Customer Service Report CS0252

Technical documentation FM457

Edition 4

Written by:

Elke Geuzens
Product Introduction & Support Manager
Date: 11 February 2013

Reviewed by:

Bram Jongen
Global Product Introduction & Support Manager
Date: Feb 13, 2013

Approved by:

Renaud Janssen
Global Director of Scientific Affairs
Date: 13/02/13

Distribution List:
Sales and Marketing, Product Introduction & Support, Site Quality Heads (Rubber) & GQRA Managers

Report type: General

1 Table of Contents

2 Description

FM457 is a bromobutyl compound with extremely high chemical purity. This purity allows to achieve compatibility in applications where so far rubber extractables posed a problem. A typical example is Water for Injection (WFI) in vials or prefilled syringes with low volume to high rubber surface area ratios. It is shown that also under stress conditions FM457 is compatible with WFI. Another example are cephalosporin powders that are known to develop turbidity after prolonged contact with rubber.

FM457 can be used as rubber compound for both closures for vials as for components for prefilled syringes or cartridges.

FM457 products are not made with natural rubber latex, dry natural rubber latex or any of its derivatives. They are not made using ingredients of animal origin and do not generate known suspicious chemicals like nitrosamines and 2-mercaptobenzothiazole (MCBT). FM457 products are unrelated to BSE/TSE risks. Obviously, these products comply with all major pharmacopoeia for pharmaceutical rubber.

It's very good particulate cleanliness properties and stability upon gamma irradiation make it a compound which is very well suited for Ready-for-Sterilization and Ready-to-Use applications where rubber parts pretreatment in the form of washing, siliconization, rinsing and eventually steam sterilization are skipped by the pharmaceutical company.

Rubber compound FM457 is filed with the FDA in a US Drug Master File (#10953) and with the Health Protection Branch in Canada (#1994-027).

Note: FM457 refers to the type of compound. The extension "/0", "/1", … refers to the colour of the said compound.
Differently coloured compounds were used for testing throughout this document. It is generally accepted that the colour is irrelevant for the properties discussed in this document.

3 Typical compound ingredients

3.1 Natural rubber latex

In line with current market expectations, FM457 products are not made with natural rubber latex, dry natural rubber latex or any of its derivatives.

3.2 Nitrosamines

Nitrosamines may be formed starting from residues of specific curing systems. These residues are in a number of cases known to be carcinogenic. FM457 products are formulated without making use of ingredients that potentially give rise to the formation of nitrosamines.

3.3 MCBT

2-mercaptobenzothiazole (2-MBT, 2-MCBT, MCBT) is a rubber chemical that is associated with a health risk. FM457 products do not contain 2-mercaptobenzothiazole (MCBT) or any of its derivatives in their composition.

3.4 BSE/TSE

Rubber compounds may contain components that are of animal origin. Most frequently it concerns fatty acids, fatty acid salts or esters that are either present as active components or as additives to active components. Compound FM457 does not use components of animal origin. FM457 products are in full compliance with the European Pharmacopoeia 5.2.8., “Minimizing the risk of transmitting Animal Spongiform Encephalopathy agents via medicinal products”.

(TSE = Transmissible Spongiform Encephalopathy; BSE = Bovine Spongiform Encephalopathy)

3.5 Heavy Metals

Both US and European legislation impose measures in order to prevent or reduce the impact of packaging and packaging waste on the environment.

FM457 products fulfill the European Community Guideline 94/62/EC for heavy metals in packaging materials. This directive states that packaging components shall not contain more than 100 ppm of Lead (Pb), Cadmium (Cd), Mercury (Hg) and Chromium (VI) (Cr).

EC Guideline 94/62/EC imposes the same requirements as the US CONEG regulation (“Toxics in Packaging Clearinghouse (TPCH)” as established by the Coalition of North-eastern Governors (CONEG) in 1992). FM457 products thus also fulfill the CONEG requirements.

3.6 GMO (Genetically Modified Organisms)

FM457 products are not made with ingredients that are derived from Genetically Modified Organisms (GMO).

3.7 Bisphenol A (BPA)

Bisphenol A (BPA) and BPA related substances may be present in certain plastic materials. They are associated with health hazards.

Datwyler confirms that FM457 products do not use Bisphenol A or the following BPA related substances in their composition:

- Polycarbonate
- Polyether sulfone
- Polycarbonate/siloxane co-polymer
- Biostable polyurethanes
- Epoxy resin
- Bisphenol A diglycidylether methacrylate (BIS-GMA)
- Bisphenol A diglycidylether (BADGE)
- Bisphenol A dimethacrylate (BIS-DMA)
- Ethoxylated bisphenol A diacrylates.

4 Shelf life

The shelf life of rubber compound FM457, intended for use in parenteral applications, stored in the original packaging under the ambient storage conditions as described in the ISO2230, “Rubber Products – Guideline for storage”, is 2 years after packing date.

Hereafter, based on the indications given in the ISO2230, an additional shelf life of 5 years can be considered.

Compatibility with the drug must be ascertained by the user.

5 Physical properties

5.1 Identification properties

The following tests are used to identify the rubber formulation following typical rubber technology standards.

The physical properties as shown in Table 1 are taken for compound FM457/0, Grey. Properties like density and ash content may differ slightly for different colours of the compound. Data per compound colour are given on the corresponding Compound Data Sheets, available as separate documents upon request.

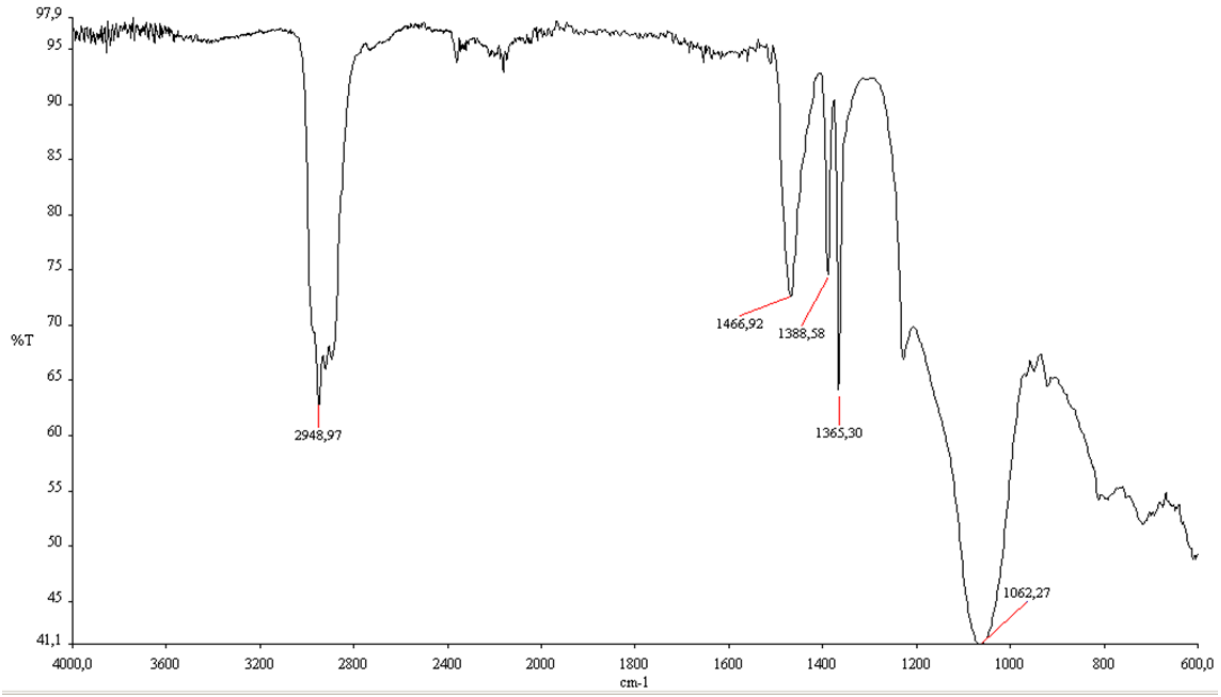
Table 1 : Physical properties – FM457

Hardness	°Shore A	ISO 7619	47 ± 5
Density	g/cm³	ISO 2781	1.265 ± 0.025
Ash	%	Internal Method(s): Calc. 4h@700°C	41.0 ± 2.0
Compression Set	%	ISO 815	max. 30
Tensile Strength	N/mm²	ISO 37	min. 4

5.2 ATR-FTIR typical spectrum

Identification of the rubber formulation supplied is quite often part of incoming inspection at Datwyler's customer end. A simple, fast and reliable method is the use of ATR-FTIR (Attenuated Total Reflectance – Fourier Transform InfraRed)[1].

Figure 1 : Typical ATR-FTIR spectrum of a cut surface of a product made in FM457



5.3 Permeability

Oxygen and water vapour transmission rates are measured as per ASTM D-3985 (oxygen) and ASTM F-1249 (water vapour). They measure the permeability of a material to oxygen or water vapour.

To be able to obtain permeability data on rubber compounds, a special mould, yielding a thin rubber slab, is used to prepare test pieces.

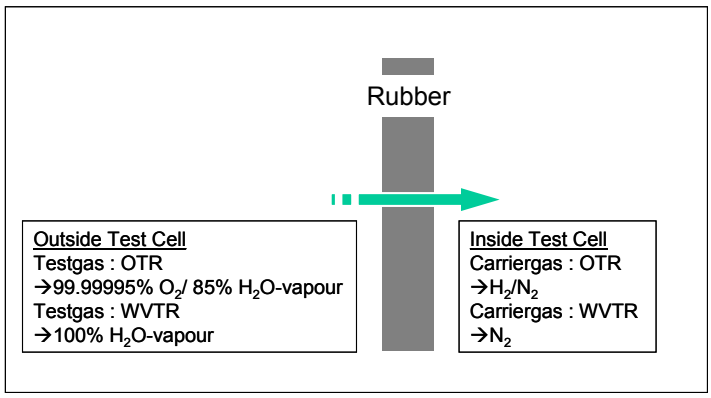
These rubber slabs, with a certain thickness (± 1.3mm), are preconditioned at 23 °C and 50% RH prior to the actual measurement.

For the test itself, a rubber slab that matches 50cm² is cut and clamped in a double chamber test cell, acting as a barrier between both chambers (Figure).

The transmission rate is recorded once the system is at steady-state.

[1] ATR-FTIR is an identification method for rubber in Pharm. Eur. 3.2.9 as from January 2014 on.

Figure 2 : Schematic principle of transmission rate measurement



5.3.1 Water Vapour Transmission Rate (WVTR)

Tested slabs: FM457 slabs with thickness 1.23 mm
Equipment: MOCON, Permatran-W 3/31 MG-module
Conditions: 38 ° C ; 90% relative humidity ; 100% flow N_2

Table 2 : WVTR – FM457

	WVTR in g/m².24h, 100% RH / 38°C
FM457	0.15

5.3.2 Oxygen Transmission Rate (OTR)

Tested slabs: FM457 slabs
Equipment: MOCON, Oxtran 2/20 ML-module
Conditions: 38 ° C ; 85 % relative humidity ; 99.99995% flow O_2

Table 3 : OTR – FM457

	OTR in cc/m².24h, 85% RH / 38°C, 99.99995% O_2
FM457	96

6 Chemical properties

6.1 Pharmacopoeial data

6.1.1 Pharm.Eur.3.2.9. / USP <381>

A revised version of USP <381> has come into force on May 1, 2009. Sample preparation, test description and the 2-tier acceptance criteria were largely harmonized with the Pharm. Eur. 3.2.9.

The table on the next page summarizes the results of FM457 chemical testing according to both the USP <381> and the European Pharmacopeia 3.2.9.

The pyrolysate IR-spectrum and the UV-absorbance curve of the Pharm. Eur. 3.2.9 / USP <381> extract is given in detail in Figure and Figure respectively.

Table 4 : Pharm.Eur.3.2.9./USP<381> data, chemical part – FM457

Characteristic		Amount tested	Units	Limit	Typical Value	
Appearance of solution	Turbidity	Sol. S	NTU	Type I: 6.0 *(*)* Type II: 18.0 *(*)*		0.1
	Colour	Sol. S		See test procedure		pass
Acidity or alkalinity		Sol. S (20 ml)	ml 0.01M HCl ml 0.01M NaOH	0.8 0.3	Blank 0.06 EP USP	0.06 0.06 0.00
Absorbance		Sol. S	A_{max}220-360 nm	Type I: 0.2 Type II: 4.0		0.01
Reducing substances		Sol. S (20 ml)	ml 0.002M $KMnO_4$	Type I: 3.0 Type II: 7.0		0.2
Extractable heavy metals		Sol. S	ppm Pb^{2+}	2	EP USP	<2 <2
Extractable zinc		Sol. S	ppm Zn^{2+}	5.0		<0.01
Ammonium		Sol. S	ppm NH_4^+	2		<2
Residue on evaporation (only for EP)		Sol. S (50 ml)	mg	Type I: 2.0 Type II: 4.0		0.2
Volatile sulphides		20 cm²	mg S^{2-}	0.02		<0.02

** By definition corresponding with reference suspensions II and III resp.*

For FM457 products Datwyler guarantees a shelf life period of 2 years after the packing date.

Compliance of FM457 with the chemical requirements of Pharm.Eur. 3.2.9 and USP <381> after 2 years shelf life is demonstrated in the table below.

Table 5 : Pharm.Eur.3.2.9./USP<381> data, chemical part – FM457

Characteristic		Amount tested	Units	Limit	Typical Value	
Appearance of solution	Turbidity	Sol. S	NTU	Type I: 6.0 *(*)* Type II: 18.0 *(*)*		0.2
	Colour	Sol. S		See test procedure		pass
Acidity or alkalinity		Sol. S (20 ml)	ml 0.01M HCl ml 0.01M NaOH	0.8 0.3	Blank 0.03 EP USP	0.06 0.06 0.03
Absorbance		Sol. S	A_{max}220-360 nm	Type I: 0.2 Type II: 4.0		0.02
Reducing substances		Sol. S (20 ml)	ml 0.002M $KMnO_4$	Type I: 3.0 Type II: 7.0		0.1
Extractable heavy metals		Sol. S	ppm Pb^{2+}	2	EP USP	<2 <2
Extractable zinc		Sol. S	ppm Zn^{2+}	5.0		<0.01
Ammonium		Sol. S	ppm NH_4^+	2		<2
Residue on evaporation (only for EP)		Sol. S (50 ml)	mg	Type I: 2.0 Type II: 4.0		0.0
Volatile sulphides		20 cm²	mg S^{2-}	0.02		<0.02

** By definition corresponding with reference suspensions II and III resp.*
(Data recorded for batch 30031514 after 2 years shelf life)

Figure 3 : Typical IR-spectrum (4000-625cm^{-1}) of a pyrolysate (according to Pharm. Eur. 3.2.9., Ed. 7) – FM457

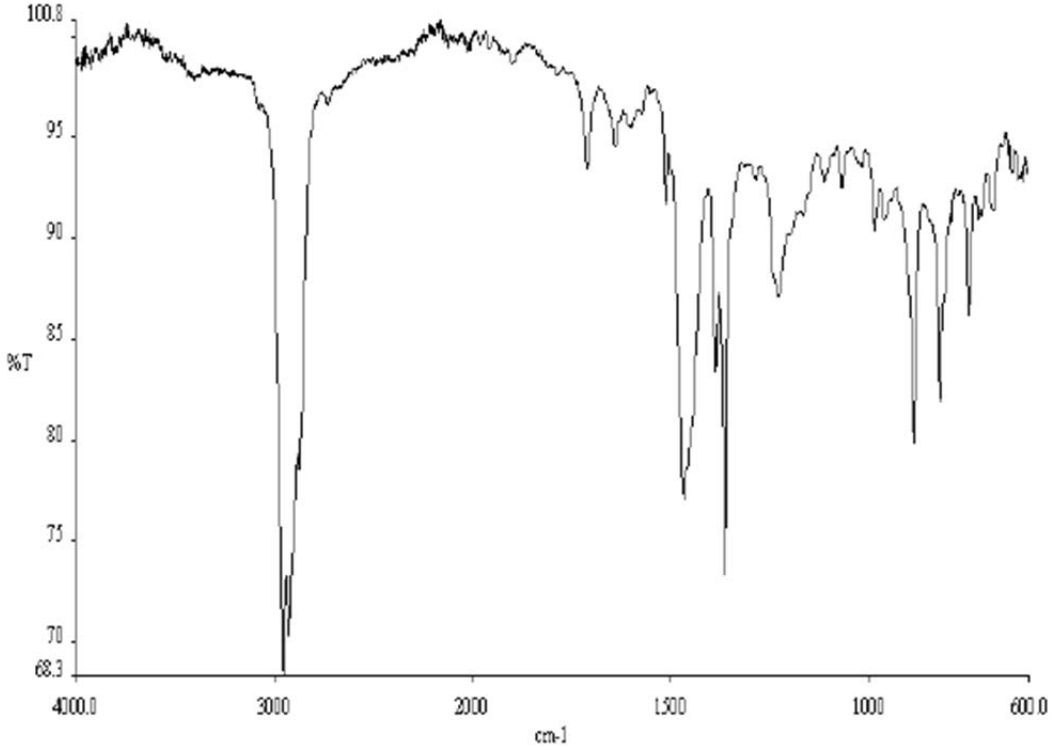
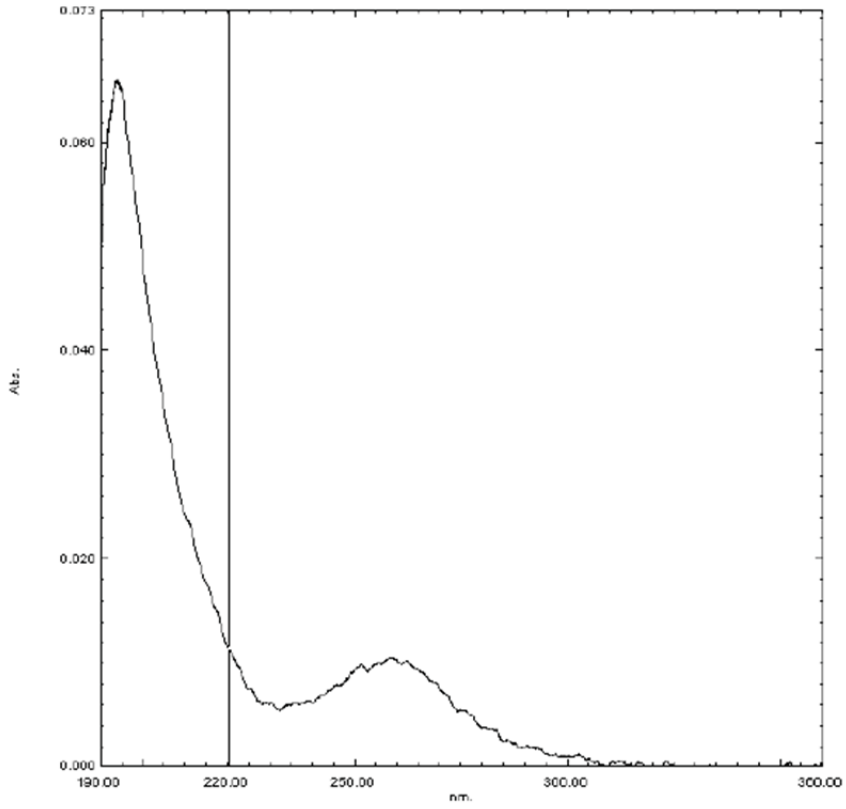


Figure 4 : Typical UV-spectrum of an aqueous extract (according to Pharm. Eur. 3.2.9./ USP <381>) – FM457



6.1.2 Japanese Pharmacopeia 7.03

Results for FM457/0, tested according to the physicochemical part of the Japanese Pharmacopeia, chapter 7.03, “Test for Rubber Closures for Aqueous Infusions”, valid version, are given in Table below. 30 g of rubber sample is autoclaved in 300 g distilled water for 60 min. at 121°.

Due to the peculiar definition of the sample preparation (by rubber mass and not by rubber surface), results are closure design dependent (surface/volume ratio dependency). Results in the table are given for a standard Datwyler 0.5 ml plunger (V9315)[2] with a volume of 0.10 cm^3, a weight of 0.13 g and a total surface of 1.77 cm^2 in compound FM457/0. Larger stopper designs expectedly will show results that are as least as good, since the surface/volume ratio of such stoppers is smaller (less rubber surface in contact with the extraction medium).

For the design given, FM457 complies with the extractable substances part of the Pharm. Jap. 7.03.

Table 6 : JP 7.03 „Extractable substances“ – FM457– ISO11040 0.5ml plunger design

CRITERIUM	AMOUNT TESTED	UNITS	LIMITS	RESULTS
Appearance (430-650 nm)	10 mm cuvet	%T at 430 nm %T at 650 nm	>99% T >99% T	100.0 100.0
Foam test	5 ml	-	foam disap. < 3 min.	Pass
pH	20 ml	pH units	Difference with blank: max. 1.0 (*)	0.05
Reducing substances	100 ml	ml 0.002 M $KMnO_4$	2.0	0.5
Evaporation residue	100 ml	mg	2.0	0.3
UV absorb. (220-350 nm)	10 mm cuvet	absorbance	0.2	0.05
Zinc	10 ml	ppm Zn^{2+}	1 ppm	0.04

(*) “-“ means more acidic than blank; “+” means more alkaline than blank
(Data recorded for batch 950905)

The results of other parts of Pharm. Jap. 7.03 carried out on the same batch were as follows :

Table 7 : JP 7.03 „Cadmium, Lead, Acute Systemic Toxicity, Pyrogen Test, Hemolysis test“ – FM457– ISO11040 0.5ml plunger design

TEST	LIMIT	RESULT
Cadmium	5 ppm	0.003 ppm
Lead	5 ppm	2.4 ppm
Acute Systemic Toxicity	Limit test	Pass
Pyrogen Test	Limit test	Pass
Hemolysis Test	Limit test	Pass

(Data recorded for batch 950905)

[2] Drawing can be found in the attachments to this document.

6.2 ISO 8871-1

The requirements of the ISO8871-1, “Elastomeric parts for parenterals and for devices for pharmaceutical use – Part 1: Extractables in aqueous autoclavates”, are identical to those set down in Pharm. Eur. 3.2.9.

Results for the Pharm. Eur. 3.2.9. are given in an earlier part of this section.

6.3 Extractable information

A detailed extractables report on FM457 involving solvents of various polarities, is available on request.

Because of their confidential nature, the results of this extractables study are not given in full detail in this report. They will be available only after conclusion of specific agreements. Please contact your Datwyler sales representative.

7 Compatibility with WFI

WFI (Water-for-Injection), because of its purity, is a very powerful extractant in contact with elastomeric materials. Under these conditions the WFI that has been prepared by suitable purification steps starting from potable water tries to saturate itself in organic and inorganic compounds that are available for extraction in the elastomeric material.

In this respect WFI is a very thankful medium to compare the extractable properties of different rubber materials.

In this section the WFI extractable properties of FM457 are compared with those of a typical bromobutyl and of a typical chlorobutyl compound. A number of pertinent properties that various pharmacopoeia impose on packaged WFI are investigated. They are complemented by a determination of zinc extraction that is typical for rubber testing. Following test criteria are discussed in this section:

- Ca, Mg (quantitative analysis)
- Zn extraction (quantitative analysis via AAS)
- Chlorides/bromides (quantitative analysis)
- pH
- Reducing substances

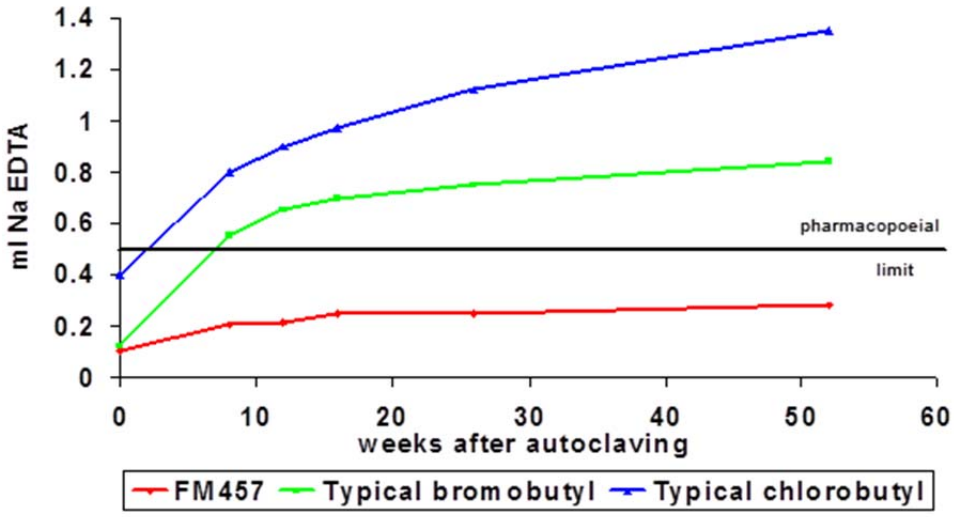
Extraction and contact conditions

At time = 0 the elastomeric material is sterilized in WFI for 30 minutes at 121°C in a ratio of 2.34 cm^2 of rubber surface area per 1 ml of WFI. After that time storage takes place at 40°C with the rubber still in contact with the WFI. The ratio of 2.34 cm^2 of rubber per 1 ml of WFI is extremely unfavourable. For reference, the pharmacopoeia extraction ratio for rubber is 1 cm^2 of rubber per 2 ml of water (USP<381> and EP 3.2.9). Equally the condition of 2.34 cm^2 of rubber per 1 ml of WFI would correspond with a 0.5 ml syringe filled with 0.1 ml of water.

7.1 Calcium and magnesium

Calcium and magnesium are 2 ions for which in Pharm. Eur. there are pharmacopoeial limits on WFI.

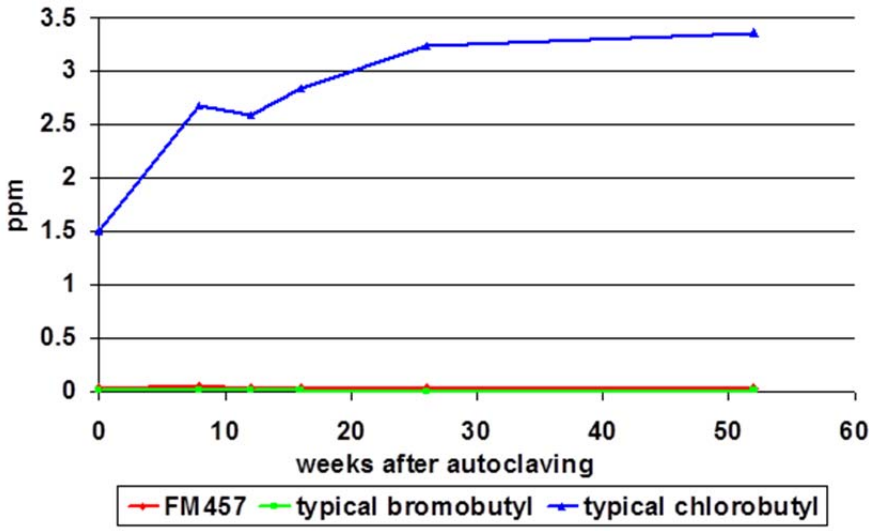
Figure 5 : Calcium and magnesium ion extractables



7.2 Zinc

Zinc has been a commonly used chemical as part of many rubber formulations and is easily extracted in aqueous solutions. Zn ions though are typically undesired in certain drug products. Determination of zinc was performed with AAS.

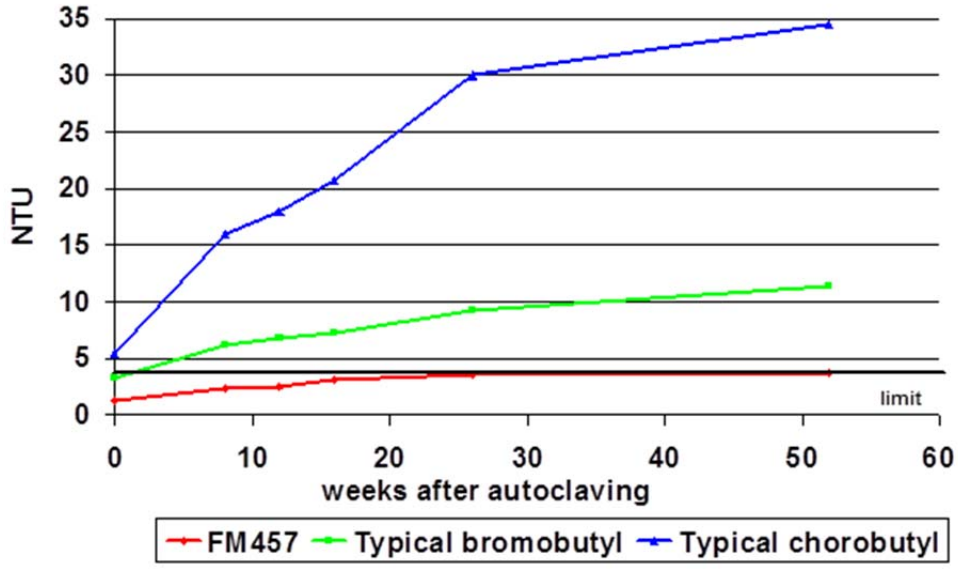
Figure 6 : Zinc ion extractables



7.3 Chlorides/Bromides (NTU)

Chloride and bromide ions are stemming from the halobutyl polymer. The presence of chloride and bromide is measured as per Pharm. Eur. via a precipitation reaction with silver nitrate and, for this study, is quantified by measuring the turbidity of the precipitate solution. Turbidity is expressed as Nephelometric Turbidity Units (NTU). The NTU test method does not allow distinguishing between the 2 types of ions.

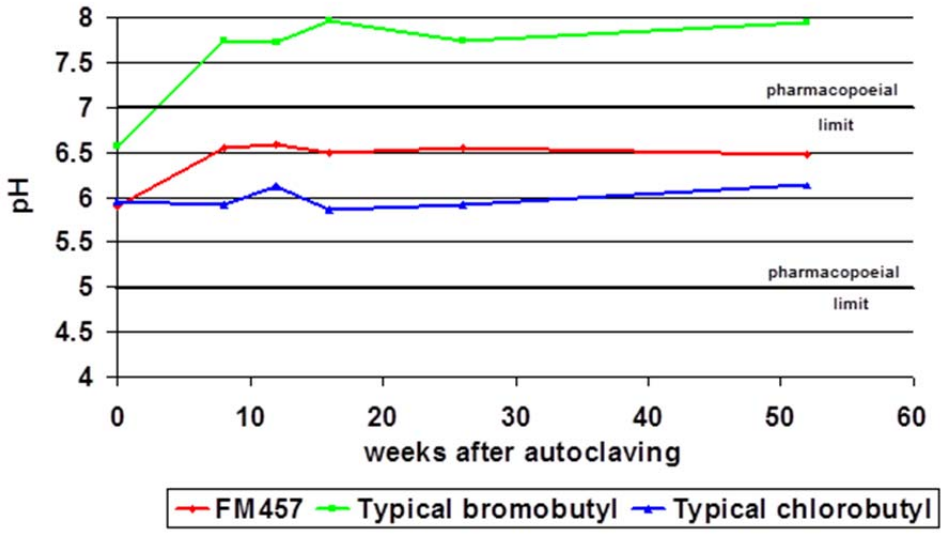
Figure 7 : chloride and bromide ion extractables



7.4 pH

The pH in function of time is given in figure 8.

Figure 8: pH

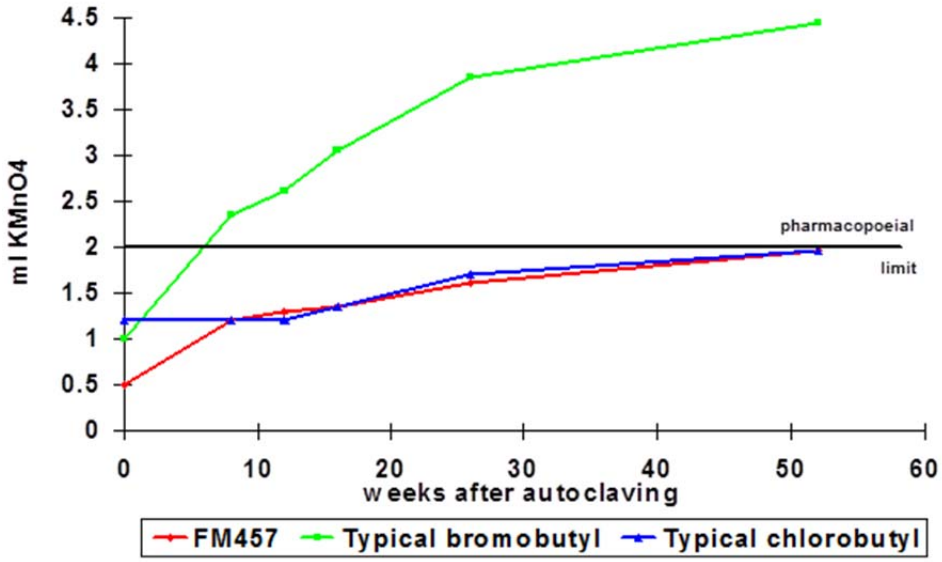


Note : 5 ≤ pH ≤ 7 was the Pharm. Jap. limit for WFI at the time of testing.

7.5 Reducing substances

Reducing substances, according to Pharm. Jap., in function of time are shown in figure 9.

Figure 9 : Reducing substances



Note : 2 ml KMnO4 0.01 N was the Pharm. Jap. limit for WFI at the time of testing.

Apart from the properties mentioned above also the tests for nitrates, sulfates, ammonium and heavy metals were carried out. For FM457 the results proved to be within limits after 12 months of storage under the conditions described.

After 12 months of storage the residue on evaporation was measured as 0.002%. The Pharm. Eur. limit value is 0.004% for packagings with a nominal volume of WFI of less than or equal to 10 ml and 0.003 % for containers with a nominal volume greater than 10 ml.

8 Compatibility with cephalosporins

Cephalosporin powders are known to be very sensitive to contact with rubber closures. Upon dissolution of the cephalosporin powder with WFI, usually a turbidity develops which in most cases can be attributed to an interaction between the rubber and the pharmaceutical product.

The present section compiles the test results of uncoated FM457 stoppers in contact with different cephalosporin powders. The study indicates the low level of turbidity in reconstituted solutions, also after dry powder storage at 40°C and 75%RH.

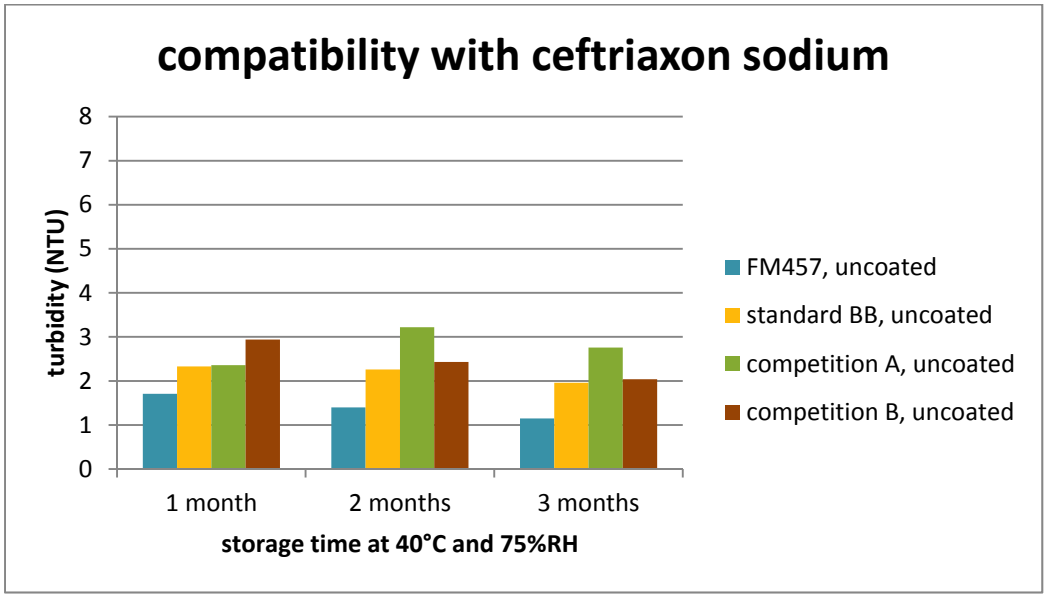
8.1 Test protocol

- Type I glass vials are washed, rinsed and dried
- Stoppers are rinsed, autoclaved and dried
- Vials are filled with 100 mg of the cephalosporin powder, closed with the 20 mm serum closures under test and capped with an aluminium seal
- The vials are stored in inverted position in a climate chamber at a temperature of 40°C and a relative humidity of 75%. The inverted position ensures direct contact between the cephalosporin powder and the rubber.
- For the test, 3ml of distilled water is added to the vials for complete dissolution of the cephalosporin powder
- The turbidity of the resulting cephalosporin solutions is measured with a HACH Model 18900 Nephelometer. The results are expressed in NTU (Nephelometric Turbidity Units)

8.2 Compatibility with ceftriaxon sodium

The turbidity data for the reconstituted solutions after storage times of 1, 2 and 3 months are presented in figure 10.

Figure 10 : Turbidity (NTU) in ceftriaxon sodium solutions

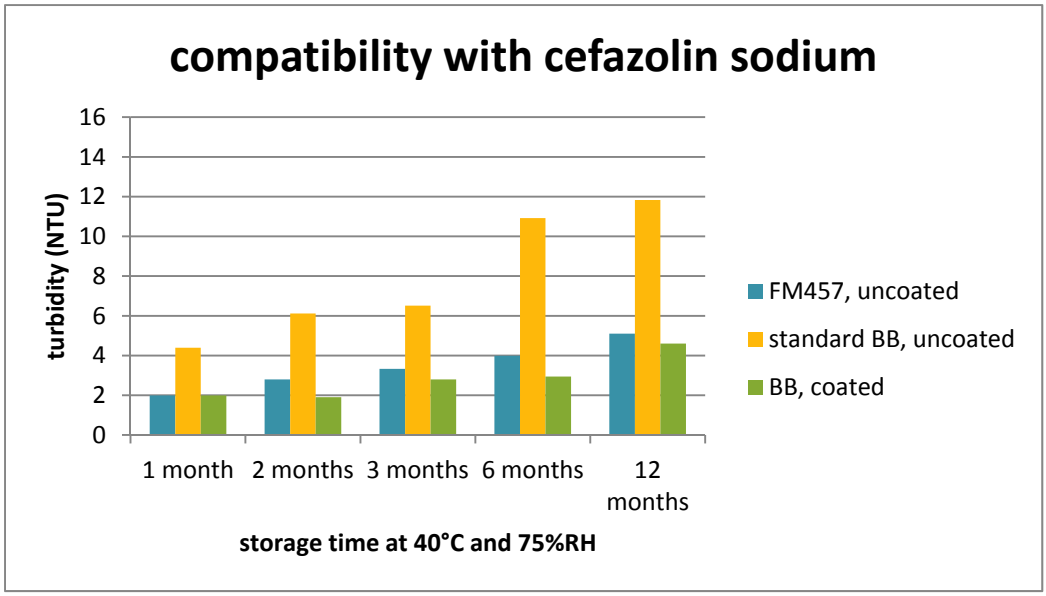


The test results indicate that FM457 uncoated closures are very compatible with ceftriaxon sodium. The turbidity which develops in the vials stoppered with FM457 uncoated closures is very low and does not increase with storage time.

8.3 Compatibility with cefazolin sodium

The turbidity data for the reconstituted solutions after storage times of 1 to 12 months are presented in figure 11.

Figure 11 : Turbidity (NTU) in cefazolin sodium solutions

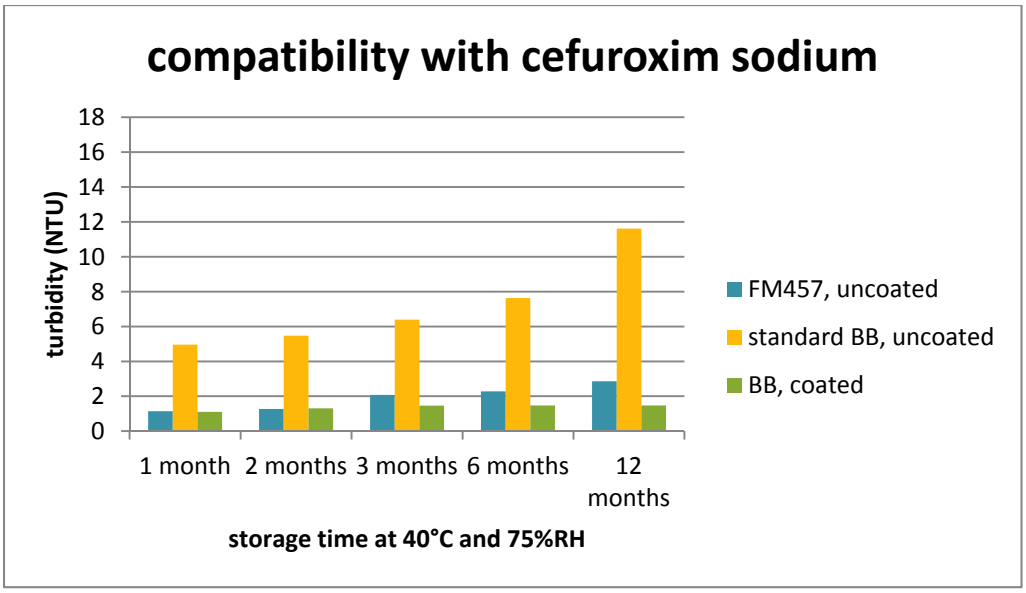


The test results indicate that FM457 uncoated closures are very compatible with cefazolin sodium. The turbidity which develops in the vials stoppered with FM457 uncoated closures is very low and, in this case, is even comparable with the turbidity measured in vials with coated closures.

8.4 Compatibility study with cefuroxime sodium

The turbidity data for the reconstituted solutions after storage times of 1 to 12 months are presented in figure 12.

Figure 12 : Turbidity (NTU) in cefuroxim sodium solutions



The test results indicate that FM457 uncoated closures are very compatible with cefuroxim sodium. The turbidity which develops in the vials stoppered with FM457 uncoated closures is very low and, in this case, is even comparable with the turbidity measured in vials with coated closures.

9 Compatibility with preservatives

The goal of this chapter is to investigate the behaviour of FM457 in contact with aqueous solutions containing preservatives that are typically used in parenteral applications.

The behaviour of FM457 is compared with other halobutyl compounds.

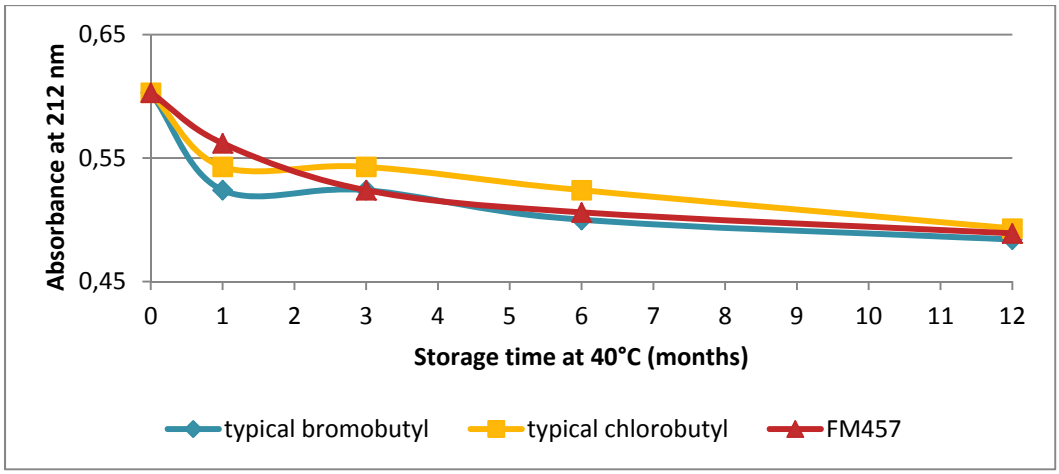
9.1 m-Cresol

A 0.25 % w/v aqueous solution of m-cresol is stored in contact with rubber at 40°C for up to 12 months.

The surface to volume ratio applied in this test is 30 cm² of rubber surface per 25 ml of a 0.25 % m-cresol solution. The glassware used is Type I.

Measuring the UV absorbance of the solution at 212 nm allows following up the m-cresol concentration .

Figure 13 : Compatibility of FM457 with m-Cresol (0.25 % w/v)



9.2 Methyl- and propyl paraben

Aqueous solutions of methyl paraben and propyl paraben of 0.582 g/l and 0.125 g/l respectively are prepared.

20 mm Type I vials are filled with 5 ml of the respective paraben solution and are stoppered with closures in the formulations under test.

After capping, the vials are stored up to 6 months in an inverted position at 40°C in a climate chamber.

The mother solution, where there is no contact with rubber, is equally stored at 40°C.

Measuring the UV absorbance of the solutions at 255 nm allows following up the paraben concentration.

Figure 14 : Compatibility of FM457 with methyl paraben (0.582 g/l)

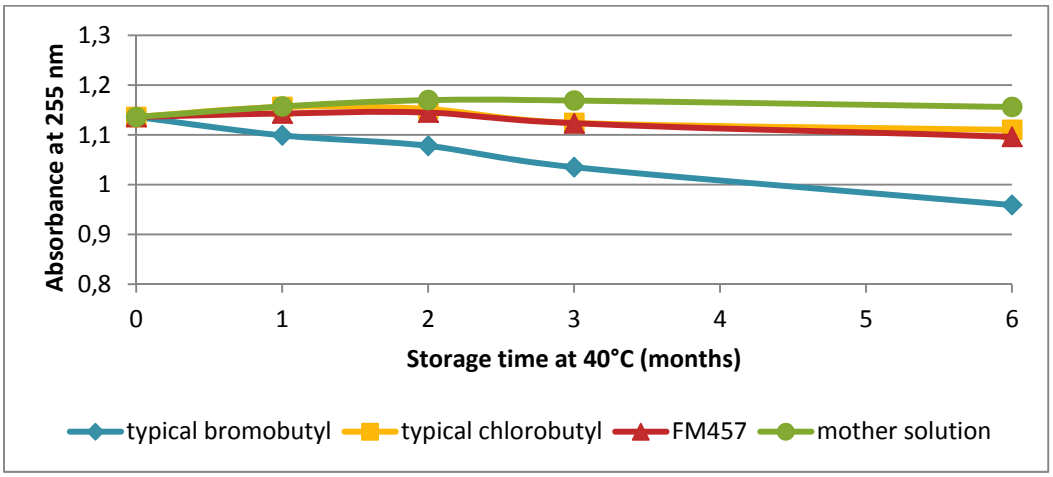
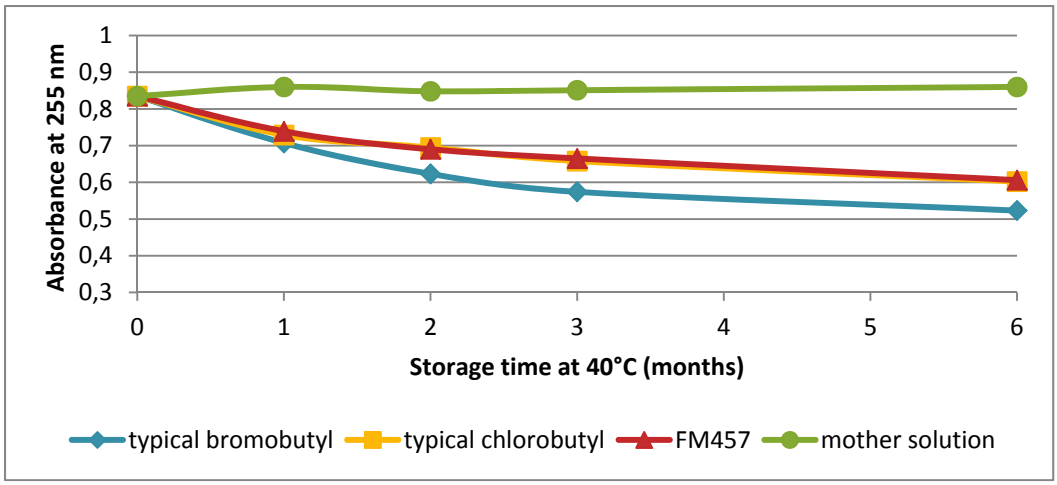


Figure 15 : Compatibility of FM457 with propyl paraben (0.125 g/l)

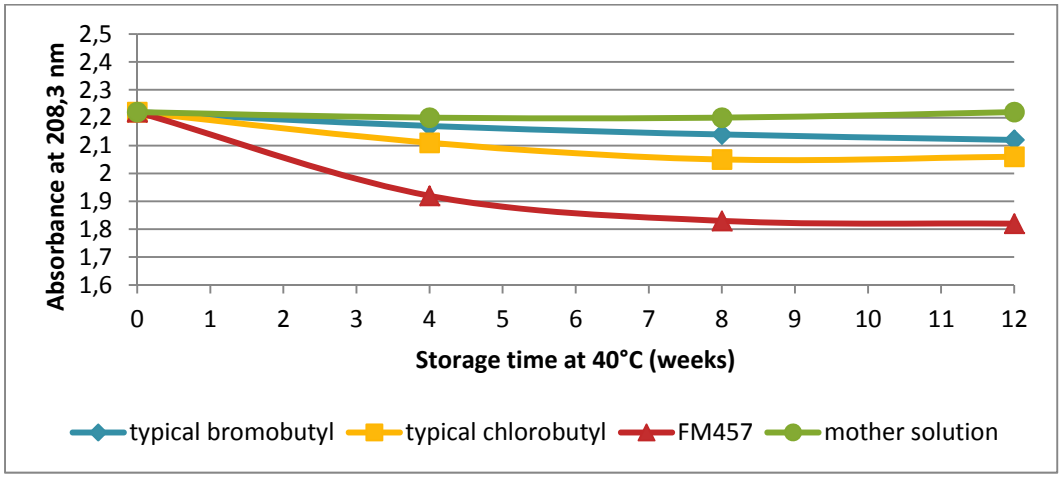


9.3 Benzalkonium chloride

A 110 mg/l aqueous solution of benzalkonium chloride (BKC) is stored in contact with rubber at 40°C for up to 3 months. The surface to volume ratio applied in this test is 300 cm² of rubber per 80 ml of BKC solution. The glassware used is Type I.

Measuring the UV peaks at 208.3 nm allows following up the benzalkonium chloride concentration .

Figure 16 : Compatibility of FM457 with benzalkonium chloride (110 mg/l)



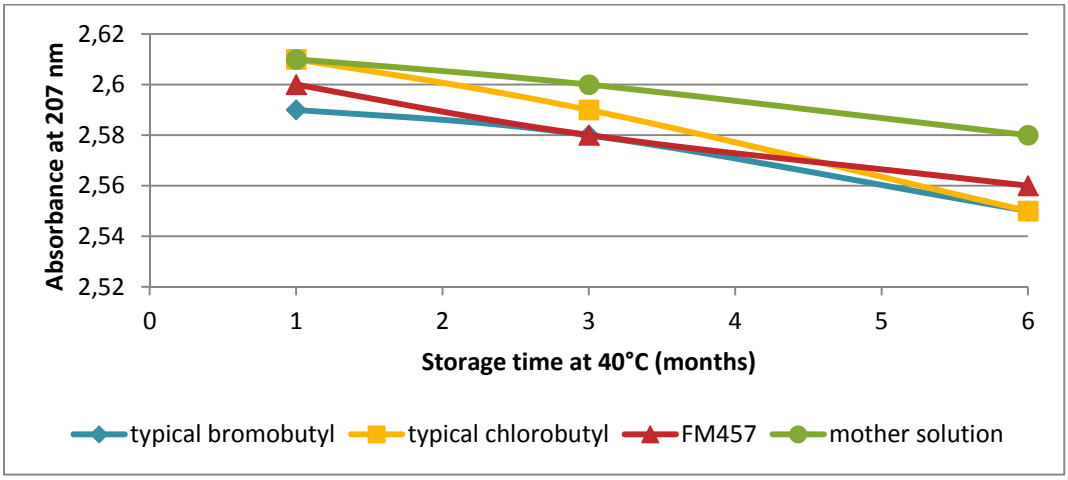
9.4 Benzyl alcohol

A 1 % v/v aqueous solution of benzyl alcohol is stored in contact with rubber at 40°C for up to 6 months.

The surface to volume ratio applied in this test is 300 cm² of rubber surface area per 80 ml of benzyl alcohol solution. All glassware used is Type I.

Measuring the UV peaks at 207 nm follows up the concentration of the benzyl alcohol.

Figure 17 : Compatibility of FM457 with benzyl alcohol (1 % v/v)



10 Functional properties

10.1 Pharm. Eur.3.2.9. / USP<381> for vial stoppers

Table 8 lists the functional properties of FM457 as per Pharm. Eur. 3.2.9 / USP <381>.

10.1.1 Penetrability

Principle

The force needed to completely pierce an elastomeric closure is measured using a universal force tester.

Sample preparation

10 closures are pretreated as described in Pharm. Eur. 3.2.9 / USP <381>:

• The closures are placed in a glass container, covered with distilled water and boiled for 5 minutes. They are rinsed 5 times with cold distilled water.

• The washed and rinsed closures are placed in a conical flask and covered with distilled water (2 ml per cm² of rubber surface area).

• The closures are autoclaved at 121°C for 30 minutes.

• The water is decanted and the closures are allowed to dry at room temperature.

Procedure

• 10 clean, standard 20 mm vials are filled with water to their nominal volume.

• The filled vials are closed with the rubber closures under test and capped with an aluminium seal.

• The closures are pierced with a 0.8 mm (21 G) hypodermic needle at a controlled speed of 200 mm/min and the force required to pierce the closure is recorded.

• The piercing force should not exceed 10 N.

10.1.2 Fragmentation (coring)

Principle

Elastomeric closures for injection vials are pierced with an injection needle. Elastomeric fragments which have been caused by piercing are collected on a filter and counted.

Sample preparation

12 closures are pretreated as described in Pharm. Eur. 3.2.9 / USP <381> (see above for description).

Procedure

• 12 clean, standard 20 mm vials are filled with 5 ml of water.

• The vials are closed with the closures to be examined and secured with an aluminium seal.

• A clean syringe is filled with distilled water .

• A hypodermic needle with external diameter 0.8 mm (21 G) is fitted to the syringe.

• The first closure is pierced, 1 ml of water is injected and 1ml of air is removed.

• This operation is done 4 times for each closure with one and the same needle. The closure is pierced at a different site each time

• A new needle is taken for each subsequent new closure.

• The liquid from 12 vials is filtered over a filter with a pore size of 0.5 µm.

• The fragments on the filter are counted by naked eye.

• The total number of fragments per filter (resulting from 12 x 4 = 48 piercings) must not exceed five.

10.1.3 Self-sealing

Principle

Determine the resealability of a rubber closure, after being punctured with a needle. The test medium is an aqueous solution.

Sample preparation

10 closures are pretreated as described in Pharm. Eur. 3.2.9 / USP <381> (see above for description).

Procedure

• 10 clean, standard 20 mm vials are filled with water, closed with the closures to be examined and secured with an aluminium seal.

• Each stopper is pierced 10 times with a hypodermic needle with external diameter 0.8 mm (21 G).

• The vials are immersed upright in a 0.1% methylene blue solution

• The external pressure is reduced with 27 kPa for 10 min.

• The atmospheric pressure is reestablished and the vials are left immersed for 30 min.

• The vials containing any trace of coloured solution are counted

• The limit is zero vials with coloured solution.

The results shown in Table below are for typical 20mm serum stoppers.

Table 8 : Pharm.Eur.3.2.9./USP<381> Functional tests – FM457

TEST	UNITS	LIMIT	TYPICAL RESULTS	STATISTICAL RESULTS (*)
Penetrability	N	10	2-3	AVG=2.7; σ = 0.7; # = 36 batches
Fragmentation	-	5	0	AVG=0.2; σ = 0.5; # = 36
Self-Sealing	-	0	0	AVG=0; σ = 0; # = 36

(*) Statistical results are obtained from the Datwyler SAP computer system for 20mm stoppers in FM457 (period 01/01/2009 – 31/12/2010)

10.2 Fragmentation behavior after multi-piercing

The Pharm. Eur. 3.2.9 procedure was followed, however the number of punctures per vial was increased from 4 to 10.

The Pharm. Eur. 3.2.9 procedure stipulates to test 12 vials, to use 0.8 mm (21 G) needles and to use 1 needle per vial. The total number of fragments for 12 vials is counted. In the case of 4 punctures per vial, this comes down to counting the number of fragments per 48 punctures. In the modified procedure that was followed here, it comes down to counting the number of fragments per 120 punctures.

Table 9: Fragmentation after multi-piercing of FM457 with a 21G needle

Sample identification		Total # of fragments / 120 piercings
V9025 [3] FM457/0	30079726	0
	30047924	1
	30094379	0

10.3 Effect of long term storage on the functional properties

Evaluation of functional properties was done according to USP <381> / Pharm. Eur. 3.2.9 after ageing for 2 years.

Table 10 : Pharm.Eur.3.2.9./USP<381> Functional tests – FM457 after 2 years of ageing

TEST	UNITS	LIMIT	RESULT
Penetrability	N	10	2.9
Fragmentation	-	5	0.5
Self-Sealing	-	0	0

(Data recorded for batch CH808934, design V9341 [4])

10.4 Seal integrity during cold storage

The container closure seal integrity during cold storage is evaluated by measuring the underpressure in the vials after different cold storage conditions. Therefore an underpressure of 930 mbar is applied in the vials. Stoppered vials (stopper design V9048 [5]) are immediately capped and capped vials are stored according to different storage conditions. After storage at low temperature, vials were stored at room temperature during 24h prior to testing for vacuum retention.

A failure in this closure seal integrity test has been defined as:
underpressure after cold storage < 0.85 x initial underpressure

Table 11 : Container closure seal integrity during cold storage of FM457 ("#vials with failure / total vials tested")

Storage conditions	refrigerator	freezer	dry ice	Room temperature
Tested temperature	**5°C**	**-23°C**	**-78°C**	**20°C**
Testing of performance after:				
T = 0	0/5	0/5	0/4	0/4
T = 1 week			0/7	0/7
T = 1 month	0/10	0/10	0/7	0/7
T = 3 months	0/10	0/10	0/7	0/7

[3] [4,5] Drawing can be found in the attachments to this document.

Adequate container closure seal integrity is observed in all conditions tested.

10.5 Functional testing on infusion stoppers

Functional tests according to ISO 8536-2, ‘ Infusion equipment for medical use – Part 2 : Closures for infusion bottles’, were performed on 32mm infusion stoppers (product design V9003) [6] in compound FM457. The stoppers comply with the piercing force test, the fragmentation test and the spike retention/sealability test. Results are shown below.

Table 12 : Functional tests according to ISO 8536-2 on FM457 V9003 infusion stoppers

Test	Unit	Limit	Result
Piercing force	Max. piercing force (N)	80	50.9
	Average piercing force (N)	75	44.2
Fragmentation	Average # fragments / 10 stoppers	20	3
Spike retention and sealability	# spike removals / # stoppers tested	0	0
	# leaks against spike / # stoppers tested	0	0

(Data recorded for batch 30122251)

In order to simulate more aggressive piercing and handling which may occur at the point of use, the ISO 8536-2 test procedure is modified *as follows*:

- Preparation, assembly and sterilization procedure performed according to ISO 8536-2
- Piercing of the stopper with the ISO spike
- *After complete piercing, the spike is sequentially tilted sideways towards the 4 quadrants*
- *The spike is moved up and down once without removal of the spike from the piercing site*
- *The spike is rotated clockwise over 90° and then back to the starting position. The same is repeated counter clockwise*

Subsequently the spike is loaded and the standard ISO 8536-2 test method is continued.

Table 13 : Spike retention and sealability properties according to ISO8536-2 on FM457 V9003 infusion stoppers after additional mechanical stress

Test	Unit	Result
Spike retention and sealability	# spike removals / # stoppers tested	0/30
	# leaks against spike / # stoppers tested	0/30

(Data recorded for batch 30122251)

Product design V9003 is the only 32mm infusion stopper in compound FM457 that is offered by Datwyler for new applications.

[6] Drawing can be found in the attachments to this document.

10.6 Gliding behavior for syringe plungers

The gliding properties of steam sterilized FM457 plungers V9283 [7] (sterilized 60 mins. at 121 °C) were examined as a function of syringe storage time. Therefore the sterilized plungers were assembled in a syringe barrel and the assemblies were sterilized for 30 min at 121°C in a lab autoclave (syringes were not filled). Half of the syringes were stored at room temperature; the other half of the syringes were stored at 40°C (75% RH). The measuring points were 0, 1, 3 and 6 months.

The gliding properties are measured on a tensile machine. The syringes are mounted on a holding device and the plunger is pushed at a speed of 40 mm/min. The highest recorded value is considered the activation force. The gliding force is recorded after 75% of the way (=30mm). The forces are shown in the figures below.

Figure 18 : Activation forces for steam sterilized FM457 V9283 plungers

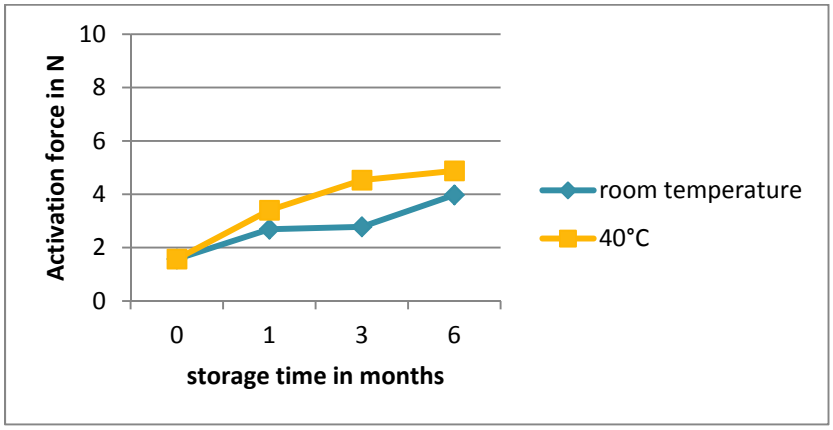
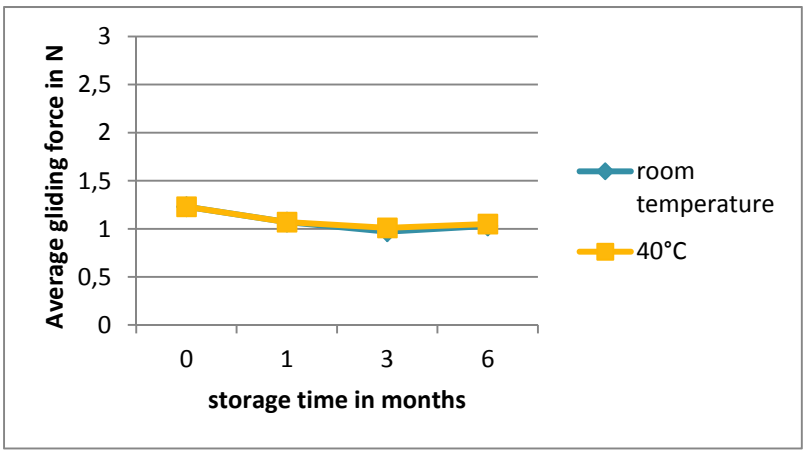


Figure 19 : Average gliding forces for steam sterilized FM457 V9283 plungers



Activation and gliding forces are found to be on an acceptably low level. Activation forces increase after storage, while gliding forces are found to remain constant over time.

[7] Drawing can be found in the attachments to this document.

11 Biological properties

11.1 USP <1031>

USP<1031>, “The Biocompatibility of Material used in Drug Containers”, stipulates that the biocompatibility of an elastomeric material is evaluated according to the two stage testing protocol specified in the USP<381>. An elastomeric material that does not meet the requirements of the first-stage testing (in vitro, USP<87>), may qualify as a biocompatible material by passing the second stage testing (in vivo, USP<88>).

No class or type distinction is made between elastomeric materials that meet the requirements of first-stage of testing and those that qualify as biocompatible meeting the second-stage requirements.

11.2 USP <87>

Biological testing (-elution test-) is carried out on a sample of FM457 as per USP<87>, “Biological Reactivity Tests, In Vitro” and is proven to be non-cytotoxic. A copy of the report can be found on the next page.

11.3 ISO 8871-4

The ISO 8871-4, “Elastomeric parts for parenterals and for devices for pharmaceutical use – Part 4: Biological requirements and test methods”, specifies biological requirements for bacterial endotoxins, bioburden, cytotoxicity and intracutaneous and systemic toxicity.

The requirements for endotoxins and bioburden are left open and shall be agreed upon between supplier and user.

For the toxicity tests, the same approach as in USP <1031> is given, including reference to the USP <87>, in vitro test, for the cytotoxicity test and the USP <88>, in vivo test for the intracutaneous and systemic toxicity test.

TOXIKON
Leaders in Life Science and Technology

TEST RESULT REPORT N°10-B1030-N1

Project Number:	**TE 10445**	**Study Number:**	**10-B1030-N1**
Sponsor:	**Helvoet Pharma Belgium NV**	**Report Date:**	**20/05/2010**
Contact:	*Mrs. Nadia Nouri*		
Address:	Industrieterrein Kolmen 1519 3570 Alken, Belgium	Date Sample Arrival: Technical Initiation:	12/05/2010 17/05/2010
PO.Number:	PB1001708	Technical Completion:	20/05/2010

Study	**Elution Test - ISO**	Temp/Time	37°C/24 hours
Test Item	V9341 FM457/0 0 kGy Gamma t=24m	Ratio	25cm²/20mL
Lot	Ch808934	Vehicle	MEM-Complete

REFERENCE: According to "ISO 10993-5, 2009: Biological Evaluation of Medical Devices- Part 5:Tests for In Vitro Cytotoxicity." and "USP 32-NF 27, 2009: <87> Biological reactivity test, in vitro." Toxikon Reference: SOP 3.1.2.3, rev. 08

PROCEDURE: The biological reactivity of a mammalian monolayer, L929 mouse fibroblast cell culture, in response to the test item extract was determined. The samples and control articles were autoclaved prior to the preparation of the extracts. Extracts were prepared at 37±1°C for 24 hours in a humidified atmosphere containing 5±1% carbon dioxide (static). Positive (natural rubber) and negative (silicone) control articles were prepared to verify the proper functioning of the test system. The maintenance medium on the cell cultures is replaced by the extracts of the test item or control article in triplicate and the cultures are subsequently incubated for 48 hours, at 37±1°C, in a humidified atmosphere containing 5±1% carbon dioxide. Biological reactivity was rated on the following scale: Grade 0 (No reactivity); Grade 1 (Slight reactivity), Grade 2 (Mild reactivity), Grade 3 (Moderate reactivity) and Grade 4 (Severe reactivity). The test item is considered non-cytotoxic if none of the cultures exposed to the test item shows greater than mild reactivity (Grade 2).

RESULTS: No reactivity (Grade 0) was exhibited by the cell cultures exposed to the test item at the 48 hours observation. Severe reactivity (Grade 4) was observed for the positive control article. The negative control article showed no signs of reactivity (Grade 0).

OPINION AND INTERPRETATION: Based on the evaluation criteria mentioned above, the test item is considered non-cytotoxic.

RECORD STORAGE: All raw data generated in this study will be archived at Toxikon Europe, according to SOP 4.2.8.

AUTHORIZED PERSONNEL

ir. Peter Cornelis
Study Director

Vanessa Ruymen
Quality Assurance

Toxikon Europe nv - Researchpark Haasrode 1724 - Romeinsestraat 12, B 3001 Leuven, Belgium - Tel. 32-16-40 04 84 - Fax 32-16-40 13 04
Fortis 230-0391575-06 - KBC 431-0697001-33 - BTW/TVA BE 0442.395.719 - H.R. Leuven 80.154 - www.toxikon.be

12 Particulate cleanliness

The level of subvisible and visible particles was measured on FM457 production batches and compared with other halobutyl compounds.

12.1 Subvisible particulate cleanliness

Datwyler procedure QA-021 “Determination of subvisible particle count” was followed. This group procedure is based on ISO 8871-3, ‘Elastomeric parts for parenterals and for devices for pharmaceutical use -- Part 3: Determination of released-particle count’.

The table below shows the subvisible particulate cleanliness results for 20mm serum V9048 stoppers in FM457 and in other compounds. The reported value is the average of a certain number of batches.

Table 14 : Subvisible particulates for V9048 serum stoppers in different compounds, ISAF1 washed

	# subvisible particles per 10 cm^2 rubber surface area		
	2-5 µm	**5-10 µm**	**10-25 µm**
FM457/0 (n = 392 batches)	388	77	9
Typical bromobutyl (n = 118)	382	84	8
Typical chlorobutyl (n = 34)	328	68	7

Data from 01/01/2010 – 31/12/2011 out of SAP

12.2 Visible particulate cleanliness

Datwyler procedure QA-020 “Determination of visible particles on rubber parts” was followed. This procedure is based on ISO 8871-3.

The table below shows the visible particulate cleanliness results for 20mm serum V9048 stoppers in FM457 and in other compounds. The reported value is the average of a certain number of batches.

Table 15 : Visible particulates for V9048 serum stoppers in different compounds, ISAF1 washed

	# visible particles per 10 cm^2 rubber surface area		
	25-50 µm	**50-100 µm**	**>100 µm**
FM457/0 (n = 392 batches)	1.1	0.6	0.2
Typical bromobutyl (n = 118)	1.5	0.9	0.3
Typical chlorobutyl (n = 34)	1.6	0.8	0.2

Data from 01/01/2010 – 31/12/2011 out of SAP

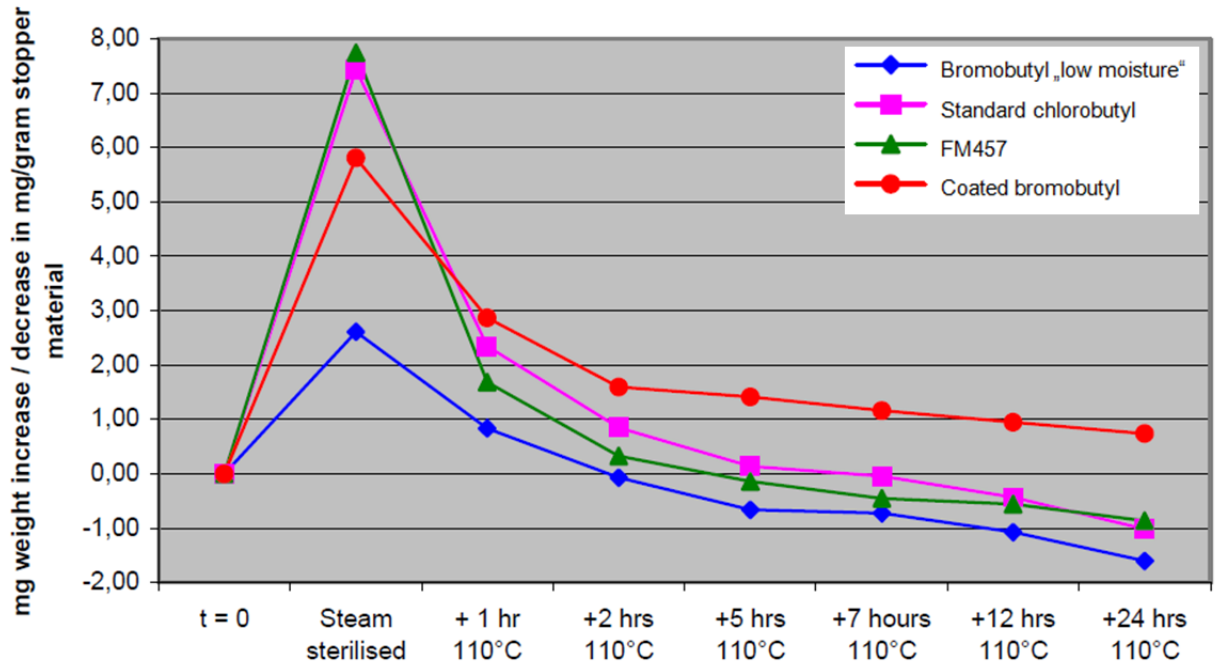
13 Moisture content

Results for moisture content that are given below are indicative only as the actual moisture content is dependent on numerous factors like stopper design, packaging way, climate, actual steam sterilization and drying equipment, etc.

The typical moisture content of rubber compound FM457 after the final treatment at Datwyler, i.e. after washing, drying and packaging, is in the range of 0.3 w/w% (3 mg water/g rubber).

Additional moisture is absorbed during the steam sterilization step. The graph below shows the uptake of some standard compounds after steam sterilization and the moisture release upon drying at 110°C.

Figure 20 : Moisture content for standard compounds after steam sterilization and drying at 110°C



14 Stability upon gamma irradiation

14.1 Effect on physical properties

Test pieces in FM457/0 were subjected to gamma irradiation treatments at doses of 30 kGy and 55 kGy. These doses grossly correspond with 1 resp. 2 sterilizations at the nominal dose of 25 kGy, that is frequently applied to rubber products. The physical properties of the test pieces after gamma treatment were compared to the properties without irradiation. Results are listed below.

Table 16 : Physical properties after gamma irradiation

Property	Unit	Irradiation level (kGy - gamma)		
		0	30	55
Modulus 100	N/mm²	1.56	1.41	1.33
Modulus 300	N/mm²	2.83	2.57	2.47
Tensile strength	N/mm²	4.78	4.46	3.93
Tear strength	N/mm	8.96	8.91	10.20
Elong. at break	%	408	396	360
Compression set	%	26	30	33.5
Hardness	° Shore A	51	50	49

Physical properties of FM457 do not significantly change upon gamma irradiation up to doses of 55 kGy.

14.2 Effect on chemical properties

The chemical properties of FM457 as per USP <381> / Pharm. Eur. 3.2.9 and Pharm. Jap. 7.03 after gamma treatment were compared to the properties without irradiation. Results are not given in full detail in this report, but they are reported in separate 'RTU' [8] documentation .Please contact your Datwyler sales representative.
Chemical properties of FM457 do not significantly change upon gamma irradiation up to doses of 40 kGy.

14.3 Effect on compatibility with WFI

Parts in FM457/0 were subjected to gamma irradiation treatments at doses of 30 kGy and 55 kGy. The parts then were autoclaved in WFI for 30 minutes at 121 °C in a ratio of 2.34 cm² rubber surface area per 1 ml of WFI. After autoclavation the rubber was left in contact with the WFI and was stored for 1 month at 40 °C. After storage the water in contact with the rubber was tested on a number of properties.

[8] ‚RTU' refers to gamma irradiated, sterile products that are 'Ready-To-Use'.

Table 17 : WFI compatibility after gamma irradiation

Test	Unit	Pharm. limit	Irradiation dose (kGy - gamma)		
			0	30	55
Ca + Mg	ml Na-EDTA	0.5	0.20	0.20	0.23
Chlorides	NTU	3.5	2.0	1.6	1.5
pH	-	5.0-7.0	6.5	6.4	6.3
Reducing substances	ml 0.01 N KMnO4 (visual test)	2	1.2	1.2	1.5
Ammonium	ppm	(colour)	pass	pass	pass
Zinc	-	-	0.058	0.066	0.078
UV absorb.	-	-	0.036	0.034	0.041

Gamma irradiation up to levels of 55 kGy has no significant effect on the compatibility of FM457 with WFI.

14.4 Effect on functional properties

The functional properties of FM457 after gamma treatment (13mm closures) were compared to the properties without irradiation. Results are not given in full detail in this report, but they are reported in separate RTU documentation .Please contact your Datwyler sales representative.
Functional properties of FM457 do not significantly change upon gamma irradiation up to doses of 40 kGy.

15 FM457 : product formats

Products in compound FM457 are available in the following formats:

1. **Bulk**
   The products are washed, siliconized and dried. After washing and drying they are packed in multiple protective polyethylene bags (non-sterilizable).

2. **Ready-for-Sterilization ('RfS')**
   The products are washed, siliconized and dried using a validated washing program. Then they are packed in steam-sterilizable bags (RfS bags) and protective non-sterilizable polyethylene overwrapping. Steam sterilization of the products in the RfS bags after removal of the protective overwrapping is performed before (aseptic) filling.

3. **Ready-To-Use ('RTU')**
   The products are washed,siliconized and dried using a validated washing program. Then they are packed in multiple multilayer bags that are compatible with gamma irradiation ('RTU bags'). The products are gamma sterilized at a contractor, using a validated irradiation process. Products in FM457 are equally available in irradiation compatible Rapid Transfer Port bags.

Supportive technical documentation on washing, Ready-for-Sterilization and Ready-To-Use is available from Datwyler. Please ask your Datwyler sales representative.

16 References

- Datwyler Technical documentation FM457, Ed. 3, 2008
- Compound data sheet FM457/0, dated October 11, 2010
- Datwyler report R0243
- Datwyler report CS0029
- Datwyler report CS0052
- Datwyler report R0045
- Datwyler report CS0069
- Datwyler report CS0120
- Datwyler report CS0061
- Datwyler report CS0230
- Datwyler report CS0111

17 History

Edition (issue date)	Change (chapter + change)	Comment (rationale)
4 (February 11, 2013)	Complete overhaul of Ed. 3 (2008)	Update to current state of knowledge and documentation

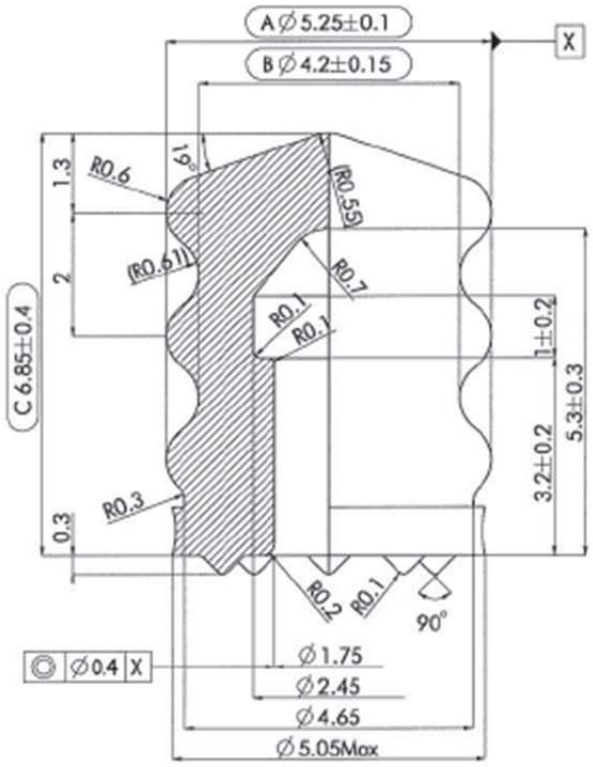
18 Attachments

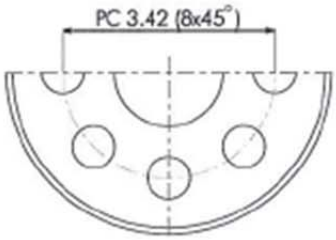
Product drawings V9315, V9025, V9341, V9003, V9283, V9048

DATWYLER

DATWYLER

PLUNGER STOPPER (0.5ML) ***PRODUCT NUMBER*** **V9315**





SCALE 1

Printed copies will not be systematically updated

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

MODIFICATIONS	NR	OBJECTS OF MODIFICATION	DATE	TRACED	CHECKED	AUTHORIZED
	2	Conversion to new cad-format	Jun 15,'10	PD		
	1	Trim edge diameter changed from max 4.95 to max 5.05	May 15,'03	KV-2		

DRAWING						
TRACED KV-1	DATE Jun 15,'10	CHECKED 23 June, 2010	INITIALS JW	FILE REF.	SCALE 10:1	
DERIVED FROM DRAWING			DATED		PROJECTION	
REPLACES PRODUCT DRAWING		V9315	DATED May 22,'03			

VALIDITY			
VALID FROM June 23, 2010	AUTHORIZED BY RJ	SIGNATURE	

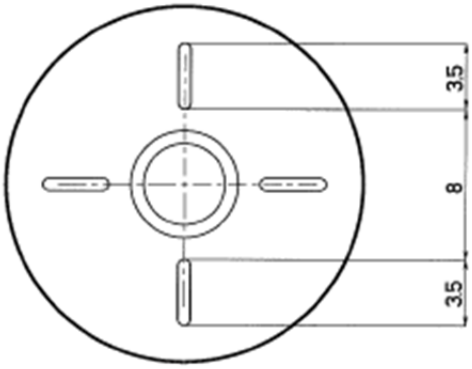
Dimensions without tolerance indication correspond to DIN ISO 2302 Class M3. Cut or punched edges can be slightly conical, excentric and/or variable.

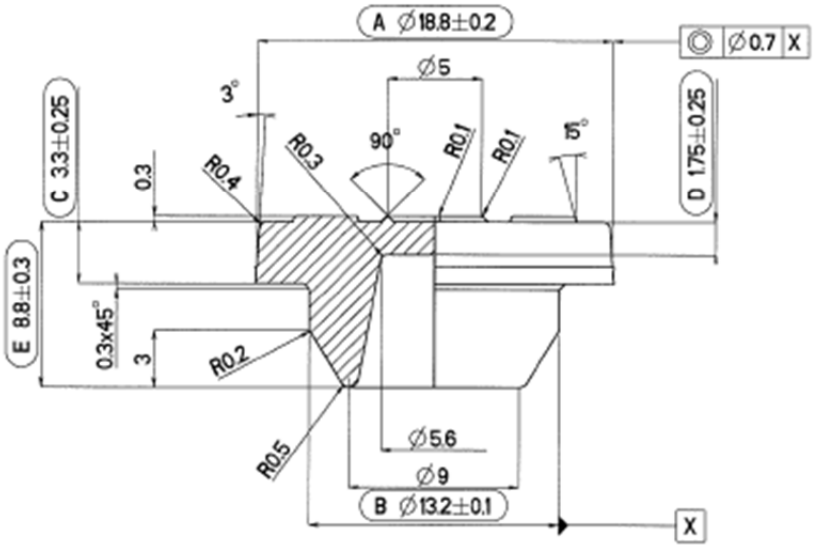
DATWYLER

DATWYLER

STOPPER **PRODUCT NUMBER** **V9025**

SCALE 1:1





DIMENSIONS											
	Apr 06,'04		FM 240	∅ 18.7	∅ 13.15	3.3	1.75	8.8			
	DATE	CHECKED	All compounds except above mentioned	A	B	C	D	E	F	G	H

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

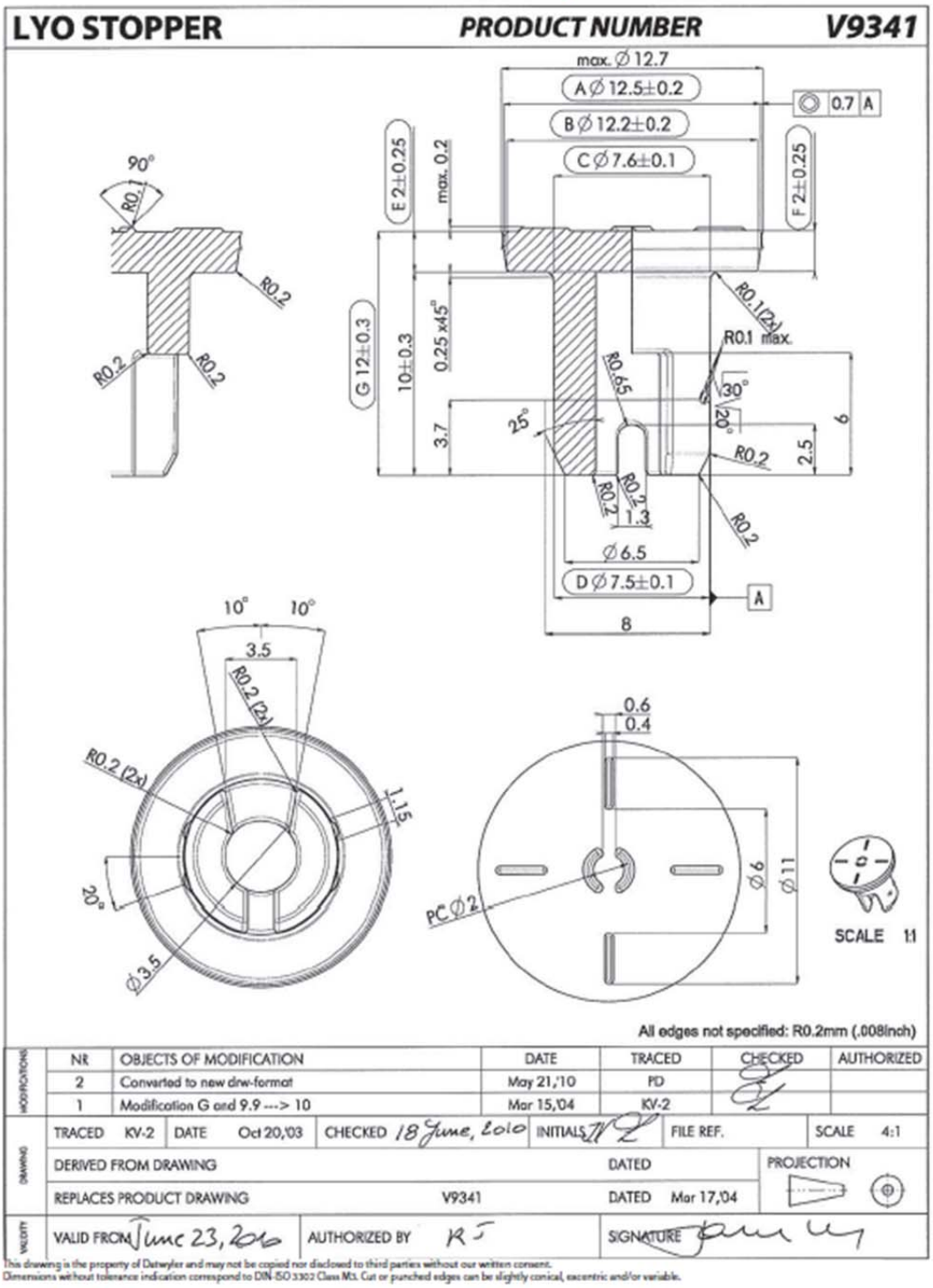
MODIFICATIONS	NR	OBJECTS OF MODIFICATION	DATE	TRACED	CHECKED	AUTHORIZED
	3	Removed max. Trimdiameter	Jan 26,'12	LBAU		
	2	Converted to new drw-format	Jun 18,'10	TCUY		

DRAWING						
TRACED KV-1	DATE Apr 06,'04	CHECKED Jan 26, 2012	INITIALS JV	FILE REF. -	SCALE 3:1	
DERIVED FROM DRAWING -			DATED -	PROJECTION		
REPLACES PRODUCT DRAWING		V9025	DATED Apr 19,'04			

VALIDITY			
VALID FROM Jan 26, 2012	AUTHORIZED BY BJON	SIGNATURE	

Printed copies will not be systematically updated

DATWYLER



MODIFICATIONS	NR	OBJECTS OF MODIFICATION	DATE	TRACED	CHECKED	AUTHORIZED
	2	Converted to new drw-format	May 21,'10	PD		
	1	Modification G and 9.9 ---> 10	Mar 15,'04	KV-2		

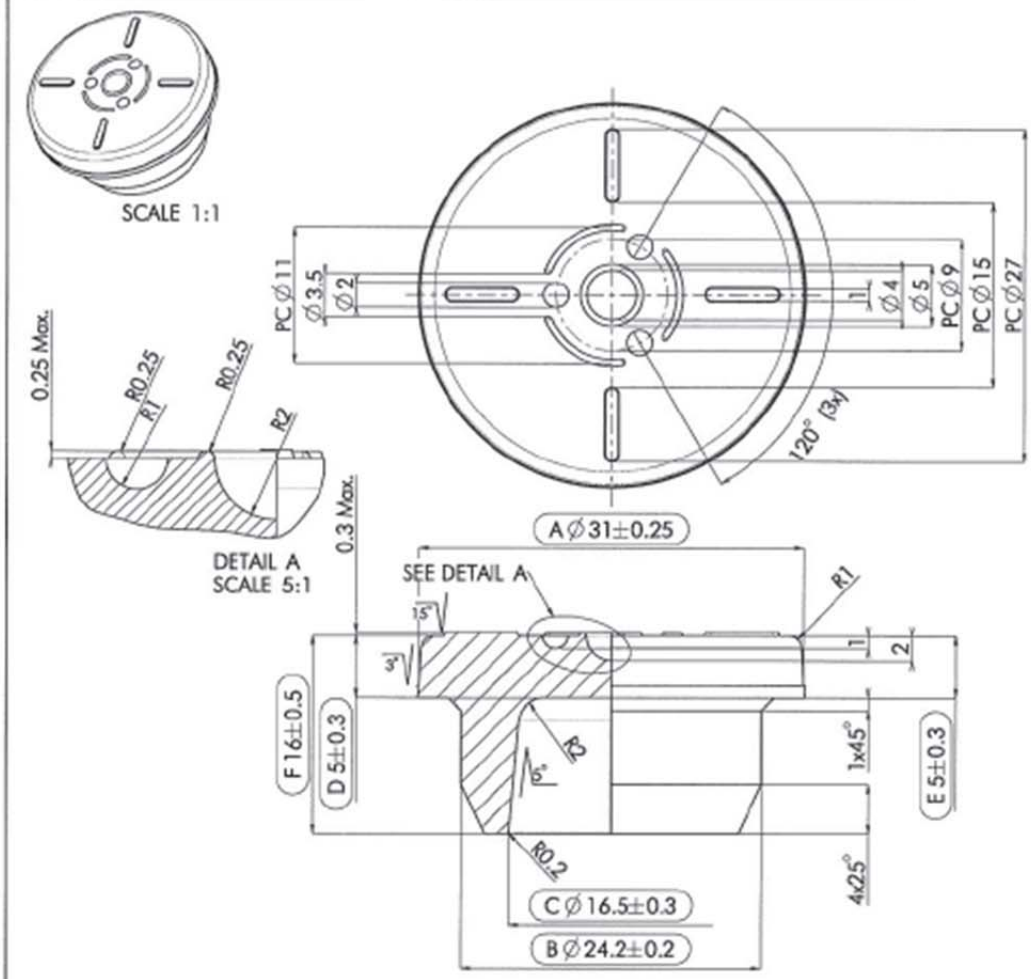
DRAWING						
TRACED KV-2	DATE Oct 20,'03	CHECKED 18 June, 2010	INITIALS	FILE REF.	SCALE 4:1	
DERIVED FROM DRAWING			DATED	PROJECTION		
REPLACES PRODUCT DRAWING	V9341		DATED Mar 17,'04			

VALIDITY			
VALID FROM June 23, 2010	AUTHORIZED BY RJ	SIGNATURE	

DATWYLER

DATWYLER

STOPPER **PRODUCT NUMBER** **V9003**



			FM257 Omniflex	Ø 31.0	Ø 24.2	Ø 16.5	5.0	5.1	16.0		
DIMENSIONS	Jan 01,'03		FM240	Ø 30.85	Ø 24.1	Ø 16.5	5.0	5.0	16.0		
	DATE	CHECKED	Deviating compounds mentioned above.	A	B	C	D	E	F	G	H

Units are in mm

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

MODIFICATIONS	NR	OBJECTS OF MODIFICATION	DATE	TRACED	CHECKED	AUTHORIZED
	2	Converted to new drw-format	May 21,'10	PD		
	1	Updated to currend CAD standard	Aug 18,'06	RT-2	RT	

DRAWING							
TRACED RT-2	DATE Aug 18,'06	CHECKED 15 June, 2010	INITIALS	FILE REF. -	SCALE 2:1		
DERIVED FROM DRAWING				DATED	PROJECTION		
REPLACES PRODUCT DRAWING		V9003		DATED Aug 25,'06			

VALIDITY			
VALID FROM June 23, 2010	AUTHORIZED BY RT	SIGNATURE	

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

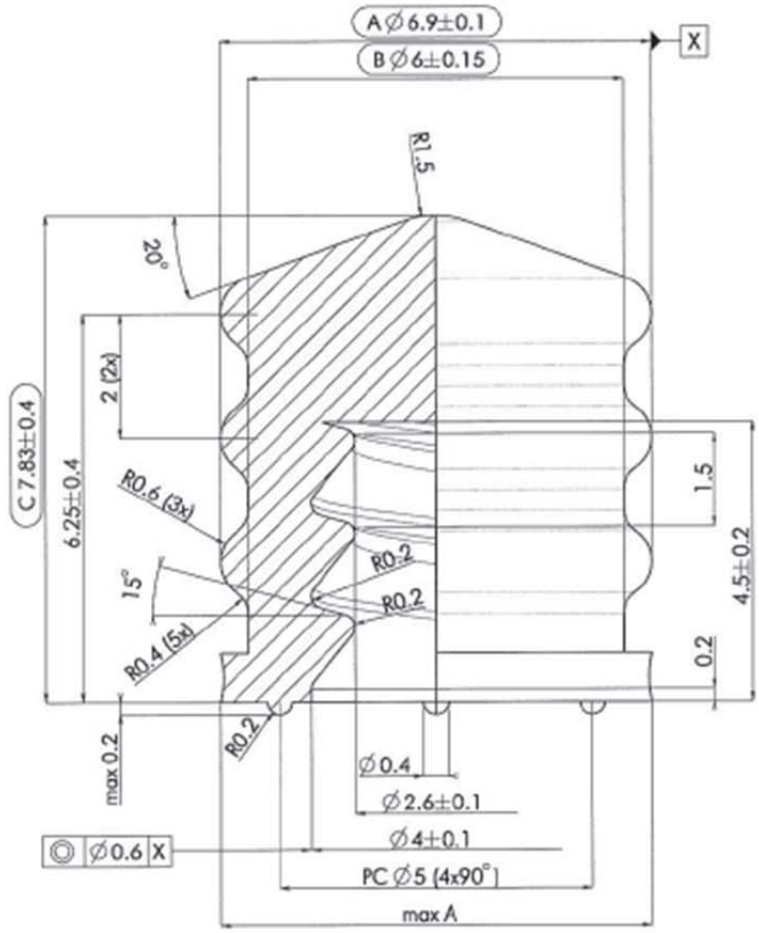
Printed copies will not be systematically updated

DATWYLER

DATWYLER

PLUNGER **PRODUCT NUMBER** **V9283**

SCALE 1:1



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

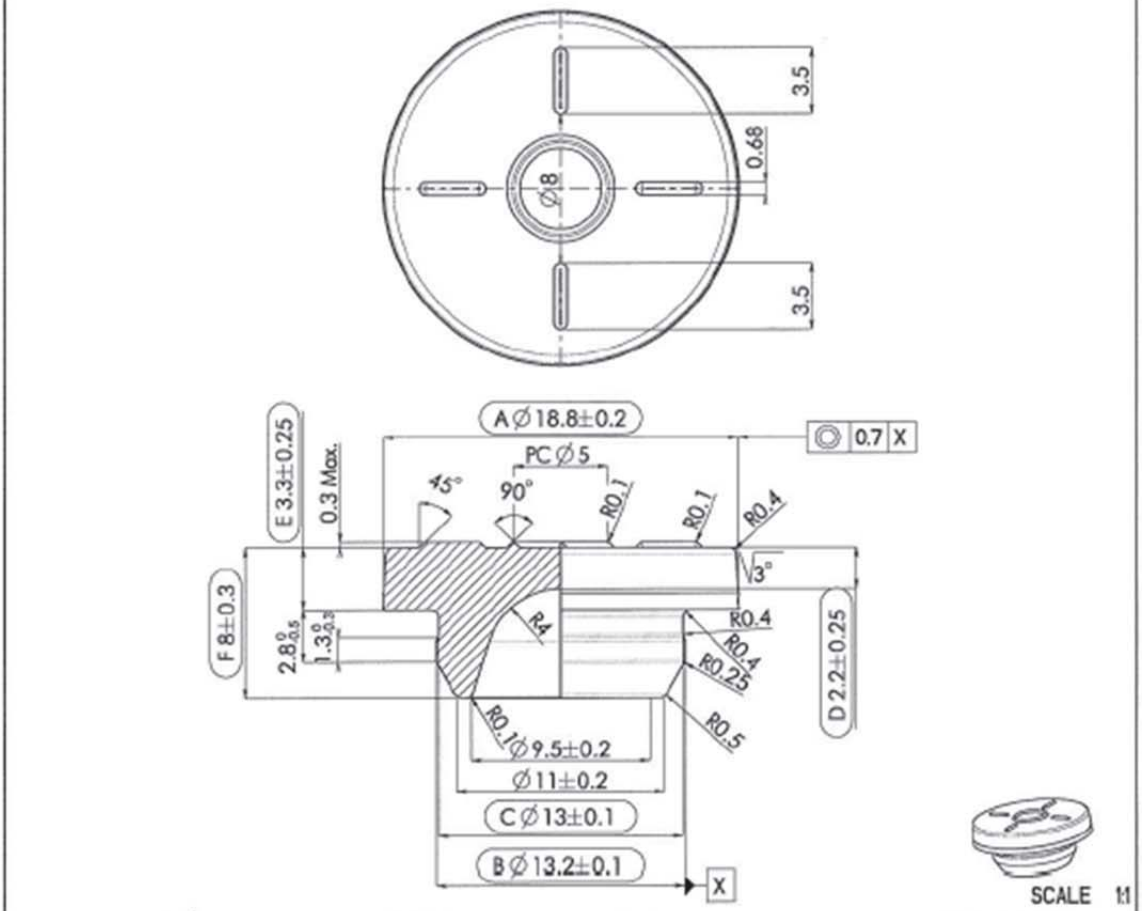
MODIFICATIONS	NR	OBJECTS OF MODIFICATION	DATE	TRACED	CHECKED	AUTHORIZED
	1	Drawing converted to new CAD-system	Oct 17,06	RT-1		
	2	Conversion to new cad-format	Jun 15,'10	PD		

DRAWING								
	TRACED RT-1	DATE Oct 17,'06	CHECKED 23 June 2010	INITIALS JV	FILE REF. -	SCALE 10:1		
	DERIVED FROM DRAWING	-	DATED -	PROJECTION				
	REPLACES PRODUCT DRAWING	V9283	DATED Oct 18,06					
VALIDITY	VALID FROM June 23, 2010	AUTHORIZED BY RJ	SIGNATURE					

DATWYLER

DATWYLER

STOPPER **PRODUCT NUMBER** **V9048**



DIMENSIONS	May 07,'96	hz	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	hz	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)

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

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

Printed copies will not be systematically updated