Datwyler Sealing Solutions

Chlorine Dioxide Sterilization Effects on

Elastomeric Closures Physicochemical and

Functional Characteristics

April 11, 2019
Bridgewater, New Jersey

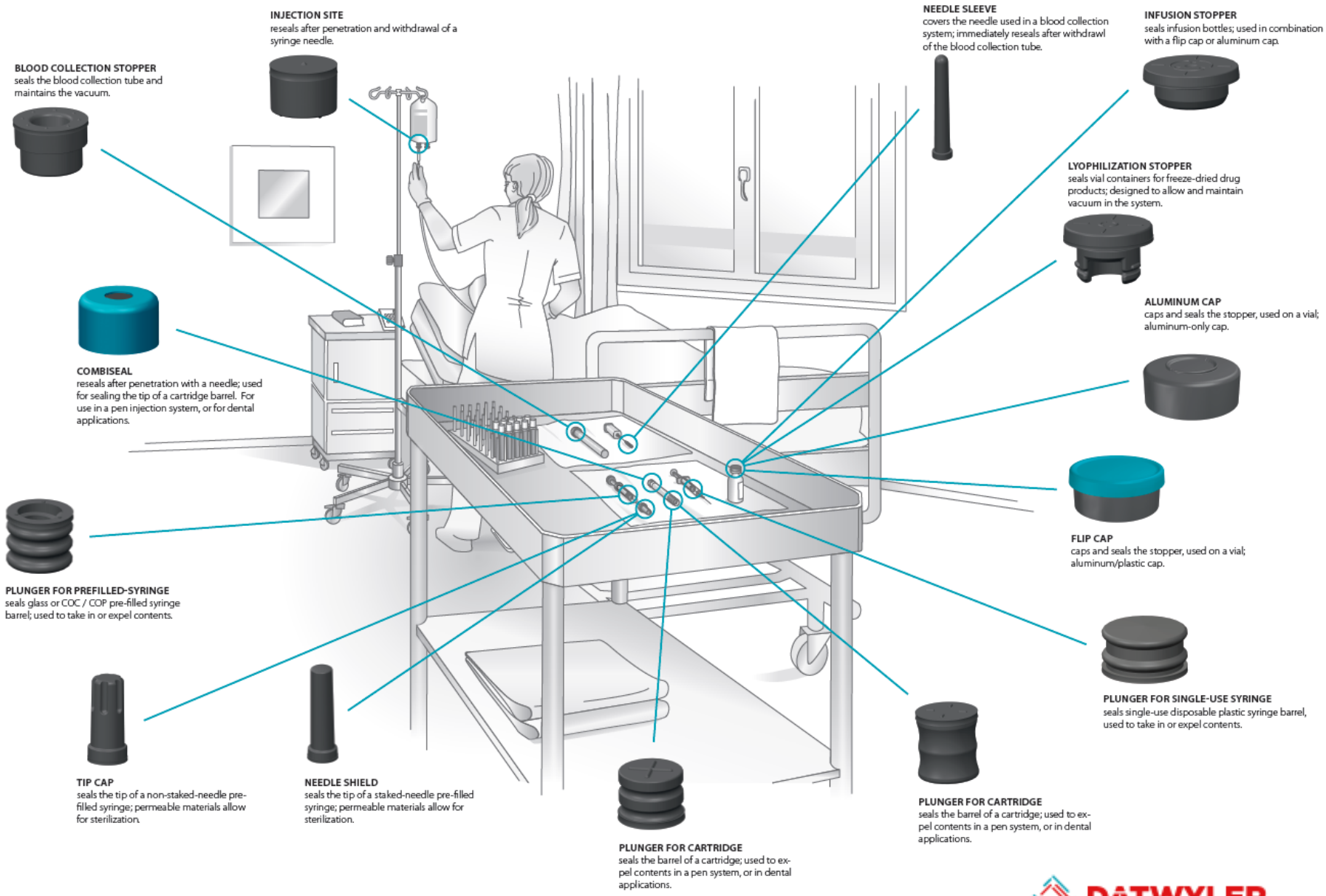
DATWYLER

Who we are

Datwyler Sealing Solutions is a **Swiss-based, leading supplier** and a key player in the global health care industry. We offer state-of-the-art solutions for **drug packaging and medical devices**. Our **unique range of services and products** includes the most advanced elastomer formulations, coatings, aluminum seals, and processing technologies.

Our **Values**


1
WE ARE
ENTRE-
PRENEURS
WE BRING
VALUE TO OUR
CUSTOMERS
WE EXCEL
IN WHAT
WE DO
WE HAVE
RESPECT FOR
OTHERS


INJECTION SITE
reseals after penetration and withdrawal of a syringe needle.
NEEDLE SLEEVE
covers the needle used in a blood collection system; immediately reseals after withdrawl of the blood collection tube.
INFUSION STOPPER
seals infusion bottles; used in combination with a flip cap or aluminum cap.
BLOOD COLLECTION STOPPER
seals the blood collection tube and maintains the vacuum.
LYOPHILIZATION STOPPER
seals vial containers for freeze-dried drug products; designed to allow and maintain vacuum in the system.
ALUMINUM CAP
caps and seals the stopper, used on a vial; aluminum-only cap.
COMBISEAL
reseals after penetration with a needle; used for sealing the tip of a cartridge barrel. For use in a pen injection system, or for dental applications.
FLIP CAP
caps and seals the stopper, used on a vial; aluminum/plastic cap.
PLUNGER FOR PREFILLED-SYRINGE
seals glass or COC / COP pre-filled syringe barrel; used to take in or expel contents.
PLUNGER FOR SINGLE-USE SYRINGE
seals single-use disposable plastic syringe barrel, used to take in or expel contents.
TIP CAP
seals the tip of a non-staked-needle pre-filled syringe; permeable materials allow for sterilization.
NEEDLE SHIELD
seals the tip of a staked-needle pre-filled syringe; permeable materials allow for sterilization.
PLUNGER FOR CARTRIDGE
seals the barrel of a cartridge; used to expel contents in a pen system, or in dental applications.
PLUNGER FOR CARTRIDGE
seals the barrel of a cartridge; used to expel contents in a pen system, or in dental applications.

Chlorine Dioxide Sterilization Overview

1. Review of typical sterilization technologies
2. Chlorine dioxide defined
3. Protocol
4. Results and discussion

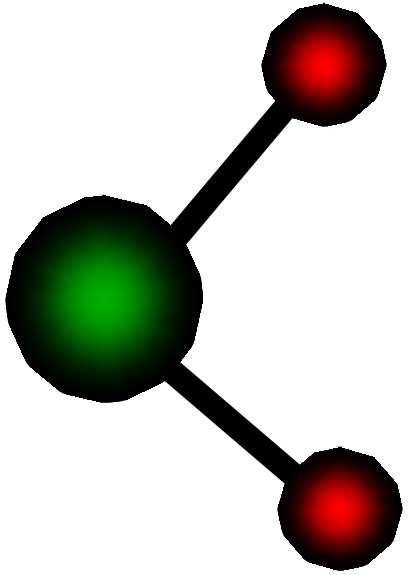
Elastomeric closure sterilization techniques

- Steam Autoclave
  - Used for centuries to sterilize medical instruments
  - Common practice to use 30 minutes at 121°C
  - Not known to cause any issues, either chemical or physical
  - Removing residual moisture with dry heat can be a concern
- Gamma Irradiation
  - Common practice to use between 10 and 40 Kgy
  - May affect certain elastomer compounds more than others due to formulation
- Ethylene Oxide
  - Used to pre-sterilize empty prefilled syringe systems
  - Can leave residuals that must be allowed to dissipate over time
  - Used on isoprene, SBR, and other highly unsaturated elastomers where it can pass through and sterilize the fluid path. Not used on butyls due to long quarantine times.
    - E.g. isoprene/SBR needle shields and tip caps

What is Chlorine Dioxide (CD)?

Properties:

- Yellow-Green Gas
- Water Soluble
- Boiling Point 11^{o}C
- Tri-atomic Molecule
- Molecular Weight 67.5



1. Ability to be monitored in real time with a photometric device.
2. Biocidal against bacteria, fungi, viruses, and bacterial spores.
3. Ability to penetrate water (not all sterilants can penetrate water, *vapors can not*).
4. EPA registered chlorine dioxide as a sterilant opening the door to applications in the medical field.

Experimental protocol

– In order to understand the functional and chemical effects of prolonged exposure to chlorine dioxide sterilization procedures we exposed closures in FM457 (BIIR) (with and without Omni Flex) and FM30 (SBR) (a commonly used needle shield compound) to standard and 20X standard gas concentrations.

– After exposure to chlorine dioxide gas and tested according to the United States Pharmacopeia <381> Elastomeric Closures for Injection for functional and chemical compliance.

– Biological indicators were placed in each load for evidence of kill.

Results and discussion

– The effect of ClO_2 sterilization on FM30, FM457 and FM457 O3G stoppers was investigated and found that **sterilization with ClO_2 can be competitive with the classical sterilization techniques**.

– The **stoppers perform equally well or even slightly better** after being subjected to ClO_2 compared to gamma radiation or EtO.

ClO_2 Sterilization
Fragmentation – Resealability – Penetrability

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

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

ClO_2 Sterilization

Chemical Cleanliness - Irradiation Resistant Bromobutyl

- 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

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

ClO_2 Sterilization

WFI Compatibility of Rubber - Irradiation Resistant Bromobutyl (COATED)

– 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

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 ɣ-rad.	2.0	0.04	6.5	0.5	1.2
	30 kGy ɣ-rad.	1.6	0.03	6.4	0.4	1.2
	55 kGy ɣ-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

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

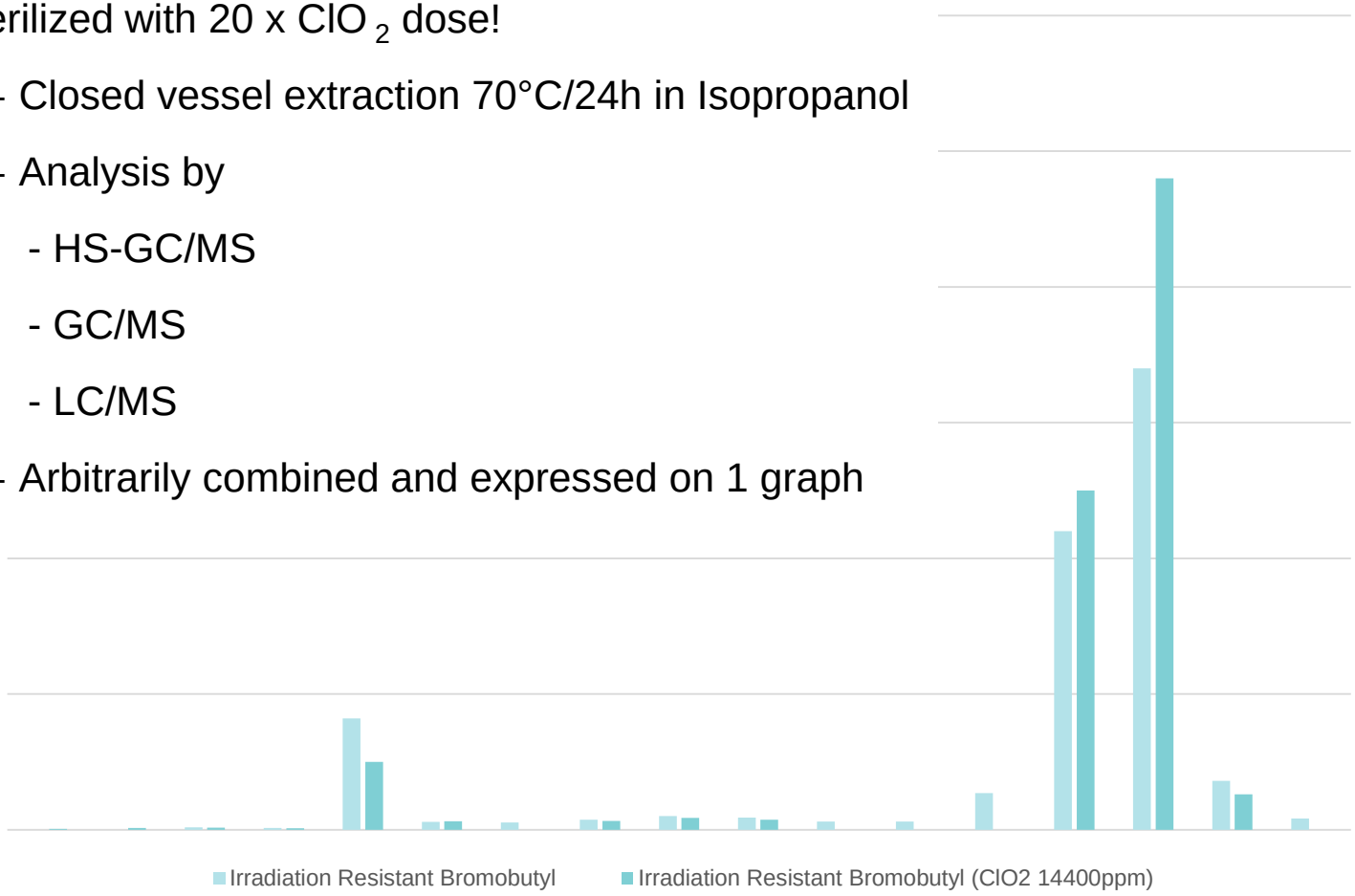
    – Analysis by

      - HS-GC/MS

      - GC/MS

      - LC/MS

    – Arbitrarily combined and expressed on 1 graph



Summary

– Biocidal at low concentration and ambient temperature
– Efficacious under vacuum or at atmospheric pressure
– Gas distributes rapidly
– Gas penetrates crevices
– Non-flammable at use concentrations
– No liquids
– Self-contained reagents
– Short cycles

– 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**.

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