.03	Pass	0.07	0.01	0.07	<2	0.02	<2	0.60	<0.02
	720	0.02	Pass	0.07	0.01	0.18	<2	0.02	<2	0.80	<0.02
	3600	0.01	Pass	0.07	0.03	0.20	<2	0.03	<2	0.20	<0.02
	14400	0.01	Pass	0.06	0.03	0.19	<2	0.03	<2	0.00	<0.02
ɣ-rad.	0	0.02	Pass	0.06	0.01	0.04	<2	0.01	<2	0.31	<0.02
	25	0.02	Pass	0.06	0.01	0.03	<2	0.01	<2	0.38	<0.02
	40	0.02	Pass	0.06	0.01	0.04	<2	0.01	<2	0.51	<0.02

- Methodology :
  - 3 different rubber formulations
  - Sterilized with different ClO_2 doses
  - Tested as per USP <381>, Pharm.Eur. 3.2.9. – chemical part
  - Compared with EtO resp. Gamma irradiated references

ClO_2 Sterilization

Chemical cleanliness - Irradiation resistant Bromobutyl COATED

Irradiation resistant Bromobutyl COATED	ClO_2 (ppm-hrs) / ɣ (kGy)	Turb. ≤ 6*	Color	Alkal. ≤0.3*	Abs. ≤0.2*	Red. Subst. ≤3.0*	Heavy metals ≤2*	Zn ≤5.0*	Amm ≤2*	Res. Evap. ≤2.0*	Vol. Sulph.
ClO_2	0	0.02	Pass	0.07	0.02	0.06	<2	0.01	<2	0.00	<0.02
	720	0.02	Pass	0.07	0.01	0.18	<2	0.01	<2	0.80	<0.02
	3600	0.01	Pass	0.07	0.02	0.02	<2	0.01	<2	0.00	<0.02
	14400	0.01	Pass	0.06	0.02	0.20	<2	0.00	<2	0.00	<0.02
ɣ-rad.	0	0.12	Pass	0.07	0.01	0.04	<2	0.01	<2	0.00	<0.02
	25	0.09	Pass	0.10	0.01	0.07	<2	0.01	<2	0.00	<0.02
	40	0.09	Pass	0.10	0.01	0.03	<2	0.01	<2	0.13	<0.02

- Methodology :
  - 3 different rubber formulations
  - Sterilized with different ClO_2 doses
  - Tested as per USP <381>, Pharm.Eur. 3.2.9. – chemical part
  - Compared with EtO resp. Gamma irradiated references

ClO_2 Sterilization

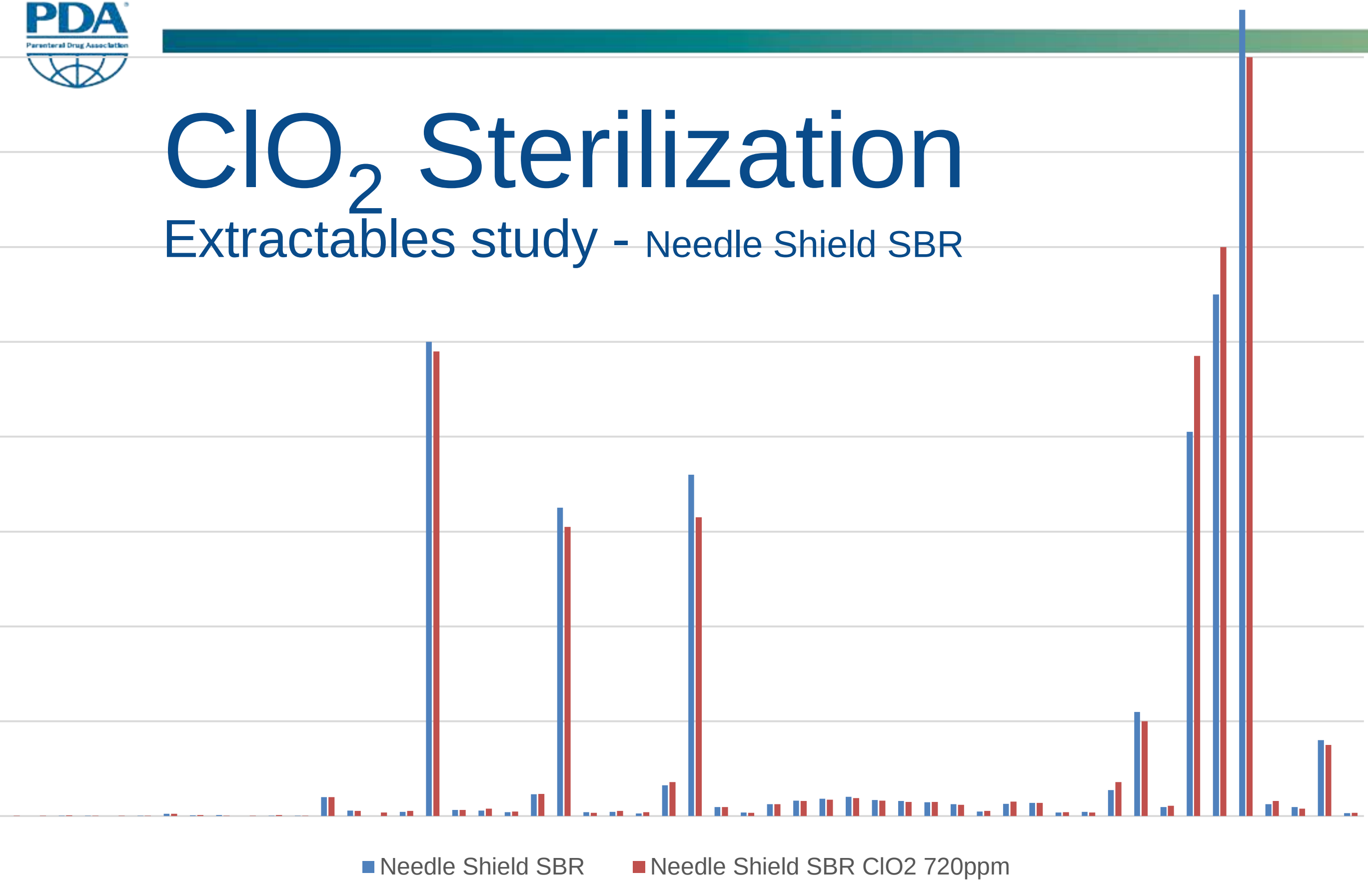
WFI compatibility of rubber - Irradiation resistant Bromobutyl (COATED)

Material	ClO_2 exposure (ppm-hrs)	Cl^-/Br^- (NTU) ≤2.29	Absorb. ≤1.0	pH units 5-7	pH shift ≤ 1	Reducing subst. ≤ 2.0 ml 0.002M $KMnO_4$
Irradiation resistant Bromobutyl	0	1.50	0.06	6.27	0.27	1.04
	720	2.07	0.08	5.97	-0.03	1.54
	3600	**3.29**	0.11	5.77	-0.23	**2.05**
	14400	**5.48**	0.16	**4.90**	**-1.10**	**2.98**
	0 kGy γ-rad.	2.0	0.04	6.5	0.5	1.2
	30 kGy γ-rad.	1.6	0.03	6.4	0.4	1.2
	55 kGy γ-rad.	1.5	0.04	6.3	0.3	1.5
Irradiation resistant Bromobutyl COATED	0	1.59	0.06	5.43	-0.57	1.05
	720	1.99	0.06	5.47	-0.53	1.18
	3600	2.03	0.07	5.14	-0.86	1.40
	14400	2.11	0.10	**4.83**	**-1.17**	1.87

- Methodology :
  - 2 best different rubber formulations of previous test
  - Sterilized with different ClO_2 doses
  - Tested using WFI tests from different Pharmacopeia = more stringent than previous slide
  - Compared with Gamma as reference

ClO_2 Sterilization

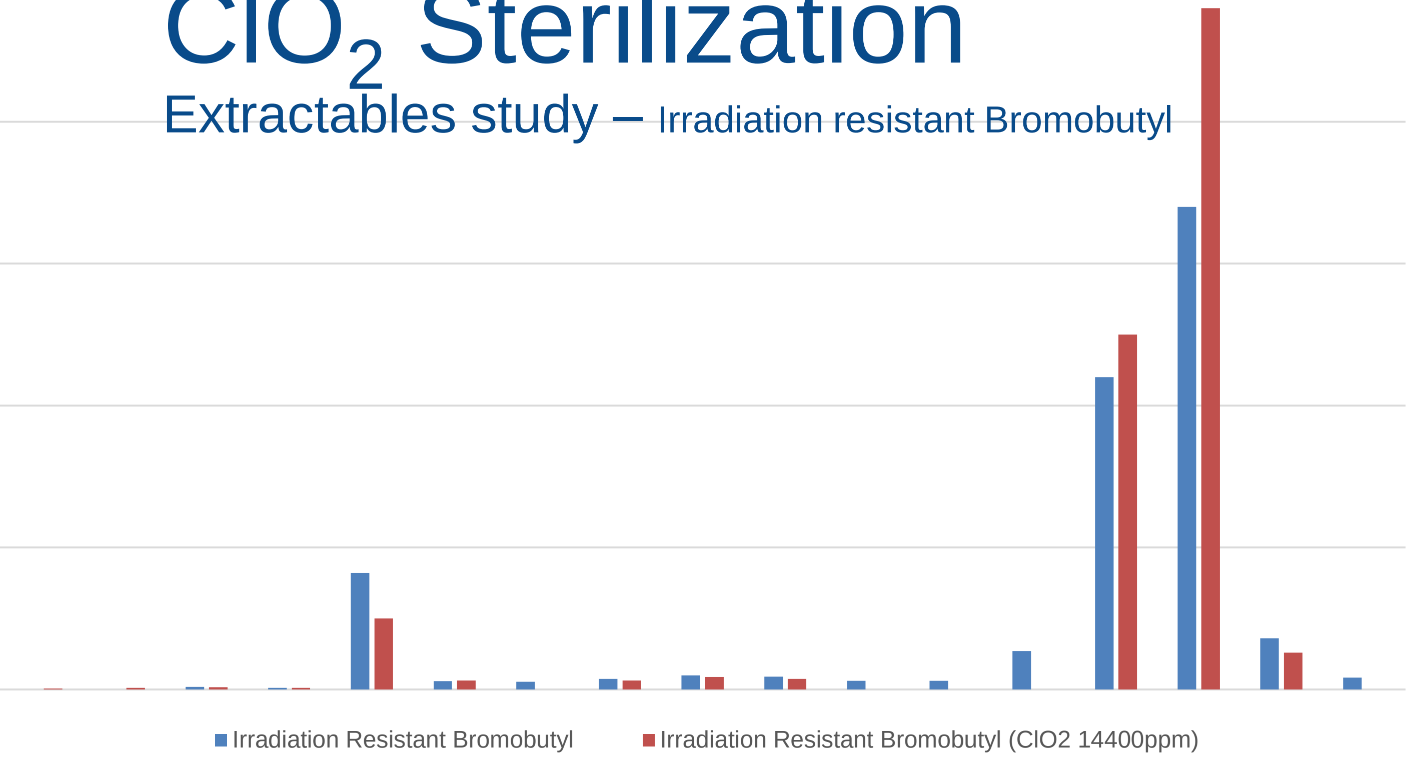
Extractables study - Needle Shield SBR



- Methodology :
  - Needle Shield SBR
  - Sterilized with standard ClO_2 dose
  - Closed vessel extraction 70°C/24h in Isopropanol
  - Analysis by
    - HS-GC/MS
    - GC/MS
    - LC/MS
  - Arbitrarily combined and expressed on 1 graph

ClO_2 Sterilization

Extractables study – Irradiation resistant Bromobutyl



- Methodology :
  - Irradiation resistant Bromobutyl
  - Sterilized with 20 x ClO_2 dose !
  - Closed vessel extraction 70°C/24h in Isopropanol
  - Analysis by
    - HS-GC/MS
    - GC/MS
    - LC/MS
  - Arbitrarily combined and expressed on 1 graph

Conclusions

X-ray sterilization as alternative to gamma irradiation

- X-Ray sterilization can be a valuable alternative method for Gamma irradiation of bulk rubber products
- X-Ray affects rubber similar to Gamma. No added value
- X-Ray may become popular in the future for other reasons (economical, environmental, political, ..)

ClO_2

- ClO_2 can be a valuable alternative method for EtO sterilization of bulk rubber products or pre-assembled Needle Shields and Tip Caps on glass syringes
- Depending on the rubber formulations, ClO_2 may help in holding a Type I classification for USP <381>/ Pharm. Eur. 3.2.9. after sterilization

Acknowlegments:

- Anita Thijs, Datwyler
- Tine Hardeman, Datwyler
- Paul Lorcheim, ClorDiSys
- Lien Riepen, Uhasselt

Thank you:

- All of you