Approval Date : 28.11.2018

CS Report CS0425-01
Edition : 4.0

Effect of ClO2 sterilization on chemical and functional properties of elastomeric closures

Written by:
Hardeman, Tine
Manager Material Development
Electronically signed on 28.11.2018

Reviewed by:
Van Oosterwijck, Chantal
Manager Material Development
Electronically signed on 28.11.2018

Approved by:
Jongen, Bram
Head of R&D Parenteral Packaging Systems
Electronically signed on 28.11.2018

---

1. Abstract

Project Number : BSC2504

Next to sterilization with steam, ionizing radiation and ethylene oxide, ClO_2 can also be used to sterilize elastomeric closures. To verify whether this is a viable option, the effect of ClO_2 exposure on the chemical and functional properties of different Datwyler 20mm stoppers was investigated. Stoppers in FM30, FM457 and FM457 with Omniflex 3G coating were exposed to the nominal, 5-fold and 20-fold ClO_2 dosage for sterilization and subsequently tested according to the chemical and functional tests as described in the United States Pharmacopoeia <381>.

In general, it is found that sterilization with ClO_2 can be competitive with the classical sterilization techniques. Stoppers in FM30 were somewhat affected by the sterilization procedure, but this is also the case with the classic EtO sterilization. In fact, the stoppers were performing slightly better after nominal ClO_2 exposure than after sterilization with EtO. Both uncoated and Omniflex 3G coated stoppers in FM457 showed no considerable change in properties after exposure to ClO_2, even when a 20-fold overexposure was used.

2. Table of Contents

1. Abstract 2
2. Table of Contents 3
3. Introduction 4
4. Conclusion 4
5. Materials and Methods 5
6. Results 5
6.1 Functional testing 5
6.2 Chemical testing 5
7. References 6
8. History 7
9. Appendices/Attachments 8
9.1 Appendix 1 : V9048 8
9.2 Appendix 2 : HPP001 9
9.3 Appendix 3: V9407 10

3. Introduction

The sterilization of elastomeric closures can be accomplished using several widely accepted methods including steam, ionizing radiation, and ethylene oxide to name a few. All of these methods have risks and benefits associated with them. The biggest risk of the first two methods, especially of ionizing radiation, is damage done to the physical properties of the elastomer causing functional aberrations such as excessive coring and fragmentation, lack of proper reseal and changes to the extractable profile of the elastomer. Ethylene oxide, while more benign to the physical and chemical properties of the elastomer, is a priority pollutant, a known carcinogen, presents flammability risk, and is difficult to remove from some elastomers with high barrier properties like butyl rubber. New and safer methods are always in demand and chlorine dioxide shows promise in this regard.

In order to understand the functional and chemical effects of prolonged exposure to chlorine dioxide, ClorDiSys has sterilized some of our closures via nominal exposure, 5-fold overexposure and 20-fold overexposure. The selected closures are 20 mm stoppers in FM30, uncoated FM457, and Omniflex 3G (O3G) coated FM457. All samples passed the sterility test using biological indicators performed at ClosDiSys. These stoppers are now tested according to the United Stated Pharmacopoeia <381> to illuminate the effect of chlorine dioxide on elastomeric closures for injection. Both chemical and functional testing is performed to get a complete overview. This work will pave the way to further studies of penetration of the gas into the elastomer to effectively sterilize beneath the surface of the elastomer in order to understand the effectivity of the gas to replace traditional ethylene oxide sterilization of medical devices.

4. Conclusion

The effect of ClO_2 sterilization on FM30, FM457 and FM457 O3G stoppers was investigated. In general, it is 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.

Because of the unsaturated backbone of the styrene-butadiene copolymer in FM30, this compound is quite susceptible to being affected by sterilization. It is indeed observed that its performance in the chemical tests after high dosage ClO_2 sterilization is deteriorating more than what is observed for FM457. However, FM30 is also significantly affected after sterilization with EtO, the typical sterilization technique that is used for this compound. In fact, FM30 still complies with USP <381> after exposure to the nominal dosage of 720 ppm-hrs ClO_2, while it no longer meets these requirements after EtO exposure. Although more data is required for statistical analyses, it does indicate that ClO_2 sterilization is a viable option that could outperform EtO sterilization.

FM457 is generally less affected by sterilization, because the saturated backbone of the elastomer is less prone to react. This observation is confirmed for both sterilization with ClO_2 and gamma radiation. In the tests described in USP <381>, almost no effect on the performance is observed for these two techniques, even when a 20-fold overexposure is used.

5. Materials and Methods

An overview of the stoppers under evaluation is given in Table 1. FM30 is a styrene-butadiene compound, while FM457 is a bromobutyl compound. FM457 Omniflex 3G consists of the same bromobutyl rubber and is covered with a fluorinated polymer coating.

Material	Design	Chlorine dioxide exposure (ppm-hrs)			
		0 (ref)	720 (nominal)	3600 (5x)	14400 (20x)
FM30	V9048	X	X		X
FM457	HPP001	X	X	X	X
FM457 O3G	V9407	X	X	X	X

Table 1: Overview of the stoppers under evaluation

The chemical and functional properties of the selected stoppers will be tested according to the United States Pharmacopoeia <381>.

6. Results

6.1 Functional testing

An overview of the results of the functional tests is given in Table 2. There is no clear effect of ClO_2 sterilization on the functional properties of any of the compounds, even when a 20-fold overexposure is used. Although a minor increase in the amounts of fragments and piercing force is observed for FM30, the difference is too small to be able to assign this as an effect of the sterilization process.

Material	ClO_2 exposure (ppm-hrs)	# fragments /48 piercings *≤5 visible fragments**	# leaking /10 vials *No leaks**	Piercing force (N) *≤10 N**
FM30	0	1	0	3.2
	720	3	0	3.3
	14400	3	0	3.7
FM457	0	0	0	3.6
	720	1	0	3.4
	3600	2	0	3.4
	14400	1	0	3.6
FM457 O3G	0	2	0	3.0
	720	3	0	3.1
	3600	1	0	3.2
	14400	1	0	3.1

*Table 2: results of the functional tests according to USP <381>. *USP <381> Limits*

6.2 Chemical testing

The results of the chemical tests can be found in Table 3 (FM30), Table 4 (FM457) and Table 5 (FM457 O3G). For FM457, both coated and uncoated, the exposure to ClO_2 has very little effect on the results. On the other hand, there are some noticeable changes in the data obtained for FM30 before and after exposure. This difference between the two compounds can be linked to the elastomer: while FM457 contains a halobutyl polymer with a saturated aliphatic backbone, the styrene-butadiene copolymer of FM30 has a significant amount of double bonds in the backbone. As a consequence, the latter is more susceptible to reaction with ClO_2.

The chemical testing of the USP <381> is used to compare the effect of ClO_2 with other classic sterilization techniques. For FM30, which is typically used for needle shields and tip caps, it is most relevant to make the comparison with EtO. On the other hand, the results of the chemical tests for FM457, both with and without coating, will be compared to ionizing radiation. Please bear in mind that 720 ppm-hrs is the standard dosage, so the comparison should be made with this sample.

As mentioned, the double bonds in the backbone of the elastomer of FM30 make this compound more susceptible to unwanted reactions during sterilization. The results in Table 3 show that this is the case for sterilization with both ClO_2 and EtO. In both cases, there is an increase for the absorbance, reducing substances and extractable zinc. However, when comparing EtO sterilization with ClO_2 sterilization using the nominal dosage of 720 ppm-hrs, it can be seen that the absorbance and reducing substances are increased to a lesser extent with ClO_2, thereby remaining (further) below the limit set by USP <381>. Furthermore, a strong decrease in turbidity is observed after ClO_2 sterilization, in contrast to the increase in turbidity after sterilization with EtO.

FM30	**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	0.42	<2	0.50	<0.02
	720	0.23	Pass	0.07	0.10	0.99	<2	1.68	<2	0.00	<0.02
	14400	0.04	Pass	0.32	0.34	3.35	<2	1.57	<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

*Table 3: FM30 results of the chemical tests according to USP <381> (Turb = Turbidity (NTU); Alkal = Alkalinity (ml 0.01M NaOH); Abs = UV absorbance (max 220-360 nm); Red. Subst. = Reducing Substances (ml 0.01M $Na_2S_2O_8$); Heavy Metals (< 2ppm Pb^{2+}); Zn = extractable zinc (ppm); Amm = Ammonium (<2ppm NH_4^+); Res. Evap = Residue on Evaporation (mg); Vol. Sulph. = Volatile sulphides. *USP <381> Type I Limits*

For FM457 and FM457 O3G, both sterilization with ClO_2 and with gamma radiation have very little effect on the results of the chemical tests of USP <381>.

FM457	**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

*Table 4: FM457 results of the chemical tests according to USP <381> (Turb = Turbidity (NTU); Alkal = Alkalinity (ml 0.01M NaOH); Abs = UV absorbance (max 220-360 nm); Red. Subst. = Reducing Substances (ml 0.01M $Na_2S_2O_8$); Heavy Metals (< 2ppm Pb^{2+}); Zn = extractable zinc (ppm); Amm = Ammonium (<2ppm NH_4^+); Res. Evap = Residue on Evaporation (mg); Vol. Sulph. = Volatile sulphides. *USP <381> Type I Limits*

FM457 O3G	**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.**
FM457 O3G	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

*Table 5: FM457 Omniflex 3G results of the chemical tests according to USP <381> (Turb = Turbidity (NTU); Alkal = Alkalinity (ml 0.01M NaOH); Abs = UV absorbance (max 220-360 nm); Red. Subst. = Reducing Substances (ml 0.01M $Na_2S_2O_8$); Heavy Metals (< 2ppm Pb^{2+}); Zn = extractable zinc (ppm); Amm = Ammonium (<2ppm NH_4^+); Res. Evap = Residue on Evaporation (mg); Vol. Sulph. = Volatile sulphides. *USP <381> Type I Limits*

7. References

R&D and Technology Project number: BSC2504

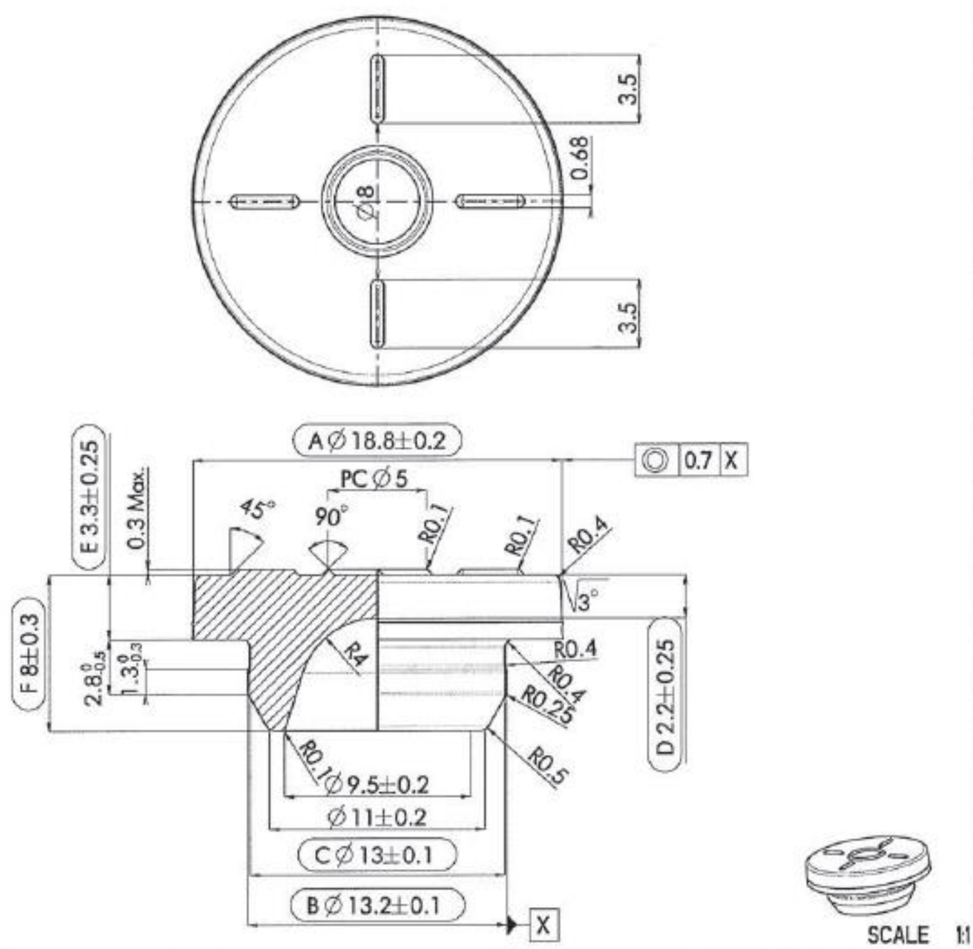
8. History

Edition - (Approval date): Comments
1.0 - (10/2/2018) :
2.0 - (10/15/2018) : Addition of USP <381> Type I limits
3.0 - (11/26/2018) : Data on the effects of EtO and gamma radiation was added for comparison
4.0 - (11/28/2018) : Source referencing problem fixed

9. Appendices/Attachments

9.1 Appendix 1 : V9048

STOPPER *PRODUCT NUMBER* *V9048*



DIMENSIONS										
May 07,'96	[signature]	FM240	Ø 18.7	Ø 13.15	Ø 13.0	2.2	3.3	8.0		
			±0.2	±0.1	±0.1	±0.25	±0.25	±0.3		
Nov 10,'06	[signature]	FM259OmniflexPlus	Ø 18.7	Ø 13.15	Ø 12.95	2.2	3.3	8.0		
			±0.2	±0.15	±0.15	±0.25	±0.25	±0.3		
DATE	CHECKED	All compounds except above mentioned	A	B	C	D	E	F	G	H

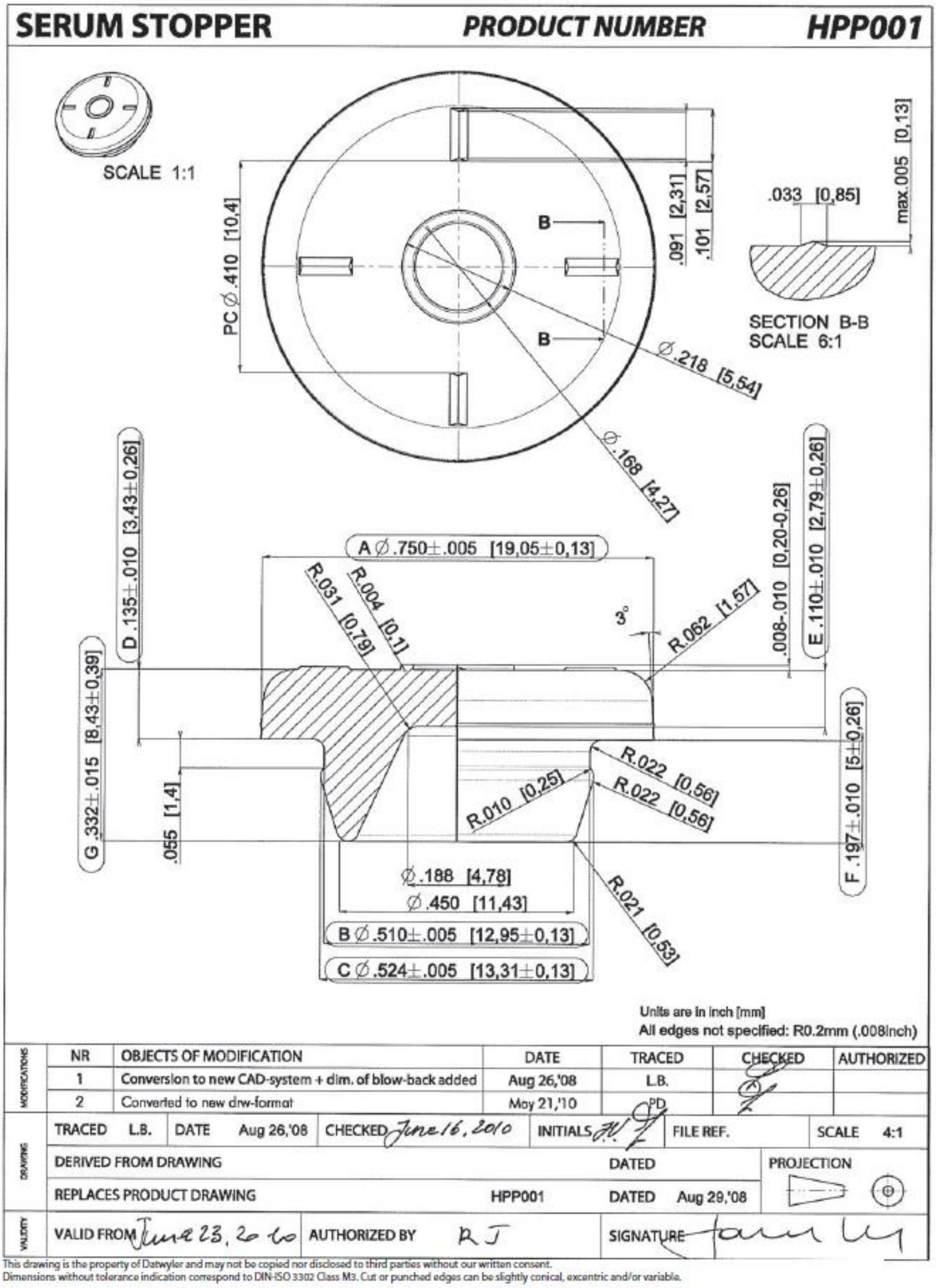
All edges not specified: R0.2mm (.008inch)

NR	OBJECTS OF MODIFICATION	DATE	TRACED	CHECKED	AUTHORIZED
2	Compound FM257Omniflex replaced by FM259OmniflexPlus	Nov 10,'06	RT-1	[signature]	
3	Converted to new drw-format	May 21,'10	PD	[signature]	

TRACED KV-2	DATE Oct 30,'03	CHECKED 23 June, 2010	INITIALS [signature]	FILE REF.	SCALE 3:1
DERIVED FROM DRAWING		DATED		PROJECTION	
REPLACES PRODUCT DRAWING	V9048	DATED Nov 14,'06			
VALID FROM June 23, 2010	AUTHORIZED BY RJ	SIGNATURE [signature]			

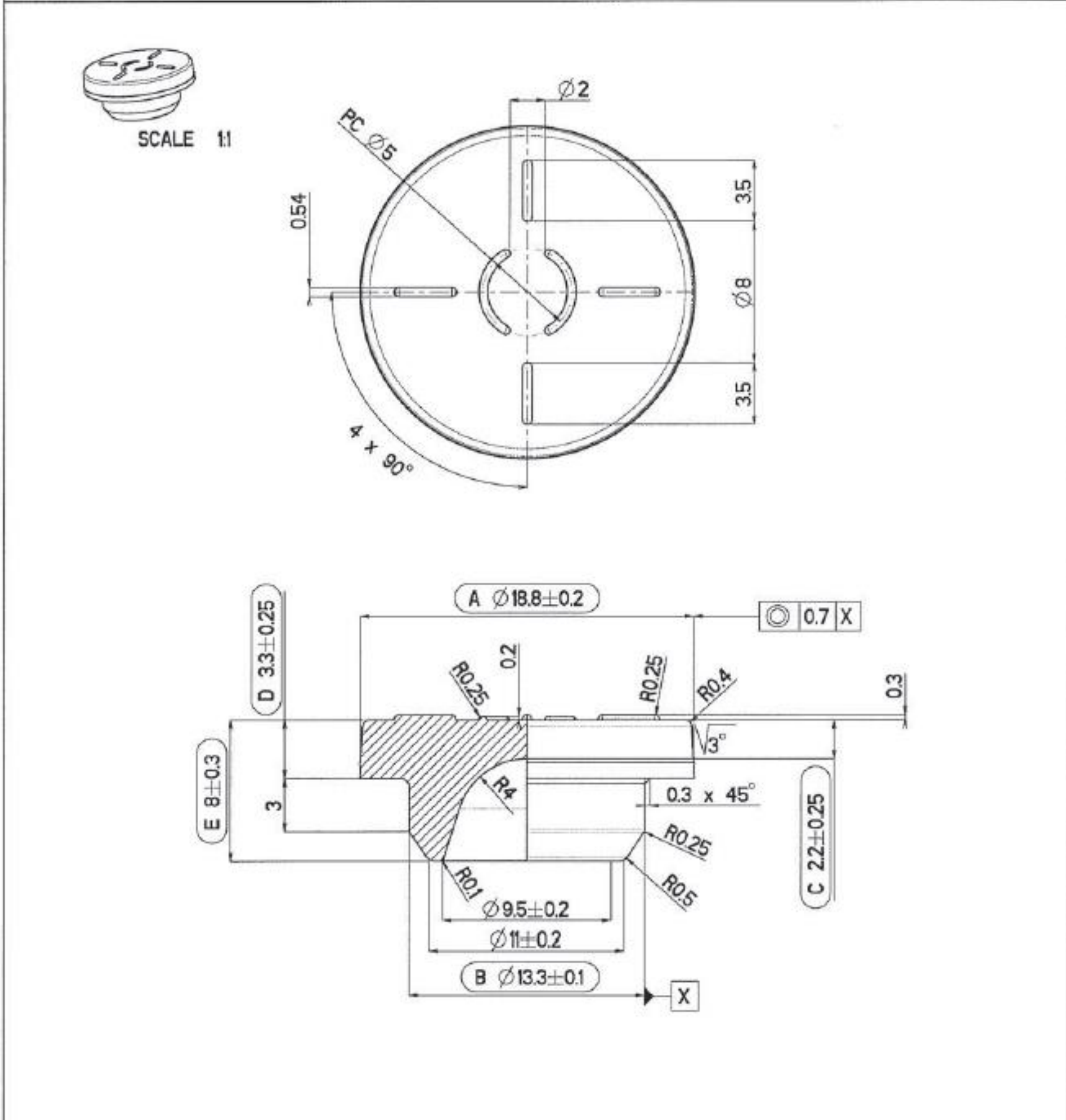
Dimensions without tolerance indication correspond to DIN-ISO 3302 Class M3. Cut or punched edges can be slightly conical, excentric and/or variable.

9.2 Appendix 2 : HPP001



9.3 Appendix 3: V9407

STOPPER | **PRODUCT NUMBER** | **V9407**



All edges not specified: R0.2mm (.008inch)

MODIFICATIONS	NR	OBJECTS OF MODIFICATION	DATE	TRACED	CHECKED	AUTHORIZED
	1	Converted to new drw-format	May 21,'10	PD		
DRAWING	TRACED PD	DATE Jan 28,'08	CHECKED June 15, 2010	INITIALS	FILE REF.	SCALE 3:1
	DERIVED FROM DRAWING			DATED	PROJECTION	
	REPLACES PRODUCT DRAWING	V9407		DATED Feb 01,'08		
VALIDITY	VALID FROM June 23, 2010	AUTHORIZED BY		SIGNATURE		

This drawing is the property of Datwyler and may not be copied nor disclosed to third parties without our written consent.
Dimensions without tolerance indication correspond to DIN-ISO 3302 Class M3. Cut or punched edges can be slightly conical, excentric and/or variable.