CUSTOMER SERVICE REPORT
CS0127

Technical Documentation
FM460

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*** The information in this report has been prepared with utmost care and, to the best of our knowledge, contains accurate information. However, the validity of this information and its application in any specific commercial or other case is subject to confirmation by Datwyler in a formal contract. ***

1. Table of Contents

2. Description

FM460 is a modern Datwyler bromobutyl compound with high chemical purity. This high chemical purity translates in a low extractables profile ensuring an increased compatibility in a wide range of applications.

FM460 is free from natural rubber or natural rubber latex and from BSE and is free from suspicious chemicals like nitrosamines and 2-mercaptobenzothiazole (MCBT). In addition, FM460 complies with all major pharmacopoeia for pharmaceutical rubber.

Physical and functional properties of FM460 are studied both before and after irradiation. These studies suggest that consideration should be given to multi-dose applications involving gamma irradiated FM460 stoppers.

FM460 shows a low permeability and has a low moisture content. At the same time, the uptake of moisture during a steam sterilisation cycle is very limited whereas the drying step is very effective with this compound.
Taking these points in consideration, FM460 is a good choice when autoclavation is used for sterilisation in combination with freeze dried drug products, irrespective of a possible moisture sensitivity of the lyo cake.

FM460 is shown in this documentation to feature a very low absorption of preservatives present in aqueous parenteral solutions.

Products in FM460 can be washed using a validated washing program (ISAF or FLNC), using Purified Water and Water-for-Injection, and can in combination with sterilizable bags be offered as Ready-for-Sterilisation (RfS).

Rubber compound FM460 is filed with the FDA in a US Drug Master File (#10953) and with the Health Protection Branch in Canada (#1994-027).

Note: FM460 refers to the type of compound. The extension "/0", "/1", … refers to the colour of the said compound.
Differently coloured compounds may have been 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, compound FM460 does not contain any natural rubber or natural rubber latex.

3.2. Nitrosamines

Nitrosamines are residues of specific curing systems. These residues are in a number of cases known to be carcinogenic.
Rubber compound FM460 is 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.
Rubber compound FM460 does not contain 2-mercaptobenzothiazole (MCBT) or any of its derivatives.

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.
Rubber compound FM460 does not use components of animal origin. FM460 is 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.

Rubber compound FM460 fulfils 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). FM460 thus also fulfils the CONEG requirements.

3.6. GMO (Genetically Modified Organisms)

Rubber compound FM460 does not contain ingredients that are derived from Genetically Modified Organisms (GMO).

3.7. Asbestos

Asbestos is known to pose a health hazard and has been subject of scrutiny by Health Authorities.
Datwyler does not use asbestos as ingredient in its rubber formulation FM460. Also all possible precautions have been taken to have no asbestos fibers in production areas.

3.8. Phthalates

Phthalates are frequently used as plasticizer in plastics and are associated with health hazards.

Datwyler does not use this category of ingredients in its rubber formulations or in its processes. Compound FM460 is therefore free of phthalates and its derivatives.

3.9. 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 FM460 does not use Bisphenol A or the following BPA related substances in its 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 FM460, intended for use in parenteral applications, stored in the original packaging under the ambient storage conditions as described in the ISO 2230, “Rubber Products – Guideline for storage”, is 2 years after packing date.

Hereafter, based on the indications given in the ISO 2230, 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 shown in Table 1 are taken for compound FM460/0, Gray. Properties like density and ash content may differ slightly for different colours of the said compound. In case more compound colours become available, data per compound colour are given on the corresponding Compound Data Sheets, available as separate documents upon request.

Table 1 : Physical properties – FM460/0

Hardness	°Shore A	ISO 7619 1 sec indentation	46 ± 5
Density	g/cm³	ISO 2781	1.348 ± 0.025
Ash	%	Internal Method(s): Calcination 4h@700°C	48.0 ± 2.0
Compression Set	%	ISO 815	max. 22
Tensile Strength	N/mm²	ISO 37	min. 4

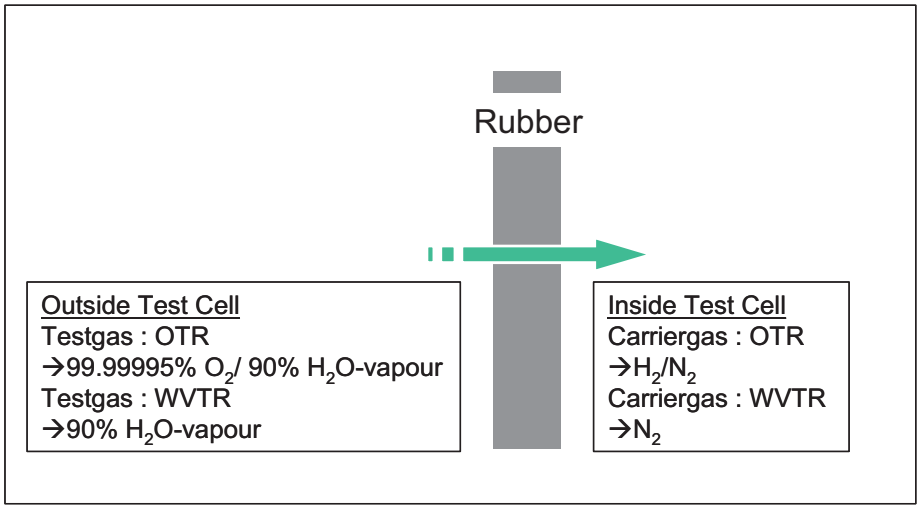
5.2. Permeability

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 viz. 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 is cut matching 50 cm² and clamped in a double chamber test cell, acting as a barrier between both chambers (Figure 1).

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

Figure 1 : Schematic principle of a transmission rate measurement



5.2.1. Water Vapour Transmission Rate (WVTR)

Equipment: **MOCON, Permatran-W 3/31 MG-module**
Conditions: **38 °C ; 90% relative humidity ; 100 flow N_2**

Table 2 : WVTR comparison

	WVTR in g/m².24h, 90% RH / 38°C
FM460	0.09

5.2.2. Oxygen Transmission Rate (OTR)

Equipment: **MOCON, Oxtran 2/20 ML-module**
Conditions: **38 °C ; 90 % relative humidity ; 99.99995% O_2**

Table 3 : OTR comparison

	OTR in cc/m².24h, 90% RH / 38°C, 99.99995% O_2
FM460	85

Water vapour and oxygen permeation through FM460 is very low and typical for halobutyl based rubber formulations, which makes this compound suitable for a wide range of pharmaceutical applications, e.g. freeze dried drug products.

6. Chemical Properties

6.1. Pharmacopeial data

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

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 below summarizes the results of FM480 chemical testing according to both USP <381> and Pharm. Eur. 3.2.9.

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

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 0.07	0.07
					EP	0.07
					USP	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		0.12
Extractable heavy metals		Sol. S	ppm Pb^{2+}	2	EP	<2
					USP	<2
Extractable zinc		Sol. S	ppm Zn^{2+}	5.0		0.02
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 respectively.*

Figure 2 : Typical IR-spectrum of a pyrolysate (4000-625cm^{-1}) – FM460/0

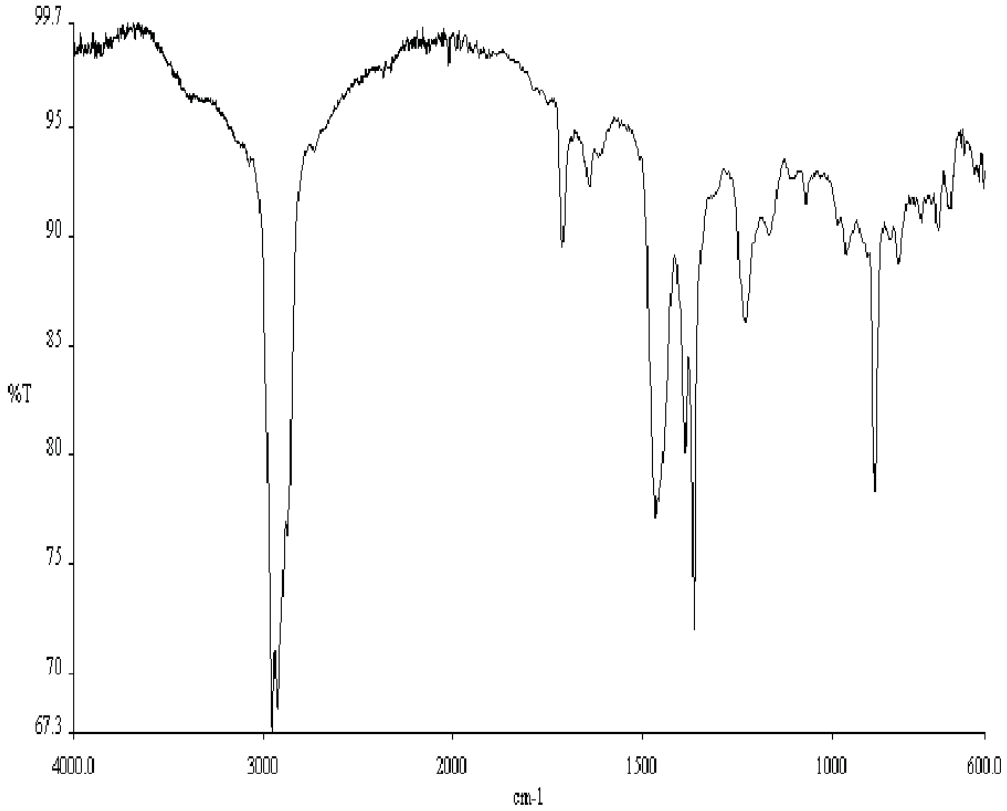
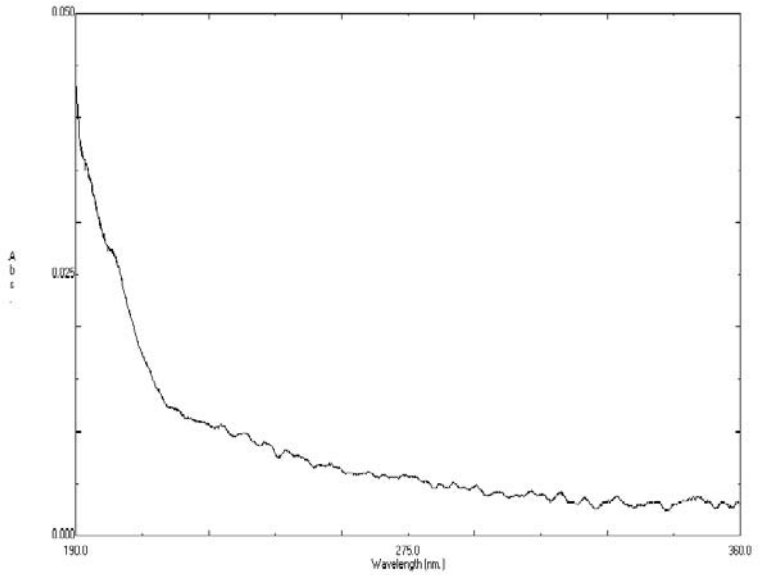


Figure 3 : Typical UV-spectrum of an aqueous extract of FM460/0 acc. to the Pharm. Eur. 3.2.9.



6.1.2. Japanese Pharmacopeia 7.03

Results for FM460/0, tested according to physicochemical part of the Japanese Pharmacopeia, chapter 7.03, “Test for Rubber Closures for Aqueous Infusions”, valid version, are given in Table 5 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 plunger with a volume of 1.46cm³, a weight of 1.97g and a total surface of 11.07cm².

For the design given, FM460 complies with the extractable substances part of the Pharm. Jap. 7.03. Other parts of the Pharm. Jap. 7.03 were not tested and hence are not documented. Please contact your Datwyler sales representative in case of need.

Table 5 : JP 7.03 – FM460

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	99.6 99.8
Foam test	5 ml	-	foam disap. < 3 min.	pass
pH	20 ml	pH units	difference with blank: max. 1.0 (*)	0.16
Reducing substances	100 ml	ml 0.002 M $KMnO_4$	2.0	0.30
Evaporation residue	100 ml	mg	2.0	0.17
UV absorb. (220-350 nm)	10 mm cuvet	absorbance	0.2	0.011
Zinc	10 ml	ppm Zn^{2+}	1 ppm	<0.01

(*) “-“ means more acidic than blank; “+” means more alkaline than blank

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 under paragraph 6.1.1.

6.3. Extractable information

A detailed extractables report on FM460 involving solvents of various polarity 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. Functional Properties

7.1. European Pharmacopeia 3.2.9.

Table 6 lists the functional properties of FM460 as per the Pharm. Eur. 3.2.9. “Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders”, valid version.
For the tests for penetrability, fragmentation and self-sealing, the same pre-treatment as described for the preparation of solution S is used (autoclaving for 30min at 121°C). Stoppers are allowed to dry.

Outline of test methods

Penetrability:
- 10 filled vials are stoppered with test stoppers and capped;
- stoppers are pierced with a 0.8 mm (21G) hypodermic needle at a controlled speed of 200 mm/min;
- the highest force is recorded;
- limit = 10 N.

Fragmentation (Coring):
- 12 filled vials are stoppered with test stoppers and capped;
- each stopper is pierced 4 times with a new 0.8 mm (21G) hypodermic needle;
- the content of 12 vials is poured over a filter;
- the number of fragments is counted by naked eye;
- limit = max. 5 fragments / 48 piercings.

Self-Sealing:
- 10 filled vials are stoppered with test stoppers and capped;
- each stopper is pierced 10 times with a new 0.8 mm (21G) hypodermic needle;
- vials are immersed upright in a 0.1% methylene blue solution;
- the external pressure is reduced with 27 kPa for 10 min;
- atmospheric pressure is reestablished and vials are left immersed for 30 min;
- vials containing any trace of coloured solution are counted;
- limit = 0 vials with coloured solution.

The results shown in Table 6 below are for a typical 20mm stopper design (ISO 8362-2 and ISO 8362-5).

Table 6 : Pharm. Eur. 3.2.9. Functional tests – FM460

TEST	UNITS	LIMIT	TYPICAL RESULTS
Penetrability	N	10	1-2
Fragmentation	-	5	0-1
Self-Sealing	-	0	0

The chemical properties according to this Pharm. Eur. 3.2.9 are described under chapter 6.1.1.

7.2. ISO 8871-5

The ISO 8871-5, “Elastomeric parts for parenterals and for devices for Pharmaceutical Use – Part 5: Functional requirements and testing” describes following normative test series:

- Penetrability
- Fragmentation
- Self-Sealing
- Container Closure Seal Integrity

Annexes A, B and C, respectively for Penetrability, Fragmentation and Self-Sealing are identical to the functional testing described in the Pharm.Eur.3.2.9. Results can be found in Table 6.

Annex D, the Container Closure Seal Integrity, becomes redundant if requirements as per Self-Sealing, Annex C, are fulfilled.

8. Biological Properties

8.1. USP <1031>

The 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.

8.2. USP <87>

Biological testing (-elution test-) is carried out on a sample of FM460 as per the USP<87>, “Biological Reactivity Tests, In Vitro” and is proven to be non-cytotoxic. A copy of the report can be found in Figure 4 on the next page.

8.3. 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 the 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.

Figure 4 : Elution test (USP<87>) – FM460

TOXIKON
EUROPE N.V.

TEST RESULT CERTIFICATE

Study Number:	**02-B0411-N1**	**Report Date:**	**05/03/2002**
Sponsor:	**Helvoet Pharma**		
Contact:	*Dhr. Luc Vanderheyden*		
Address:	Industriepark Kolmen 1519 B - 3570 Alken		
		Technical Initiation:	01/03/2002
PO.Number:	000185 OM	Technical Completion:	05/03/2002

Study	Elution Test – USP 24, NF 19	Temp/Time	37°C/24 Hr.
Test Article	FM 460/0 V9258	Ratio	60 cm²/ 20 ml
Lot	050201	Vehicle	MEM Complete

REFERENCE: This study was conducted based on the procedure described in the International Organization for Standardization, Biological Evaluation of Medical Devices-Part 5: Tests for In Vitro Cytotoxicity, USP 24,NF19, pp 1831-1832, 2000

PROCEDURE: The biological reactivity of a mammalian monolayer, L929 mouse fibroblast cell culture, in response to the test article extract was determined. Extracts were prepared at 37±1°C for 24 hours in a humidified atmosphere containing 5±1% carbon dioxide. 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 article or control article in duplicate 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 a scale from Grade 0 (No reactivity) to Grade 4 (Severe reactivity).
The test article meets the requirements of the test if none of the cultures exposed to the test article shows greater than a mild reactivity (Grade 2).

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

CONCLUSION: The test article is considered non-cytotoxic and meets the requirements of the Elution Test, USP 24, NF19 , pp1831-1832,2000

AUTHORIZED PERSONNEL

Dr. Ine Janssen
Study Director

Ing. Ingrid Lenotte
Quality Assurance

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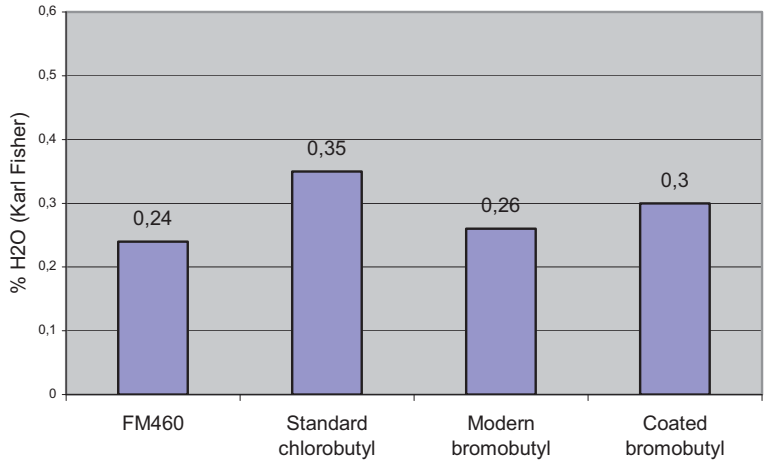
9. Moisture content

Rubber closures serve as barrier against ingress of moisture in the container/closure system, that is a critical parameter for freeze-dried products.

Rubber as such contains in equilibrium state a certain percentage of moisture. The graph below shows the percentage of moisture in different rubber formulations, measured in the delivery state condition (ready to ship).
The moisture content of all compounds in test is in the range of 0.2-0.4w/w%.

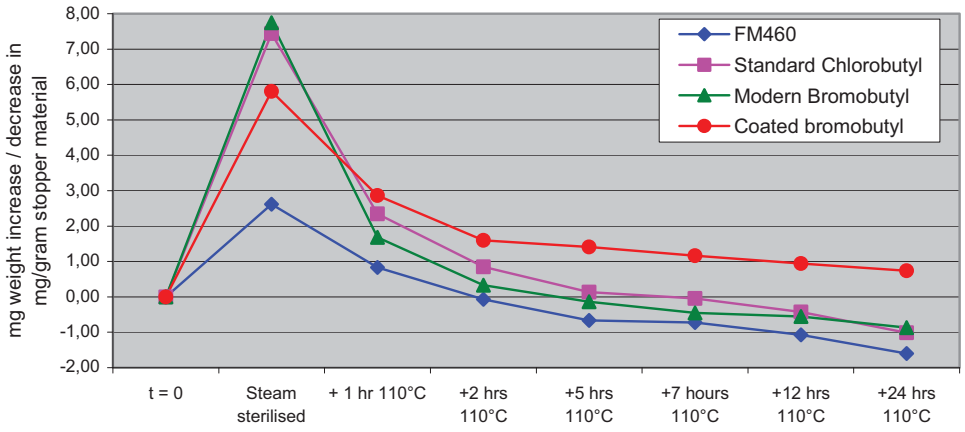
Figure 5 : Percentage (w/w%) moisture content in delivery state condition



An increase in moisture content will be seen during a steam sterilisation and will be released again during subsequent drying.
Figure 6 shows the uptake of moisture during a standard steam sterilisation of 30min at 121°C. Results are expressed in mg/gram stopper. The starting point was set to 0, thus the moisture content in delivery state was not taken into account.
All subsequent time points on the graph show the corresponding moisture content during drying at 110°C.

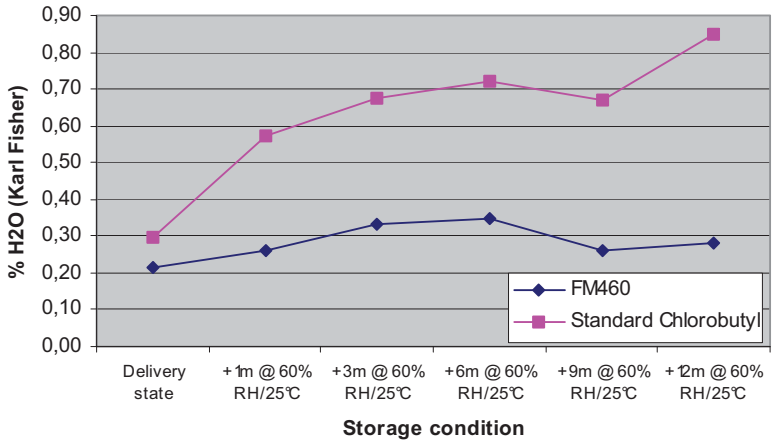
At all times, FM460 shows the lowest moisture content profile of all compounds in test. The moisture uptake during the steam sterilisation step is very limited and the subsequent drying step progresses after 2hours at 110°C already below the 0 % border on the graph, indicating that further drying is repelling the moisture already present at delivery.

Figure 6 : Weight decrease in mg/gram stopper material by drying at 110°C after a steam sterilisation process



A 12 month storage study has been performed for selected compounds, by using standard stoppers in Ready-for-Sterilisation bags (Tyvek Bags) and in a climate chamber at 60% RH / 25°C.
Figure 7 clearly shows that the uptake of moisture over time for FM460 is very limited.

Figure 7 : Effect of storage at 60% RH /25°C on moisture content of rubber stoppers.



For the studied compounds, FM460 comes out as a compound with a low moisture uptake during storage and during steam sterilisation and a fast desorption of moisture during the subsequent drying phase.
Low residual moisture guarantees that as little as possible moisture is transferred to the drug product. In applications where this is critical, FM460 is recommended.

10. Stability upon gamma irradiation

10.1. Influence of gamma irradiation on physical properties

The table below lists the results of the impact of gamma sterilization on some physical properties of FM460.
Measurements are performed at 2 irradiation levels: 30 kGy and 50 kGy. The former one is close to 25 kGy and represents a condition that is often met in practice. The dose of 50 kGy is chosen to illustrate the impact of worst-case conditions, due to uneven dose distribution or to a double sterilization at 25 kGy.

Determination is done as per the relevant rubber standards and is carried out on the test objects described in those standards.

Table 7 : Physical data before and after gamma irradiation and after ageing

Test criterion	Unit		0 kGy	30 kGy	50 kGy
Mod100	N/mm²	no ageing	1.27	1.57	1.57
		ageing 1wk 70°C	*1.32*	*1.61*	*1.71*
Mod 300	N/mm²	no ageing	2.60	2.50	2.26
		ageing 1wk 70°C	*2.75*	*2.66*	*2.58**
Tensile strength	N/mm²	no ageing	6.57	4.53	3.50
		ageing 1wk 70°C	*5.67*	*3.97*	*3.45*
Elongation at break	%	no ageing	599	476	347
		ageing 1wk 70°C	*535*	*422*	*301*
Hardness	°Shore A	no ageing	47.1	48.8	50.0
		ageing 1wk 70°C	*47.8*	*49.1*	*50.4*
Compression set	%	no ageing	18.1	16.6	15.9
		ageing 1wk 70°C	*14.9*	*11.7*	*9.4*

* *some samples break before reaching 300%*

Small effects of gamma irradiation on the physical properties of FM460 can be seen and are bigger with increasing irradiation dose.
The effect of ageing is less significant as the gamma irradiation treatment itself.

10.2. Influence of gamma irradiation on chemical properties (Pharm.Eur. 3.2.9.)

Tests are performed according to the European Pharmacopoeia, section 3.2.9. “Rubber closures for containers for aqueous parenteral preparations, for powders and freeze dried powders”.
100cm² rubber surface is autoclaved in 200ml distilled water for 30min. at 121°C
(Solution S)

Table 8 : Chemical properties after gamma irradiation (Pharm.Eur.3.2.9.) – FM460

CRITERIUM	TEST OBJECT	UNITS	LIMITS	0 kGy	25 kGy	45 kGy
Appearance (430-650 nm)	Sol. S	NTU	Type I : 6.0* Type II : 18*	0.54	0.05	0.08
Colour	Sol. S		See test procedure	pass	pass	pass
Alkaline matter	20 ml S	ml 0.01M HCL ml 0.01M NaOH	0.8 0.3	- 0.04	- 0.04	- 0.04
Absorption 220-360 nm	Sol. S	absorbance	Type I : 0.2 Type II : 4.0	0.009	0.013	0.026
Reducing substances	20 ml S	ml 0.002M $KMnO_4$	Type I : 3.0 Type II : 7.0	0.1	0.1	0.2
Heavy metals	Sol. S	ppm Pb^{2+}	2	<2	<2	<2
Zinc	Sol. S	ppm Zn^{2+}	5.0	0.00	0.00	0.02
Ammonium	Sol. S	ppm NH_4^+	2	<2	<2	<2
Evaporation residue	50 ml S	mg	Type I : 2.0 Type II : 4.0	0.1	0.0	0.0
Sulphide	20 cm²	mg S^{2-}	0.02	<0.02	<0.02	<0.02

** By definition corresponds with reference suspensions II and II resp.*

Gamma irradiation up to levels of 45 kGy has no noticeable effect on the chemical properties of closures in FM460. All results are within the limits of Pharm. Eur. 3.2.9.

10.3. Influence of gamma irradiation on functional properties (Pharm.Eur. 3.2.9.)

Table 9 : Functional properties after gamma irradiation, procedure acc. the Pharm.Eur.3.2.9. – FM460

PROPERTY	UNIT	LIMIT	GAMMA IRRADIATION DOSE		
			0 kGy	30 kGy	50 kGy
Penetrability	N	10	1.5	1.6	1.7
Fragmentation	average # fragments / 48 piercings	5	1	7	16
Resealability	/	0	0	0	1

Functional properties are dependent on the closure design. For this test, Datwyler design V9025 was chosen being an ISO 8362-2 based 20mm injection stopper. The piercing thickness (relevant dimension for these tests) is 1.75±0.25mm.

Care must be given when using FM460 closures in multi-piercing applications where the closures are gamma irradiated at doses of 25 kGy or higher. It is recommended to contact your Datwyler sales representative with questions specific to your application when gamma sterilisation is considered. Other Datwyler halobutyl formulations may be more suitable. There is no concern at all when closures are not gamma irradiated, but steam-sterilized.

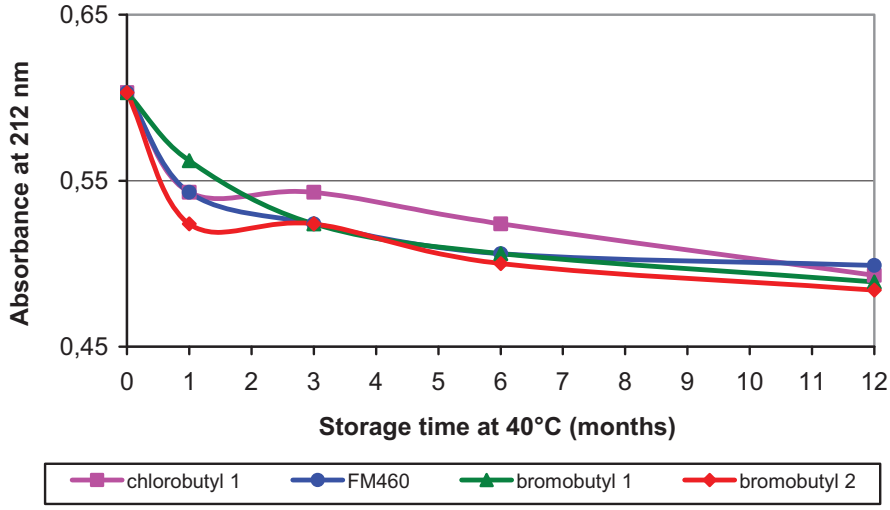
11. Compatibility with preservatives

The goal of this chapter is to investigate the behaviour of FM460 in contact with aqueous solutions containing preservatives that are typically used in parenteral applications.
The behaviour of FM460 is compared with that of other halobutyl compounds.

11.1. 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 follows up the concentration of the m-cresol.

Figure 8 : Compatibility with m-Cresol



m-Cresol absorption of FM460 is low and is in a range comparable to that of other halobutyl compounds.

11.2. 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 2 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 follows up the paraben concentration.

The lowest absorption of methyl and propyl paraben can be seen for FM460, hence compatibility is best with this compound.

Figure 9 : Compatibility with methyl paraben

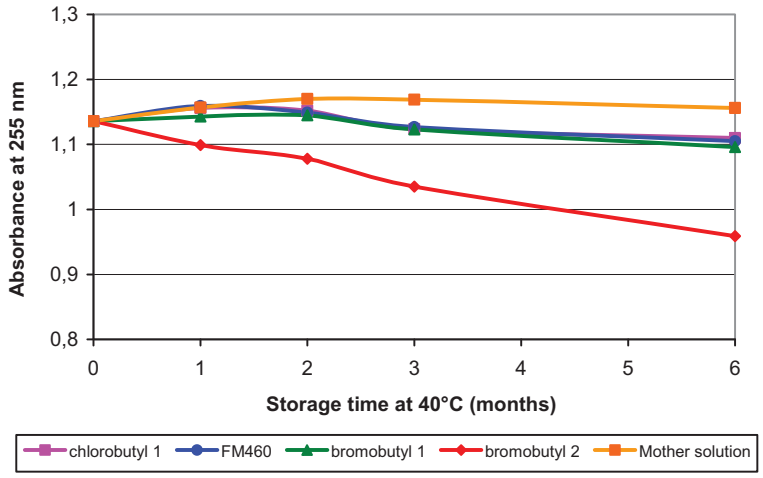
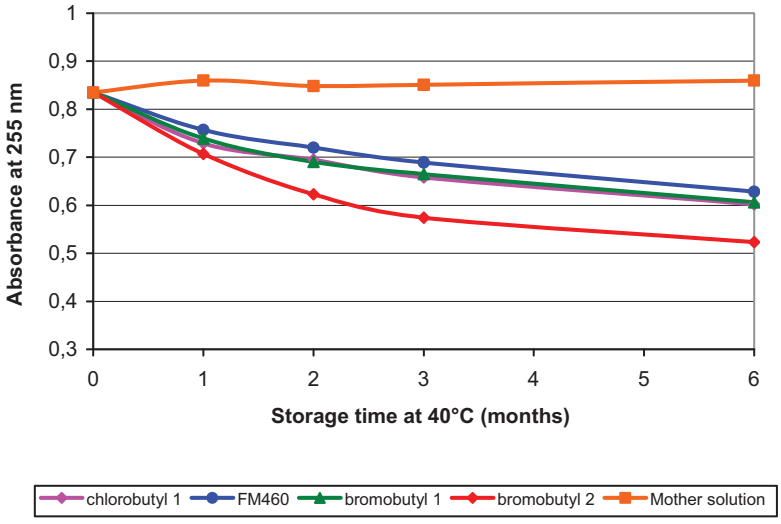


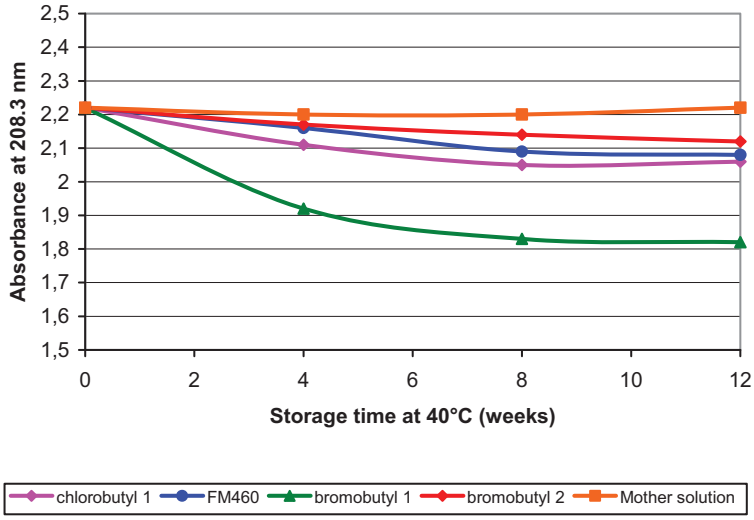
Figure 10 : Compatibility with propyl paraben



11.3. 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 follows up the concentration of the benzalkonium chloride.

Figure 11 : Compatibility with benzalkonium chloride (208.3nm)



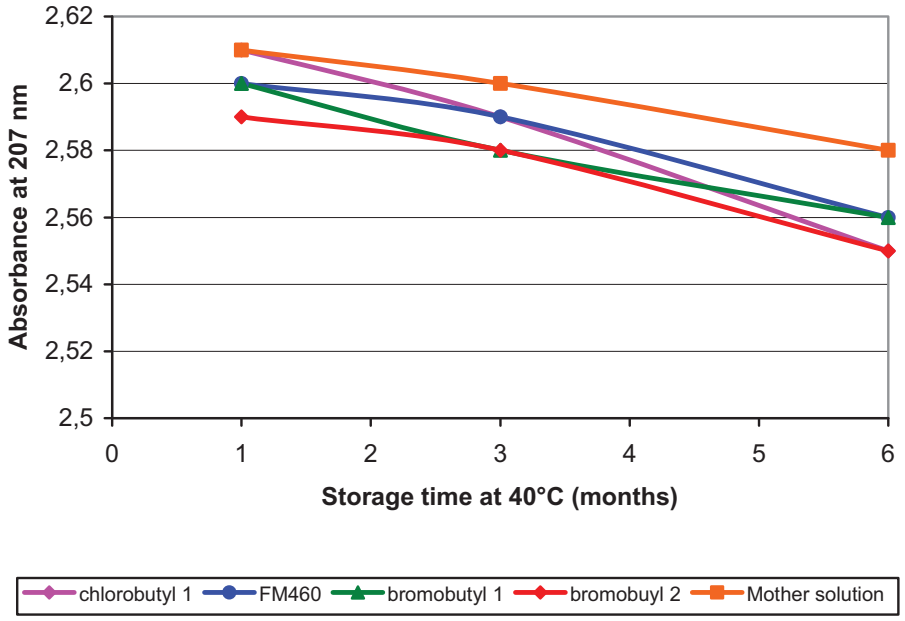
Absorption of BKC for FM460 is comparable with the other halobutyl compounds.

11.4. 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.

Absorption of benzyl alcohol can be considered as very low.

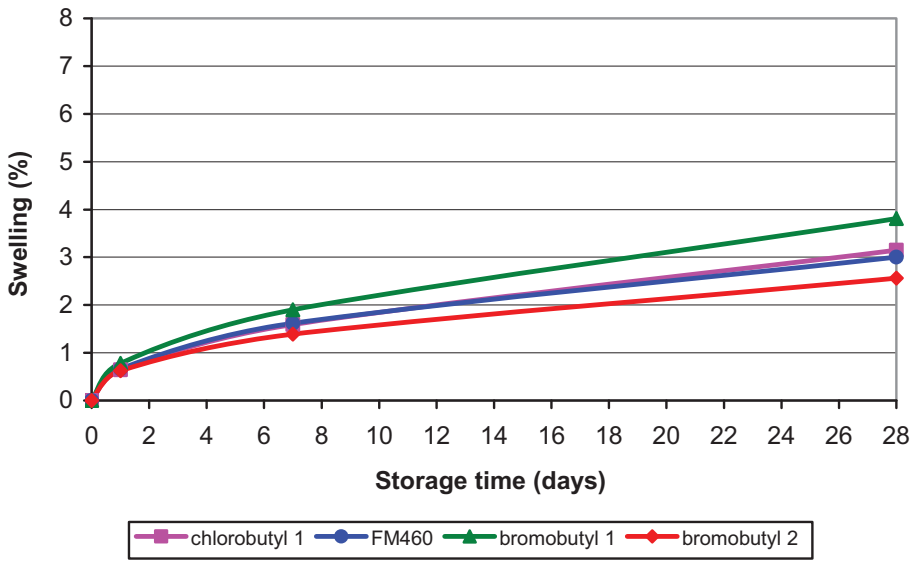
Figure 12 : Compatibility with benzyl alcohol (207nm)



12. Compatibility with vegetable oil

Vegetable oil may be used in some parenteral applications.
Halobutyl rubber and vegetable oil are considered to be compatible on the condition that the weight increase of the rubber, as a consequence of contact with the oil, is low. This weight increase, when expressed as a percentage of the original weight of the rubber, is also called “swelling in vegetable oil”.
Peanut oil is used in this test. Storage is at room temperature and goes up to 4 weeks.

Figure 13 : Compatibility with vegetable oil



FM460 is compatible with peanut oil. No major swelling is observed after 4 weeks of direct contact at room temperature. Swelling is in the same order of magnitude as for the other halobutyl compounds tested.

13. History

Edition (Issue Date)	*Change (chapter + change)*	*Comment (Rationale)*
1 (October 2009)	Complete revision of July 2003 version	First document