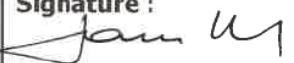
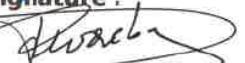


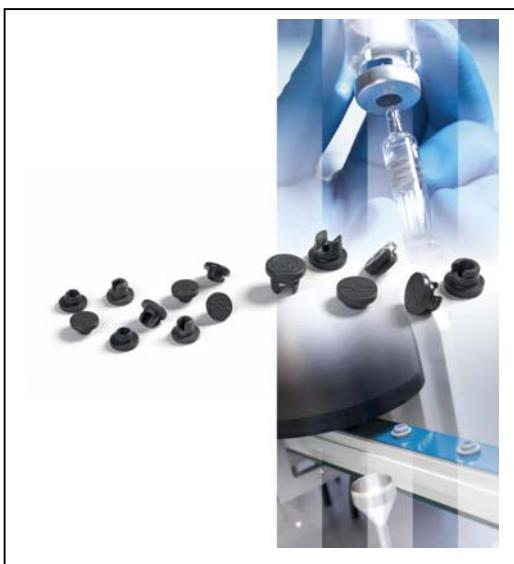
CUSTOMER SERVICE REPORT

CS0078

Technical documentation Omniflex3G

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Excerpted from internal reports R104, R0132, R0145, R0153, R0170, R0186 and R0187.



www.datwyler.com

Edition 4, April 28, 2011

*** 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. ***

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Omniflex3G - Description

This Technical Documentation describes the properties of the third generation of coated closures based on Datwyler's proprietary Omniflex technology.

The Omniflex technology is a spray coating technology that deposits a fluoropolymer coating on rubber closures. Coatings applied via this technology are inert and flexible and they cover the entire closure product surface, including the trim edge. Coated closures in this family do not require siliconization and still allow good machineability .

The first family of coated closures in this range was launched in 1992 under the trade name of 'Omniflex'.

The second generation followed in 1999 under the name of 'Omniflex Plus'. Omniflex Plus showed improved behaviour in the field of coring and resealing and assured extra comfort on the point of non-stickiness during steam sterilization and drying.

The increasing demand towards coated stoppers have guided Datwyler towards the development of a new generation of coated stoppers.

In the beginning of 2008 the third generation of Datwyler coated closures is brought to the market under the trade name of 'Omniflex3G'.

With Omniflex3G Datwyler combines all the valued benefits of Omniflex and OmniflexPlus with innovative properties such as an exceptionally pure compound, increased closure/vial seal integrity assurance (also in extreme conditions as encountered during cold chain applications), enhanced designs and the best coating available. Therefore Omniflex3G is offered in selected 20 mm and 13 mm freeze-dry and serum configurations.

While Omniflex Plus is applied on bromobutyl compound FM259/0, dark grey, the Omniflex3G coating is applied on Datwyler's ultralow extractable bromobutyl compound FM457/0, dark grey. The substrate for coating thus qualitatively is different.

Differences between the OmniflexPlus and Omniflex3G coatings are limited to quantitative changes, i.e. both coatings use exactly the same ingredients, however in slightly different proportions. The coating technology in both cases is identical.

The chemical inertness of the Omniflex3G coating provides a very high degree of compatibility with pharmaceutical products, similar to the compatibility obtained with fluoropolymer film coated products.

Coring and resealing characteristics of Omniflex3G closures are excellent, both in unirradiated and irradiated (25 kGy) conditions.

Omniflex3G is recorded in Datwyler's US DMF file and in Datwyler's file with the Canadian Health Protection Branch.

Omniflex3G - Product range

At the time of issuing this documentation Omniflex3G closures are offered in the following product geometries :

Lyophilization closures :

- 20 mm – igloo design : V9397
- 20 mm – two leg design : V9396

- 13 mm – igloo design : V9402
- 13 mm – two leg design : HPP079

Serum closures :

- 20 mm serum : V9407
- 13 mm serum : V9401

PRODUCT DRAWINGS CAN BE FOUND IN ATTACHMENT 1 OF THIS DOCUMENTATION.

FM457, substrate for Omniflex3G

FM457 is a bromobutyl compound with extremely high chemical purity. It is characterized by low gas permeability and by an ultralow level of extractables. Its purity allows achieving compatibility in applications where so far rubber extractables posed a problem.

Apart from its excellent chemical purity and compatibility behaviour FM457 is also characterized by an excellent stability after gamma irradiation.

The Compound Data Sheet of FM457/0, dark grey, is attached (see attachment 2). For further information on the characteristics of uncoated FM457 reference is made to the 'FM457 Technical Documentation' that can be made available upon request.

1. Chemical properties

1.1. European Pharmacopoeia 3.2.9

Three different production batches of FM457/0 V9154 Omniflex3G have been tested for chemical properties according to European Pharmacopoeia, section 3.2.9.
Each batch has been evaluated on extractables in duplicate.

Uncoated siliconized closures in the same product design V9154 are tested in parallel.

Identification of evaluated batches:

Omniflex3G	FM457/0 V9154 Omniflex3G batch 628001 FM457/0 V9154 Omniflex3G batch 638006 FM457/0 V9154 Omniflex3G batch 639001
FM457/0 non-coated	FM457/0 V9154 non-coated, siliconized, batch 605412

The average of the chemical extractable results is given in the table below.

Tests are performed according to **European Pharmacopoeia, Section 3.2.9 :**

" Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders"
100 cm² rubber surface was autoclaved in 200 ml distilled water for 30 min at 121°C (solution S)

Criterium	Amount tested	Units	Limit	FM457/0 V9154 Omniflex3G	FM457/0 V9154 non-coated
Appearance (430-650 nm)	Solution S	NTU	Type I : 6.0(*) Type II: 18(*)	0.02	0.09
Colour	Solution S		See test procedure	pass	pass
Alkaline matter	20 ml sol.S	ml 0.01 M HCl OR ml 0.01 M NaOH	0.8 0.3	- 0.10	- 0.10
Absorption 220-360 nm	Solution S	Absorbance A_{\max} 220-360 nm	Type I: 0.2 Type II: 4.0	0.012	0.012
Reducing substances	20 ml sol.S	ml 0.002 M KMnO4	Type I: 3.0 Type II: 7.0	0.18	0.21
Heavy metals	Solution S	ppm Pb ²⁺	2	<2	<2
Zinc	Solution S	ppm Zn ²⁺	5	<0.01	<0.01
Ammonium	Solution S	ppm NH ₄ ⁺	2	<2	<2
Evaporation residue	50 ml sol.S	mg	Type I: 2.0 Type II: 4.0	0.02	0.05
Sulphide	20 cm ²	mg S ₂₋	0.02	<0.02	<0.02

Conclusion:

Omniflex3G passes all European Pharmacopoeia. 3.2.9, Type I criteria.

1.2. USP <381>, 'Physicochemical testing'

Three different production batches of FM457/0 V9154 Omniflex3G have been tested for chemical properties according to USP <381>, 'Physicochemical test procedures'. Each batch has been evaluated on extractables in duplicate.

Uncoated siliconized closures in the same product design V9154 are tested in parallel.

Data about the UV spectrum of the USP extracts have been recorded as extra information.

Identification of evaluated batches:

Omniflex3G	FM457/0 V9154 Omniflex3G batch 628001 FM457/0 V9154 Omniflex3G batch 638006 FM457/0 V9154 Omniflex3G batch 639001
FM457/0 non-coated	FM457/0 V9154 non-coated, siliconized, batch 605412

The average of the chemical extractable results is given in the table below.

Physicochemical tests performed according to **USP current edition <381>** "Elastomeric closures for Injections, Physicochemical test procedures" 100 cm² rubber surface area was autoclaved in 200 ml distilled water for 2 hours at 121°C

Criterium	Amount tested	Units	FM457/0 V9154 Omniflex3G	FM457/0 V9154 non-coated
Reducing Agents	50 ml	ml 0.01 N I ₂ per 50 ml	0.01	0.01
Heavy metals	20 ml	ppm Pb ²⁺ <i>(reference solution is 1 ppm)</i>	pass	pass
pH change	20 ml	pH change (*)	-0.2	0.0
Turbidity	-	NTU	0.01	0.03
Total extractables	100 ml	mg	0.4	0.3
<i>(*)</i> : - means more acidic than blank; + means more alkaline than the blank				
Extra test				
UV absorbance (220-350nm)	10mm cuvet	absorbance	0.017	0.013

Conclusion:

USP<381> at present does not use limit values. The chemical extractable data for FM457/0 Omniflex3G represent extremely low results.

1.3. Japanese Pharmacopoeia 7.03

Three different production batches of FM457/0 V9154 Omniflex3G have been tested for chemical properties according to Japanese Pharmacopoeia 7.03, 'Rubber Closure for Aqueous Infusions'.

Each batch has been evaluated on extractables in duplicate.

Uncoated siliconized closures in the same product design V9154 are tested in parallel.

Identification of evaluated batches:

Omniflex3G	FM457/0 V9154 Omniflex3G batch 628001 FM457/0 V9154 Omniflex3G batch 638006 FM457/0 V9154 Omniflex3G batch 639001
FM457/0 non-coated	FM457/0 V9154 non-coated, siliconized, batch 605412

Also fluoropolymer film coated 20 mm lyo stoppers (2-leg design) were tested according to Japanese Pharmacopoeia 7.03.

The average of the chemical extractable results is given in the table below.

Note: between from Japanese Pharmacopoeia 14th Ed . and from Japanese Pharmacopoeia 15th Ed. the number for the chapter 'Rubber Closure for Aqueous Infusions' changed from Japanese Pharmacopoeia XIV 59 into Japanese Pharmacopoeia XV 7.03. The testing itself however was not changed in any respect.

Tests are performed according to **Japanese Pharmacopoeia 14th Edition**, Part I, Chapter 59, "Rubber Closures for Aqueous Infusions". 30 g of rubber sample was autoclaved in 300 g distilled water for 60 min. at 121 °C.

Criterium	Amount tested	Units	Limit	FM457/0 V9154 Omniflex3G	FM457/0 V9154 non-coated	fluoropolymer film coated, 2-leg
Appearance (430/650 nm)	10 mm cuvet	%T at 430 nm %T at 650 nm	>=99,0 >=99,0	100.0 99.9	100.1 100.0	99.7 100.0
Foam test	5ml	—	foam disappears within 3 min	pass	pass	pass
pH	20 ml	pH-unit	difference with blank (*) max 1,0	-0.24	-0.23	-0.13
Reducing substances	100 ml	ml 0,002 M KMnO4	2	0.42	0.39	1.1
Evaporation residue	100 ml	mg	2	0.03	0.25	0.43
UV absorption (220-350 nm)	10 mm cuvet	absorbance	0.2	0.03	0.03	0.01
Zinc	10 ml	ppm Zn ²⁺	1	<0.01	<0.01	<0.01

(*): - means more acidic than blank; + means more alkaline than the blank

Conclusion:

Omniflex3G largely passes all Japanese Pharmacopoeia 7.03 requirements.

1.4. Influence of gamma irradiation on chemical extractables according to Japanese Pharmacopoeia 7.03

The same batches as in the previous section equally were tested for chemical properties according to Japanese Pharmacopoeia 7.03, 'Rubber Closure for Aqueous Infusions' after gamma irradiation at a dose of 25 kGy.

Each batch has been evaluated on extractables in duplicate.

Uncoated siliconized closures in the same product design V9154 are tested in parallel.

Identification of evaluated batches:

Omniflex3G	FM457/0 V9154 Omniflex3G batch 628001 FM457/0 V9154 Omniflex3G batch 638006 FM457/0 V9154 Omniflex3G batch 639001
FM457/0 non-coated	FM457/0 V9154 non-coated, siliconized, batch 605412

Fluoropolymer film coated 20 mm lyo stoppers (2-leg design) were tested too.

Tests are performed according to Japanese Pharmacopoeia 14th Edition. Part I. Chapter 59, "Rubber Closures for Aqueous Infusions".
30 g of rubber sample was autoclaved in 300 g distilled water for 60 min. at 121 °C.

Criterium	Amount tested	Units	Limit	FM457/0 V9154 Omniflex3G		Fluoropolymer film coated, 2-leg	
				Before gamma	After gamma	Before gamma	After gamma
Appearance (430/650 nm)	10 mm cuvet	%T at 430 nm	>=99.0	100.0	99.8	99.7	100
		%T at 650 nm	>=99.0	99.9	99.9	100	100
Foam test	5ml	–	foam disappears within 3 min	pass	pass	pass	pass
pH	20 ml	pH-unit	difference with blank (*) max 1.0	-0.24	-1.54	-0.13	-1.58
Reducing substances	100 ml	ml 0.002 M KMnO4	2	0.42	0.6	1.1	1.39
Evaporation residue	100 ml	mg	2	0.03	0.08	0.43	0.3
UV absorption (220-350 nm)	10 mm cuvet	absorbance	0.2	0.03	0.04	0.01	0.028
Zinc	10 ml	ppm Zn ²⁺	1	<0.01	<0.01	<0.01	<0.01

(*): - means more acidic than blank; + means more alkaline than the blank

Criterium	Amount tested	Units	Limit	FM457/0 V9154 non-coated	
				Before gamma	After gamma
Appearance (430/650 nm)	10 mm cuvet	%T at 430 nm	>=99.0	100.1	99.8
		%T at 650 nm	>=99.0	100.0	99.7
Foam test	5ml	–	foam disappears within 3 min	pass	pass
pH	20 ml	pH-unit	difference with blank (*) max 1.0	-0.23	-0.01
Reducing substances	100 ml	ml 0.002 M KMnO4	2	0.39	0.51
Evaporation residue	100 ml	mg	2	0.25	0.10
UV absorption (220-350 nm)	10 mm cuvet	absorbance	0.2	0.03	0.03
Zinc	10 ml	ppm Zn ²⁺	1	<0.01	0.015

(*): - means more acidic than blank; + means more alkaline than the blank

Conclusion:

As for fluoropolymer film coated products, also Omniflex3G results in an acidic Japanese Pharmacopoeia extract after gamma irradiation.

1.5. Extractables study

A detailed extractables study on Omniflex3G involving solvents of various polarity is available on request.

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

2. Biological properties

2.1. USP <87>, Biological Reactivity Tests 'In Vitro', Elution test



TEST RESULT CERTIFICATE

Project Number:	TE 07155	Study Number:	07-B0453-N1
Sponsor:	Helvoet Pharma	Report Date:	08/03/2007
Contact:	Mrs. Anita Thijss		
Address:	Industriepark Kolmen 1519		
	B-3570 Alken		
	Belgium		
PO.Number:	PB0700643	Technical Initiation:	05/03/2007
		Technical Completion:	08/03/2007

Study	Elution Test – USP	Temp/Time	37°C/24 hours
Test Item	FM457/0 V9154 OmniflexPlus-Modified	Ratio	25cm ² /20mL
Lot	639001	Vehicle	MEM-Complete

REFERENCE: Based on USP 29-NF 24, 2006: <87> Biological reactivity test, in vitro.
 Toxikon Reference: SOP 3.1.2.3, rev.04.

PROCEDURE: The biological reactivity of a mammalian monolayer, L929 mouse fibroblast cell culture, in response to the test item 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 item 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 item meets the requirements of the test 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).

CONCLUSION: 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

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Study Director

Gaby Boonen
Quality Assurance

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Conclusion :

Omniflex3G passes USP <87> requirements.

Note: at the time of testing Omniflex3G was identified with its research code name 'FM457/0, OmniflexPlus modified'.

2.2. USP <88>, Biological Reactivity Tests 'In Vivo', Systemic Injection test

The biological testing in USP is a two stage process. Both USP <1031> and USP <381> state that elastomeric materials that meet the requirements of the in vitro tests (USP <87>) are not required to undergo in vivo testing (<USP 88>).

Notwithstanding this USP <88> in vivo testing was carried out too. The results are given in this and in the following section.



Sponsor Address	Helvoet Pharma Industriepark 3570 Alken Belgium	Technical Initiation Technical Completion	4/9/2007 4/12/2007
Contact P.O. Number	Anita Thijss PB0700643	Report Date Project Number	4/13/2007 07-1087-N1
Test Article	FM457 / 0 V9154 OmniflexPlus-Modified	Ratio	25 cm ² /20.0 mL
Lot/Batch #	lot 639001	Vehicle	USP 0.9% Sodium Chloride for Injection (NaCl) and Cottonseed Oil (CSO)
Study	Systemic Injection Test – USP	Extraction Conditions	70 ± 2 °C for 24 ± 2 hours
Comments	Extraction ratio for elastomers = 25 cm ² /20 mL (12.77cm ² / stopper)		

REFERENCES: The study was conducted based upon the following references: United States Pharmacopeia 29, National Formulary 24, 2006. <88> Biological Reactivity Tests, *In Vivo*, Systemic Injection Test.

ISO/IEC 17025, 2005, General Requirements for the Competence of Testing and Calibration Laboratories.

GENERAL PROCEDURE: The Systemic Injection Study is designed to screen test article extracts for potential toxic effects as a result of a single-dose systemic injection in mice. The extraction conditions were performed as stated above. The extracts were injected intravenously at 50 mL per kg (NaCl) and intraperitoneally at 50 mL per kg (CSO) in groups of five mice. Similarly, groups of five mice were injected with the control articles (vehicles). Body weight measurements were made prior to dose administration, and then daily for 3 days. The animals were observed for signs of biological reactivity for 72 hours post inoculation.

RESULTS: None of the animals injected with the test article extracts or the control articles (vehicles) exhibited any signs of toxicity through the observation period.

CONCLUSION: The animals treated with the test article extracts did not exhibit biological reactions which were greater than the controls. Therefore, the test article meets the requirements of the USP guidelines for the Systemic Injection Test.

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Conclusion :

Omniflex3G passes the USP <88> requirements for systemic injection testing.

Note: at the time of testing Omniflex3G was identified with its research code name 'FM457/0, OmniflexPlus modified'.

2.3. USP <88>, Biological Reactivity Tests 'In Vivo', Intracutaneous test



► Leaders in Life Science and Technology

TEST RESULT CERTIFICATE

Sponsor Address	Helvoet Pharma Industriepark 3570 Alken Belgium	Technical Initiation	4/9/2007
Contact P.O. Number	Anita Thijss PB0700643	Technical Completion	4/12/2007
		Report Date Project Number	4/17/2007 07-1087-N2

Test Article	FM457 / 0 V9154 OmniflexPlus-Modified	Ratio	25 cm ² /20 mL
Lot/Batch #	lot 639001	Vehicles	USP 0.9% Sodium Chloride for Injection (NaCl) and Cottonseed Oil (CSO)
Study	Intracutaneous Injection Test – USP	Extraction Conditions	70 ± 2 °C for 24 ± 2 hours
Comments	Extraction ratio for elastomers = 25 cm ² /20 mL (12.77 cm ² /stopper)		

REFERENCES The study was conducted based upon the following references: United States Pharmacopeia 29, National Formulary 24, 2006. <88> Biological Reactivity Tests, *In Vivo*, Intracutaneous Test.

ISO/IEC 17025, 2005, General Requirements for the Competence of Testing and Calibration Laboratories.

GENERAL PROCEDURE: The Intracutaneous Test is designed to evaluate local responses to the extracts of test articles, following intracutaneous injection into rabbits. The extraction conditions were performed as stated above. Control extracts were prepared, in a similar manner, with each extracting medium. Two rabbits were injected intracutaneously, using one side of the animal for the test article extracts and the other side for the control extracts, at 0.2 mL per site. The injected sites were examined at 24, 48, and 72 hours post inoculation for gross evidence of tissue reaction such as erythema, edema, and necrosis. Observations were scored according to the Classification System for Scoring Skin Reactions and included all clinical signs. All average erythema and edema scores for the test and control sites at 24, 48, and 72 hours were totaled separately and divided by 12 (2 animals × 3 scoring periods × 2 scoring categories) to determine the overall mean score for the test article versus the corresponding control article. The requirements of the test are met if the difference of the mean reaction score (erythema/edema) for the test article and the control article is 1.0 or less.

RESULTS: Both of the test animals increased in weight. None of the animals exhibited overt signs of toxicity at any of the observation points. The requirements of the test were met because the difference of the mean reaction score for the test article and control article was 0.0.

CONCLUSION: The test article meets the requirements of the Intracutaneous Test, USP guidelines using extracts prepared with NaCl and CSO.

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Conclusion :

Omniflex3G passes the USP <88> requirements for intracutaneous testing.

Note: at the time of testing Omniflex3G was identified with its research code name 'FM457/0, OmniflexPlus modified'.

3. Functional properties

3.1. ISO 8871-5 before and after gamma irradiation

Traditionally fragmentation (= coring), resealing and penetrability are tested according to the methods described in European Pharmacopoeia 3.2.9.
ISO 8871-5¹ is a copy of European Pharmacopoeia 3.2.9.

In this paragraph compliance of Omniflex3G with ISO 8871-5 is demonstrated for 20 mm lyophilization closures (type V9154). Demonstration of compliance is given for unirradiated closures and for gamma irradiated (25 kGy) closures.

Uncoated siliconized closures in the same product design V9154 are tested in parallel.

V9154 has the same piercing thickness as V9396 and therefore representative for demonstration of functional properties of Omniflex3G.

Identification of evaluated batches:

Omniflex3G	FM457/0 V9154 Omniflex3G batch 628001 FM457/0 V9154 Omniflex3G batch 638006 FM457/0 V9154 Omniflex3G batch 639001
FM457/0 non-coated	FM457/0 V9154 non-coated, siliconized, batch 605412

Results

Before gamma	Procedure: Unit:	FRAGMENTATION ISO 8871-5 # fragments per 48 piercings	RESEALING ISO 8871-5 # leaking vials	PENETRABILITY ISO 8871-5 penetration force (in N)
	Limit :	<5	0	<10 N
20mm lyo 2-leg				
V9154 FM457/0 Non-coated, siliconized batch 605412		0	0	2.8
V9154 FM457/0 Omniflex3G	batch 628001	0	0	3.3
	batch 638006	1	0	3.4
	batch 639001	1	0	3.2

After 25 kGy	Procedure: Unit:	FRAGMENTATION ISO 8871-5 # fragments per 48 piercings	RESEALING ISO 8871-5 # leaking vials	PENETRABILITY ISO 8871-5 penetration force (in N)
	Limit :	<5	0	<10 N
20mm lyo 2-leg				
V9154 FM457/0 Non-coated, siliconized batch 605412		1	0	2
V9154 FM457/0 Omniflex3G	batch 628001	2	0	2.8
	batch 638006	1	0	2.9
	batch 639001	1	0	2.8

¹ : ISO8871-5 : Elastomeric parts for parenterals and for devices for pharmaceutical use – Part 5 : Functional requirements and testing

Conclusion

Omniflex3G passes all functional requirements of ISO 8871-5 both unirradiated and after gamma irradiation (25 kGy).

3.2. ISO 8871-5 after cold storage during 2 years

The functional properties of Omniflex3G were also tested after storage of 2 years at room temperature, 5°C and -23 °C.

Also in this case, the model V9154 was tested, but since V9154 has the same piercing thickness as V9396 it is therefore representative for demonstration of functional properties of Omniflex3G.

Identification of evaluated batches:

Omniflex3G	FM457/0 V9154 Omniflex3G batch 528001
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Results

	Fragmentation # fragments per 48 piercings Specification : < 5			Resealing # leaking vials Specification : 0			Penetrability (N) Specification : < 10N		
	RT	5°C	-23°C	RT	5°C	-23°C	RT	5°C	-23°C
	V9154 Omniflex 3G	3	2	0	0	0	0	2.62	2.59

Conclusion

Omniflex3G passes all functional properties of ISO8871-5 after a storage of 2 years at room temperature, 5°C and -23°C.

3.3. Gas permeability

Gas permeabilities of coated closures are determined by their bulk materials only (bulk material = material on which coating is deposited). This bulk material in the case of Omniflex3G is FM457/0. This material is a bromobutyl. Halobutyl compounds of which bromobutyrs are a subclass are known to have the lowest possible gas permeability among all industrially available elastomeric materials.

The relatively thin coating layer will not affect the basic permeability that is attributed to the closure by the bromobutyl bulk material (thickness expressed in millimeters).

The table below shows the gas permeabilities of FM457/0.

A typical styrene butadiene (SBR) compound characterized by higher permeability values is included for reference purposes. In comparison to SBR, permeabilities for poly-isoprene compounds that are commonly encountered for use in medical devices would still be higher.

	Water vapour transmission 38 °C, 90% RH g / m² . 24 hrs	Oxygen transmission 38°C, 90% RH cc/m² . 24 hrs
FM457/0	0.15	96
SBR	3.9 (*)	971 (**)

(*) at 100 % relative humidity (RH)

(**) at 50 % RH

1 mm slab thickness

Conclusion

FM457/0 is characterized by low permeability values.

3.4. Lyophilization closures

This paragraph compiles vacuum retention results for FM457, Omniplex3G in comparison with plug film coated stoppers. All results concern the retention viz. partial loss of vacuum between stoppering and capping, i.e. for vials that are stoppered, but still are in uncapped condition.

Vacuum loss clearly also depends on the vial type that is used. For this reason, different vial types (with blow back (*), without blow back, from different manufacturers, moulded and tubular) have been used in the vacuum retention studies.

(*) The term 'blow back' refers to the presence of a protruding rim on the internal part of the opening of the vial. This rim is intended to serve as a no-pop feature. More information can be found in e.g. ISO 8362-1, 'Injection containers and accessories -- Part 1: Injection vials made of glass tubing'.

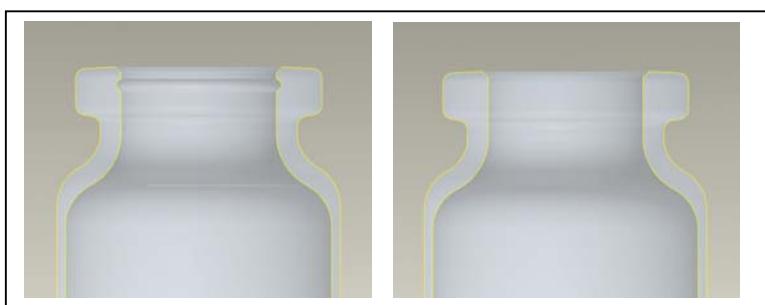


Figure : blow back (left) and non-blow back vial (right)

The majority of the studies in this paragraph have been performed by using a lab exsiccator that has been modified so that with the aid of a vacuum pump it can be brought under underpressure.

Freeze-drying closures that are positioned in their lyophilization position on the vials in the exsiccator are pushed into the vial at the moment that an underpressure of +/- 900 mbar (i.e. with an absolute pressure in the vial of +/- 100 mbar) has been reached. For each set of 25 vials the underpressure in 5 vials is measured immediately after removal from the lab exsiccator. This gives the value for the underpressure in the vials at time zero ($t=0$). The other 20 vials are further stored in the lab at ambient conditions, however without capping the vials with an aluminum cap. This simulates the practice at customers where vials coming out of the lyophilization chamber are not immediately capped. After a storage time of 3 hrs at ambient conditions the underpressure in the 20 vials is measured, which gives a value for the underpressure in the vials at $t= 3\text{hrs}$.

The choice for 900 mbar underpressure in the vials as well as for 3 hours waiting time after removal from the exsiccator are in a way arbitrary. These parameters are kept constant throughout all studies. They allow easy comparison of vacuum retention properties of the different stopper/vial combinations.

The measurement of the underpressure in the vials is performed by means of a pressure gauge connected to a needle. Since the gauge has a certain dead volume the pressure readings from this instrument must not be taken in absolute terms. However for comparative measurements this method yields valuable results.

A picture of the lab equipment (lab exsiccator and pressure gauge) is given in attachment 3 of this Technical Documentation.

In a later phase of the project a lyophilization chamber was available for creating underpressure in the vials. Also Lighthouse equipment for non-destructive measurement of headspace pressure in the uncapped vials was available.

A picture of the lyophilization chamber and of the Lighthouse equipment is equally given in attachment 3.

3.4.1. 20mm lyo –igloo design in 7 different vial types – stoppers from trial mould

In this paragraph the vacuum retention properties of a product P8506M, FM457/0, Omniplex3G are reported. Drawing of this product can be found in attachment 1. The latter product is obtained from a trial mould that was constructed for R&D purposes. This trial mould allowed to generate enough parts for development purposes, however is not suitable for industrial production. On industrial scale 20 mm igloo lyo stoppers are obtained from an industrial mould with number V9397.

7 different vial types have been used to evaluate the vacuum retention properties of 3 different production batches of P8506M, FM457/0, Omniplex3G.

As reference a plug film coated 20mm lyo igloo design has been tested.

Test description

Identification of vials:

1. Supplier A tubular vial with European blow back ('supplier A Eur BB' in fig.)
2. Supplier A tubular vial with US blow back ('supplier A US BB' in fig.)
3. Supplier C moulded vial ('supplier C moulded' in fig.)
4. Supplier D tubular vial with blow back ('supplier D BB' in fig.)
5. Supplier D tubular vial without blow back ('supplier D without BB' in fig.)
6. Supplier G without blow back ('supplier G without BB' in fig.)
7. Supplier B tubular vial with blow back ('supplier B BB' in fig.)

Identification of coated lyo stoppers:

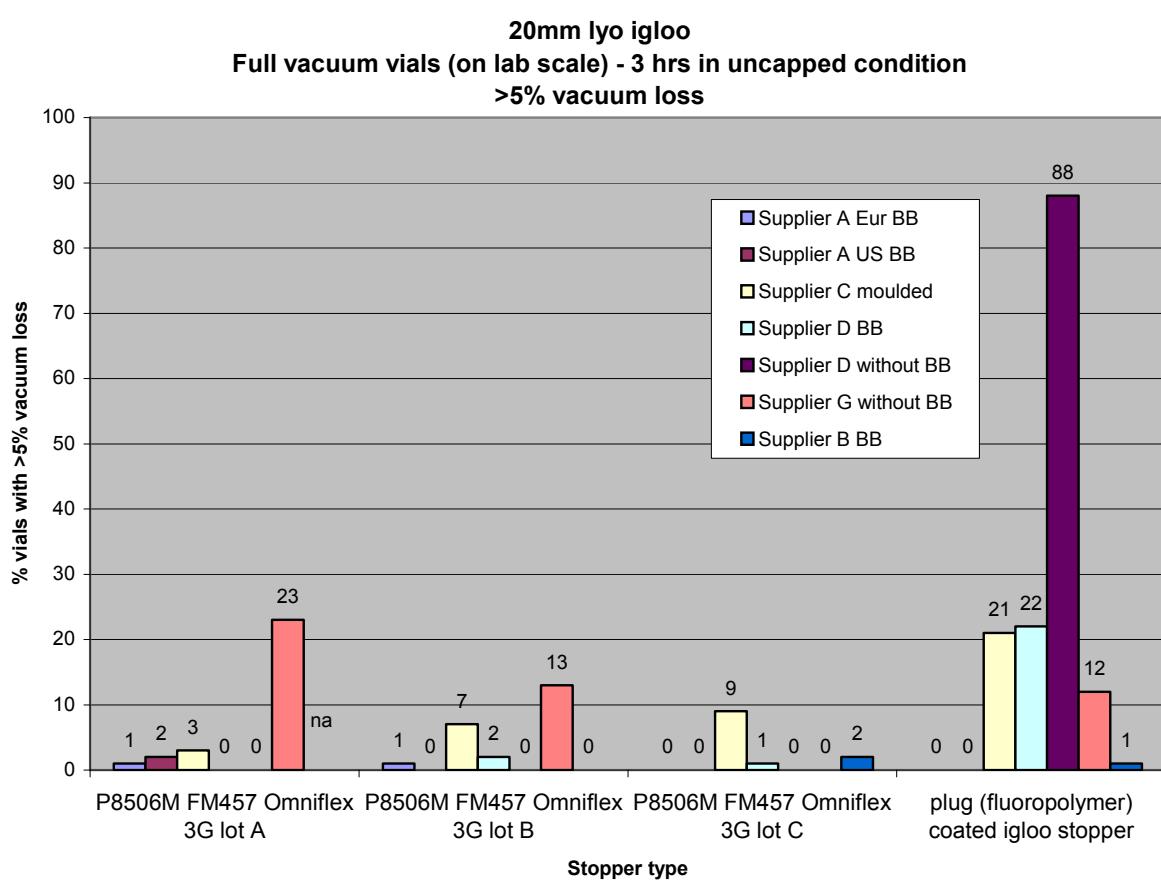
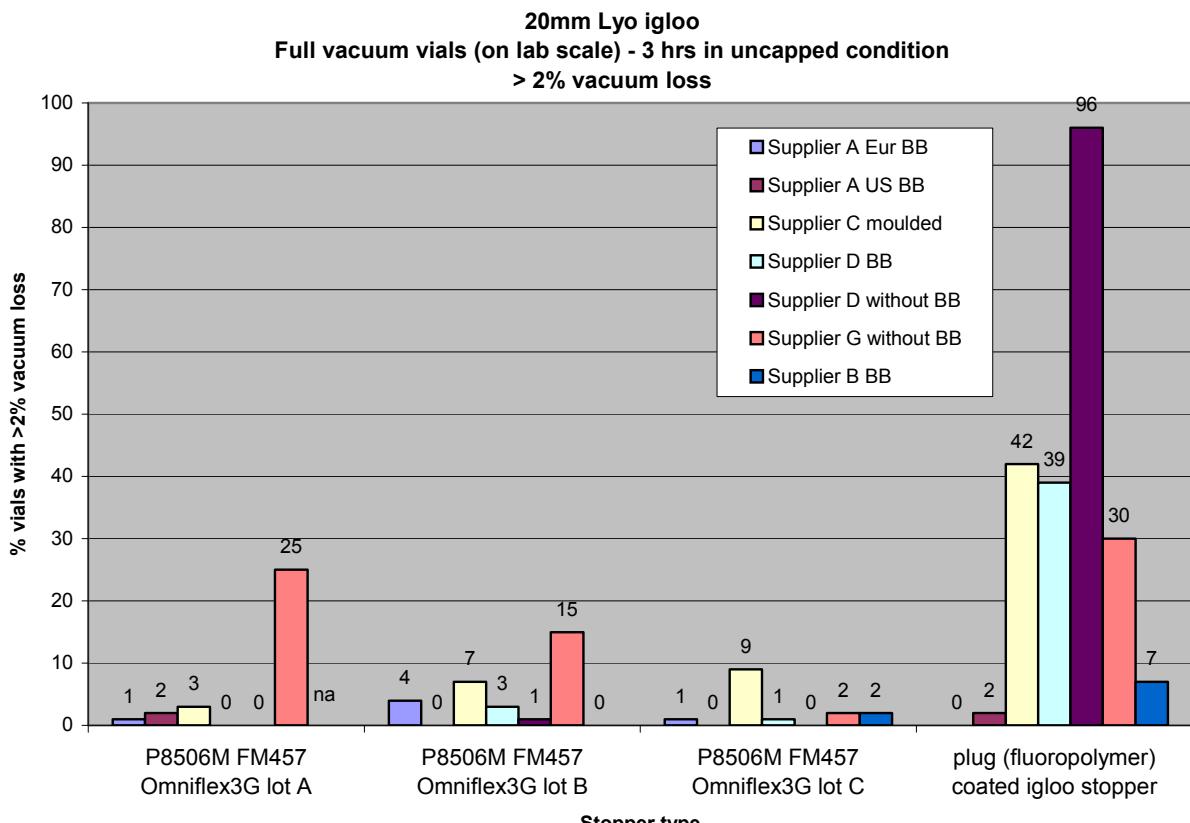
1. Omniplex3G coated product :
FM457/0 P8506M Omniplex3G, batch 628002 ('lot A' in fig.)
FM457/0 P8506M Omniplex3G, batch 638007 ('lot B' in fig.)
FM457/0 P8506M Omniplex3G, batch 639002 ('lot C' in fig.)
2. plug (fluoropolymer) film coated igloo stopper

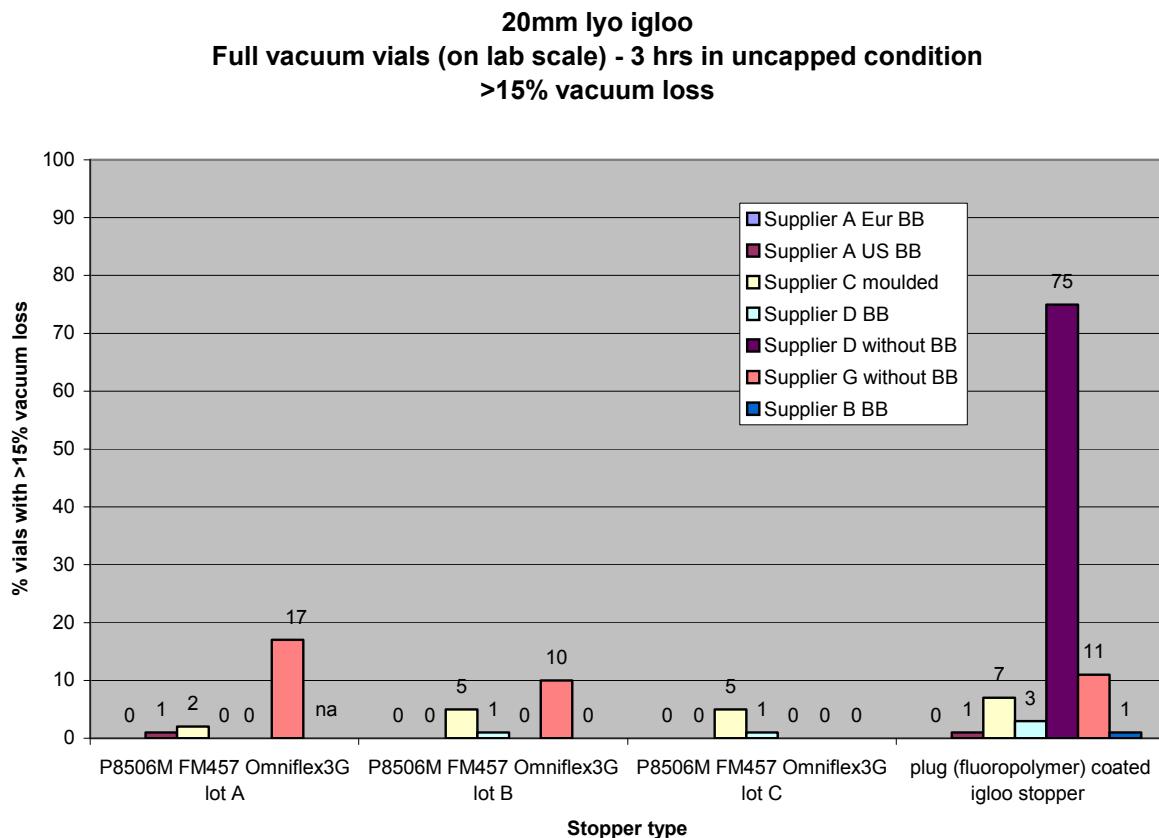
Test method:

- Vials are brought in a lab exsiccator. On the vials freeze-drying stoppers are put in their lyophilization position. The exsiccator is closed.
- Underpressure is created in the vials by use of a vacuum pump that is connected to the exsiccator. The pressure in the vials in the exsiccator is installed at +/- 100 mbara (mbar absolute pressure).
- At that pressure the stoppers are pressed down from their lyophilization to their seating position.
- 100 vials are tested per product sample and per vial type.
- The residual underpressure in the vials is measured after 3 hours storage in uncapped condition by using a pressure gauge with a needle (destructive measurement).

Results

Figures below give for each product and for each vial type the percentage of vials with more than 2%, resp. more than 5% and resp. more than 15% of loss of the originally installed vacuum under the conditions of the test and of the measurement as described above. 2%, resp. 5% and resp 15% can be seen as 3 different acceptance criteria for vacuum loss (in decreasing order of criticality). The numbers of 2, 5 and 15 are in a kind arbitrary. Final judgement is here to the user of the stopper.





Conclusions:

1. The plug (fluoropolymer) film coated igloo stopper shows more vacuum loss in combination with certain vials than FM457/0, Omniflex 3G.
2. The specific results are depending on the type of vial.
3. The 'supplier G' vial in the test in combination with FM457/0 Omniflex3G still shows some vacuum loss. The same is seen for the 'Supplier C' vial.

Careful selection by the pharmaceutical manufacturer of a suitable vial in connection with lyophilization closures is highly indicated.

3.4.2. 20mm lyo –igloo design in 4 different vial types – stoppers from industrial mould

In this paragraph the vacuum retention properties of a product V9397, FM457/0, Omniflex3G are reported. The latter product (20 mm lyo igloo) is obtained from an industrial mould.

4 different vial types have been used to evaluate the vacuum retention properties of V9397 FM457/0, Omniflex3G.

As reference P8506M, FM457/0, Omniflex3G was tested.

The plug film coated 20 mm lyo igloo design was not tested in this case.

The test method has been slightly adapted in comparison with the previous tests. The BOC Edwards lyo chamber has been used to create a headspace underpressure in the vials and vacuum retention was tested at full and partial vacuum :

- Full vacuum : absolute headspace pressure of +/- 100 mbar (+/- 76 Torr) in all vials before stoppering.
- Partial vacuum : absolute headspace pressure of +/- 500 mbar (+/- 380 Torr) in all vials before stoppering.

The Lighthouse equipment has been used to follow up the headspace pressure in the stoppered/uncapped vials. This pressure reading is in Torr instead of mbar. All results are reported in Torr.

Test description

Identification of vials:

1. Supplier A vial with European blow back
2. Supplier C moulded vial
3. Supplier D vial without blow back
4. Supplier B vial with blow back

Identification of coated lyo stoppers:

1. Sample mould product in Omniflex3G :
P8506M FM457/0 Omniflex3G , batch 707003
2. Production mould product in Omniflex3G :
V9397 FM457/0 Omniflex3G, batch 737002

Test method:

- underpressure in vials with BOC Edwards lyo chamber: first test series with absolute pressure in vials of +/- 100 mbar (+/- 76 Torr) ; second test series with absolute pressure in vials of +/- 500 mbar (+/- 380 Torr).
- 50 vials prepared per product sample and per vial type for each pressure condition
- measurement of underpressure in vials by using the Lighthouse equipment (non-destructive)
- measurement after 3 hrs storage at ambient conditions (stoppered/uncapped)

Results

Full Vacuum, uncapped condition during 3 hrs

Tested for 50 vials per sample,

Result expressed in % vials with more than 5% or more than 15% vacuum loss

Condition: **100 mbara pressure in vials and then further stored in uncapped condition for 3 hrs.**

	Supplier A vial Eur BB Vacuum loss >5%	>15%	Supplier D vial without BB Vacuum loss >5%	>15%
igloo lyo: P8506M FM457 Omniflex3G, batch 707003 V9397 FM457/0 Omniflex3G, batch 737002	0%	0%	0%	0%
	0%	0%	0%	0%

	Supplier C, moulded vial Vacuum loss >5%	>15%	Supplier B vial BB Vacuum loss >5%	>15%
igloo lyo: P8506M FM457 Omniflex3G, batch 707003 V9397 FM457/0 Omniflex3G, batch 737002	0%	0%	0%	0%
	0%	0%	0%	0%

Partial Vacuum, uncapped condition during 3 hrs

Tested for 50 vials per sample,

Result expressed in % vials with more than 5% or more than 15% vacuum loss

Condition: **500 mbara pressure in vials and then further stored in uncapped condition during 3 hrs.**

	Supplier A vial Eur BB Vacuum loss >5%	>15%	Supplier D vial without BB Vacuum loss >5%	>15%
igloo lyo: P8506M FM457 Omniflex3G, batch 707003 V9397 FM457/0 Omniflex3G, batch 737002	0%	0%	0%	0%
	0%	0%	0%	0%

	Supplier C, moulded vial Vacuum loss >5%	>15%	Supplier B vial BB Vacuum loss >5%	>15%
igloo lyo: P8506M FM457 Omniflex3G, batch 707003 V9397 FM457/0 Omniflex3G, batch 737002	0%	0%	0%	0%
	4%	0%	0%	0%

Conclusions:

Experimental results with coated 20 mm lyo igloo parts from industrial mould V9397 are in the same line as for parts from the trial mould P8506M. Results obtained with stoppers manufactured from an industrial tool thus confirm the small scale results. The specific results are depending on the type of vial.

3.4.3. 20mm lyo –2-leg design in 7 different vial types – stoppers from trial mould

In this paragraph the vacuum retention properties before capping of a product P8345B, FM457/0, Omniplex3G are reported. Drawing of this product can be found in attachment 1. The latter product again is obtained from a trial mould.

On industrial scale 20 mm 2-leg lyo stoppers are obtained from an industrial mould with number V9396.

7 different vial types have been used to evaluate the vacuum retention properties of 3 different production batches of P8345B, FM457/0, Omniplex3G.

As reference a plug film coated 20mm lyo 2-leg design has been tested.

Test description

Identification of vials: (same as sub 3.3.1)

1. Supplier A tubular vial with European blow back
2. Supplier A tubular vial with US blow back
3. Supplier C moulded vial
4. Supplier D tubular vial with blow back
5. Supplier D tubular vial without blow back
6. Supplier G without blow back
7. Supplier B tubular vial with blow back

Identification of coated lyo stoppers:

1. Omniplex3G coated product:
FM457/0 P8345B Omniplex3G, batch 628004 ('lot A' in fig.)
FM457/0 P8345B Omniplex3G, batch 638008 ('lot B' in fig.)
FM457/0 P8345B Omniplex3G, batch 639003 ('lot C' in fig.)
2. plug (fluoropolymer) film coated igloo stopper

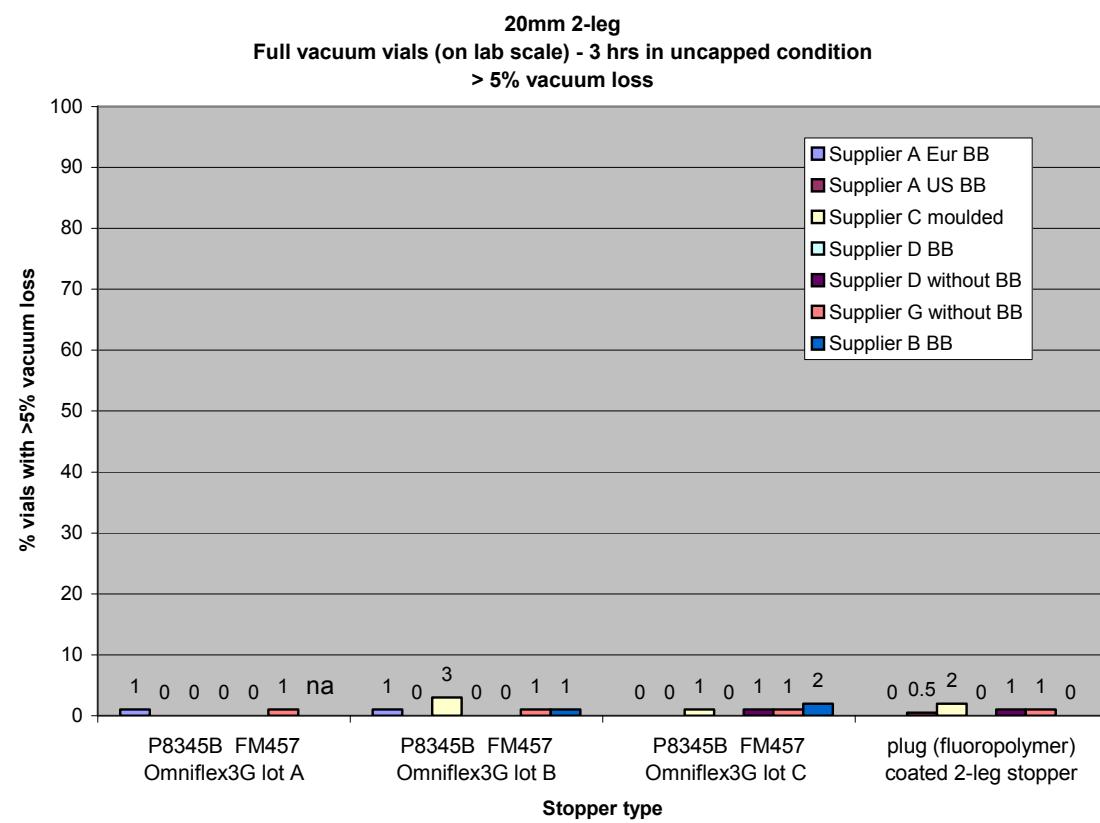
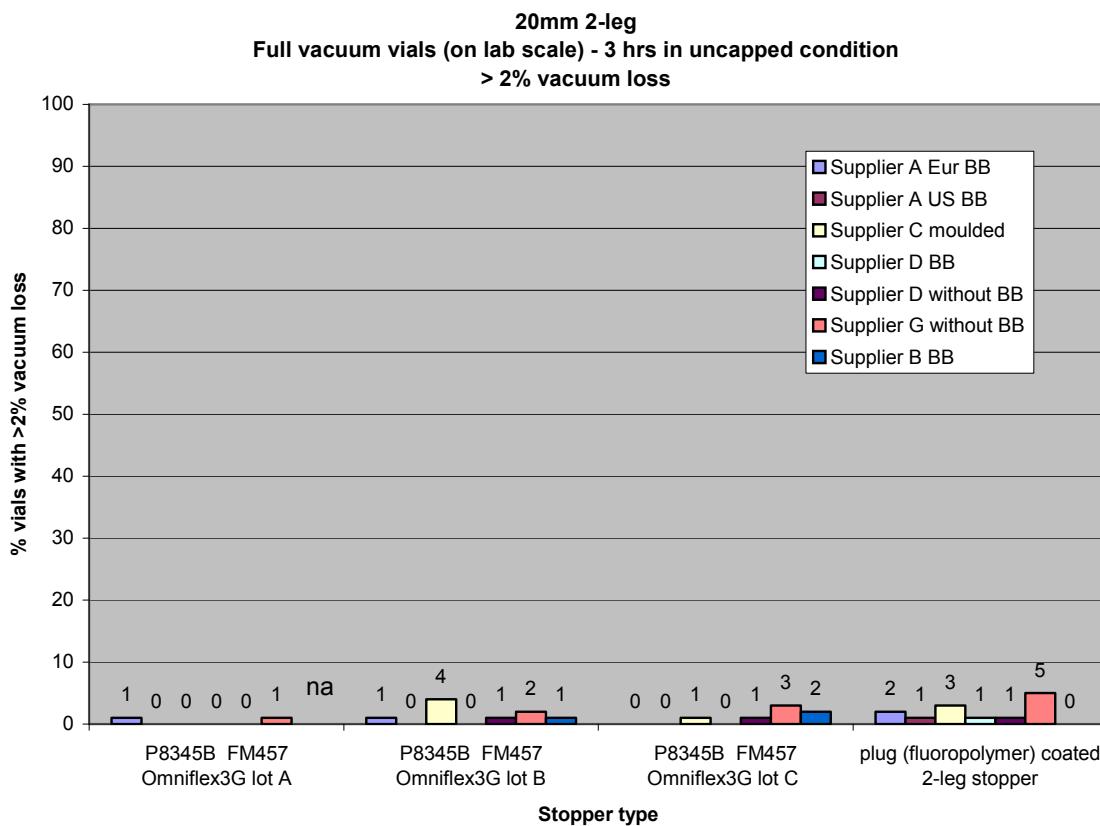
Test method: (same as sub 3.4.1)

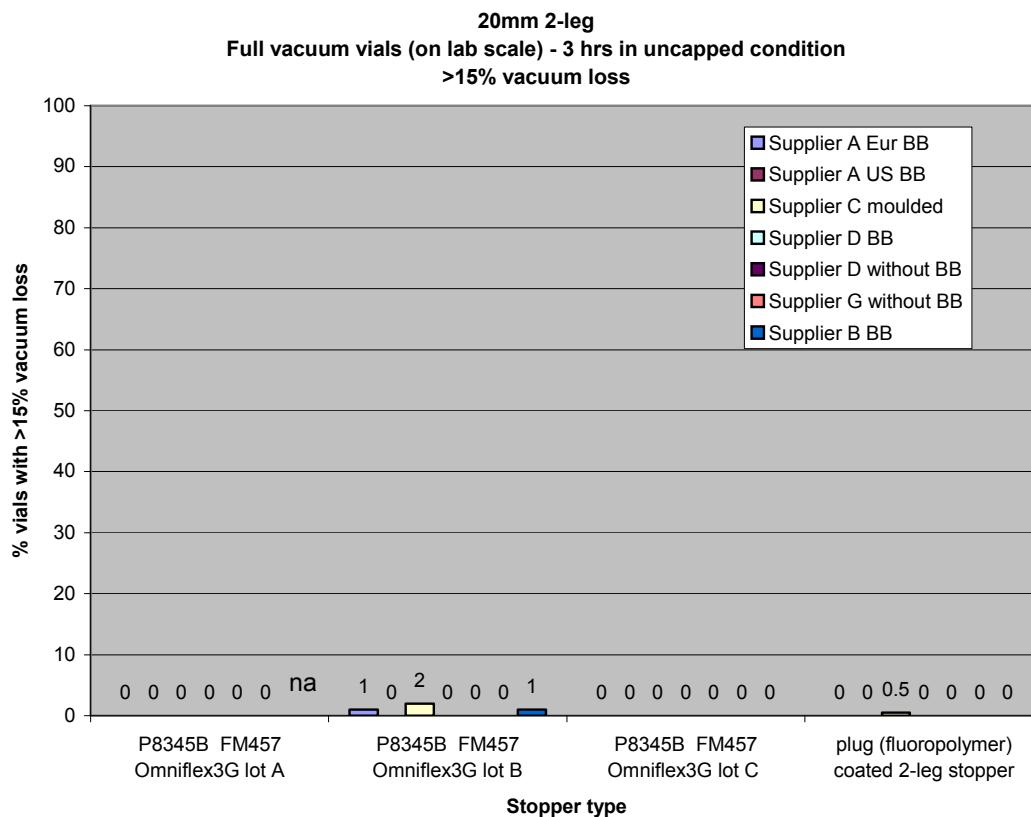
- Vials are brought in a lab exsiccator. On the vials freeze-drying stoppers are put in their lyophilization position. The exsiccator is closed.
- Underpressure is created in the vials by use of a vacuum pump that is connected to the exsiccator. The pressure in the vials in the exsiccator is installed at +/- 100 mbara (mbar absolute pressure).
- At that pressure the stoppers are pressed down from their lyophilization to their seating position.
- 100 vials are tested per product sample and per vial type, except for plug (fluoropolymer) film coated 2-leg stopper : 200 vials were tested.
- The residual underpressure in the vials is measured after 3 hours storage in uncapped condition by using a pressure gauge with a needle (destructive measurement).

Results

Figures below give for each product and for each vial type the percentage of vials with more than 2%, resp. more than 5%, resp. more than 15% of loss of the originally installed vacuum under the conditions of the test and of the measurement as described above.

2% resp. 5% resp 15% can be seen as 3 different acceptance criteria for vacuum loss (in decreasing order of criticality). The numbers of 2, 5 and 15 are in a kind arbitrary. Final judgement is here to the user of the stopper.



**Conclusions:**

- Closure/vial seal integrity in uncapped condition of FM457/0, Omniflex3G is comparable to the plug (fluoropolymer) film coated stopper.
- The specific results are depending on the type of vial.

Careful selection by the pharmaceutical manufacturer of a suitable vial in connection with lyophilization closures is highly indicated.

3.4.4. 20mm lyo –2-leg design in 4 different vial types – stoppers from industrial mould

In this paragraph the vacuum retention properties of a product V9396, FM457/0, Omniflex3G are reported. The latter product is obtained from an industrial mould

4 different vial types have been used to evaluate the vacuum retention properties of V9396 FM457/0, Omniflex3G.

As reference P8506M, FM457/0, Omniflex3G was tested.

The plug film coated 20 mm lyo-igloo design was not tested in this case.

Test description

Identification of vials:

1. Supplier A vial with European blow back
2. Supplier C vial with blow back
3. Supplier D vial without blow back
4. Supplier B vial with blow back

Identification of coated lyo stoppers:

1. Sample mould product in Omniflex3G :
P8345B FM457/0 Omniflex3G, batch 707004
2. Production mould product in Omniflex3G :
V9396 FM457/0 Omniflex 3G, batch 737001

Test method (same as sub 3.4.2) :

- underpressure in vials with BOC Edwards lyo chamber: first test series with absolute pressure in vials of +/- 100 mbar (+/- 76 Torr) ; second test series with absolute pressure in vials of +/- 500 mbar (+/- 380 Torr).
- 50 vials prepared per product sample and per vial type for each pressure condition
- measurement of underpressure in vials by using the Lighthouse equipment (non-destructive)
- measurement after 3 hrs storage at ambient conditions (stoppered/uncapped)

Results

Full Vacuum, uncapped condition during 3 hrs

Tested for 50 vials per sample.

Result expressed in % vials with more than 5% or more than 15% vacuum loss

Condition: 100 mbara pressure in vials and then further stored in uncapped condition during 3 hrs.

	Supplier A vial Eur BB Vacuum loss >5% >15%		Supplier D vial without BB Vacuum loss >5% >15%	
2-leg lyo: P8345B FM457 Omniplex3G, batch 707004	0%	0%	2%	2%
V9396 FM457/0 Omniplex3G, batch 737001	2%	2%	0%	0%

	Supplier C, moulded vial Vacuum loss >5% >15%		Supplier B vial BB Vacuum loss >5% >15%	
2-leg lyo: P8345B FM457 Omniplex3G, batch 707004	2% 2%		0% 0%	
V9396 FM457/0 Omniplex3G, batch 737001	0%	0%	0%	0%

Partial Vacuum, uncapped condition during 3 hrs

Tested for 50 vials per sample.

Result expressed in % vials with more than 5% or more than 15% vacuum loss

Condition: 500 mbara pressure in vials and then further stored in uncapped condition during 3 hrs.

	Supplier A vial Eur BB Vacuum loss >5%		Supplier D vial without BB Vacuum loss >5%	
2-leg lyo: P8345B FM457 Omniplex3G, batch 707004	0%	0%	0%	0%
V9396 FM457/0 Omniplex3G, batch 737001	0%	0%	2%	2%

	Supplier C moulded vial Vacuum loss >5% >15%		Supplier B vial BB Vacuum loss >5% >15%	
2-leg lyo: P8345B FM457 Omniplex3G, batch 707004	12%	6%	0%	0%
V9396 FM457/0 Omniplex3G, batch 737001	6%	4%	2%	0%

Conclusions :

Experimental results with coated 20 mm lyo 2-leg parts from industrial mould V9396 are in the same line as for parts from the trial mould P8345B. Results obtained with stoppers manufactured from an industrial tool thus confirm the small scale results. The specific results are depending on the type of vial.

3.4.5. 13mm lyo –igloo design in 4 different vial types – stoppers from trial mould

In this paragraph the vacuum retention properties of a product P8219F, FM457/0, Omniflex3G are reported. Drawing of this product can be found in attachment 1.

The latter product is obtained from a trial mould.

On industrial scale 13 mm igloo lyo stoppers for Omniflex3G execution will be obtained from an industrial mould with number V9402.

4 different vial types have been used to evaluate the vacuum retention properties of 3 different production batches of P8219F, FM457/0, Omniflex3G.

As reference a fluoropolymer plug film coated 13 mm lyo igloo design stopper has been tested.

Test description

Identification of vials:

1. Supplier A tubular vial with European blow back
2. Tubular vial with blow back, received from customer B
3. Supplier E tubular vial with blow back
4. Supplier B tubular vial with blow back

Identification of coated lyo stoppers:

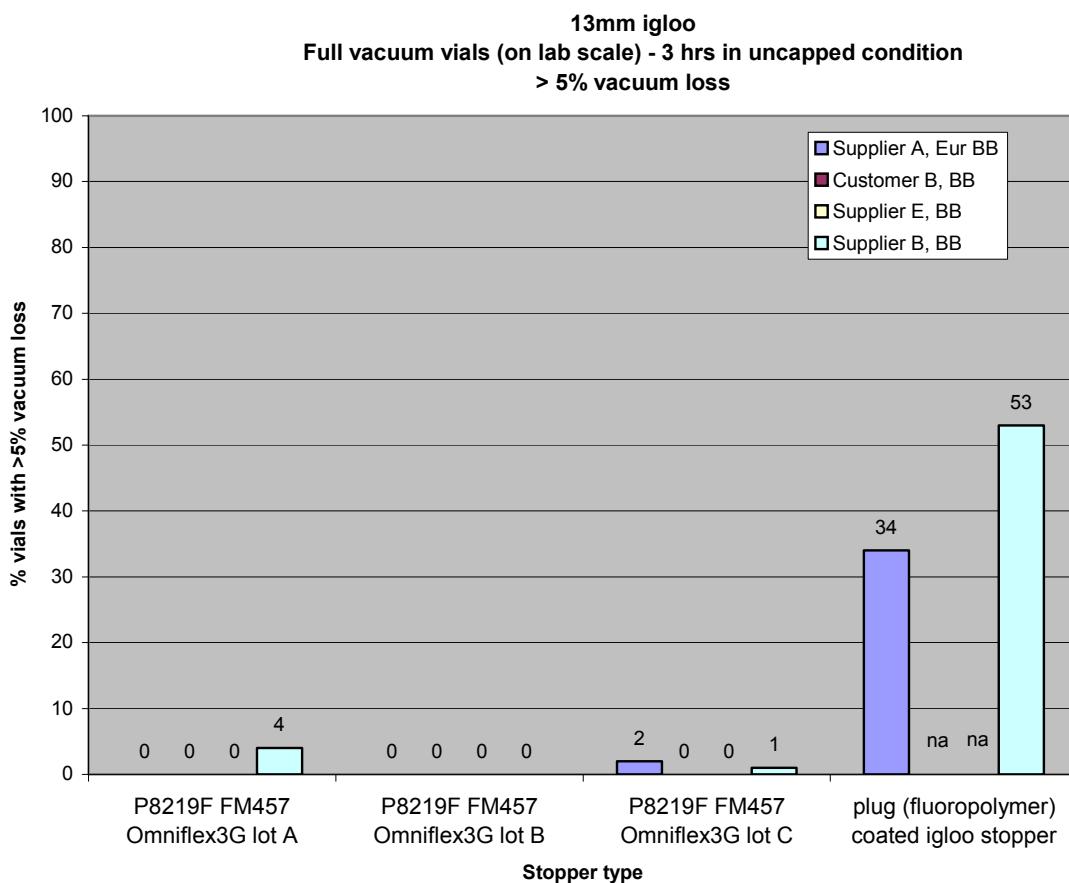
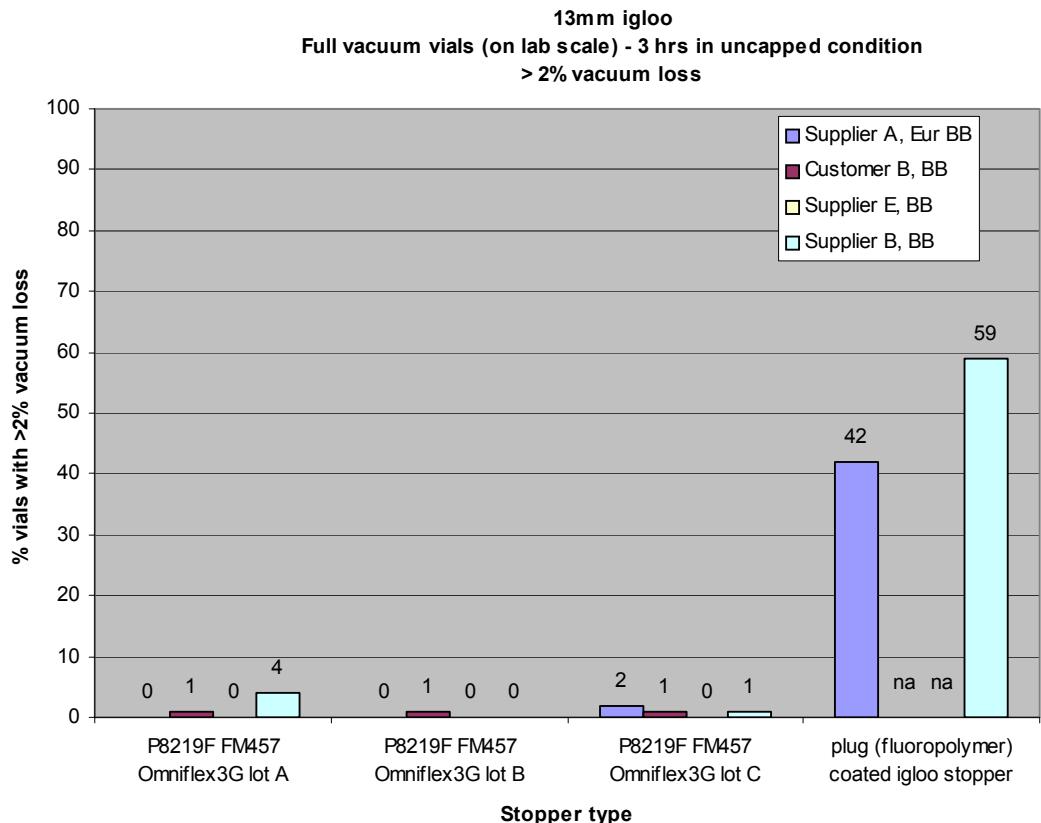
1. Omniflex3G coated product:
FM457/0 P8219F Omniflex3G, batch 641002 ('lot A' in fig.)
FM457/0 P8219F Omniflex3G, batch 704002 ('lot B' in fig.)
FM457/0 P8219F Omniflex3G, batch 704004 ('lot C' in fig.)
(product drawing : see attachment 1)
2. a plug (fluoropolymer) film coated stopper

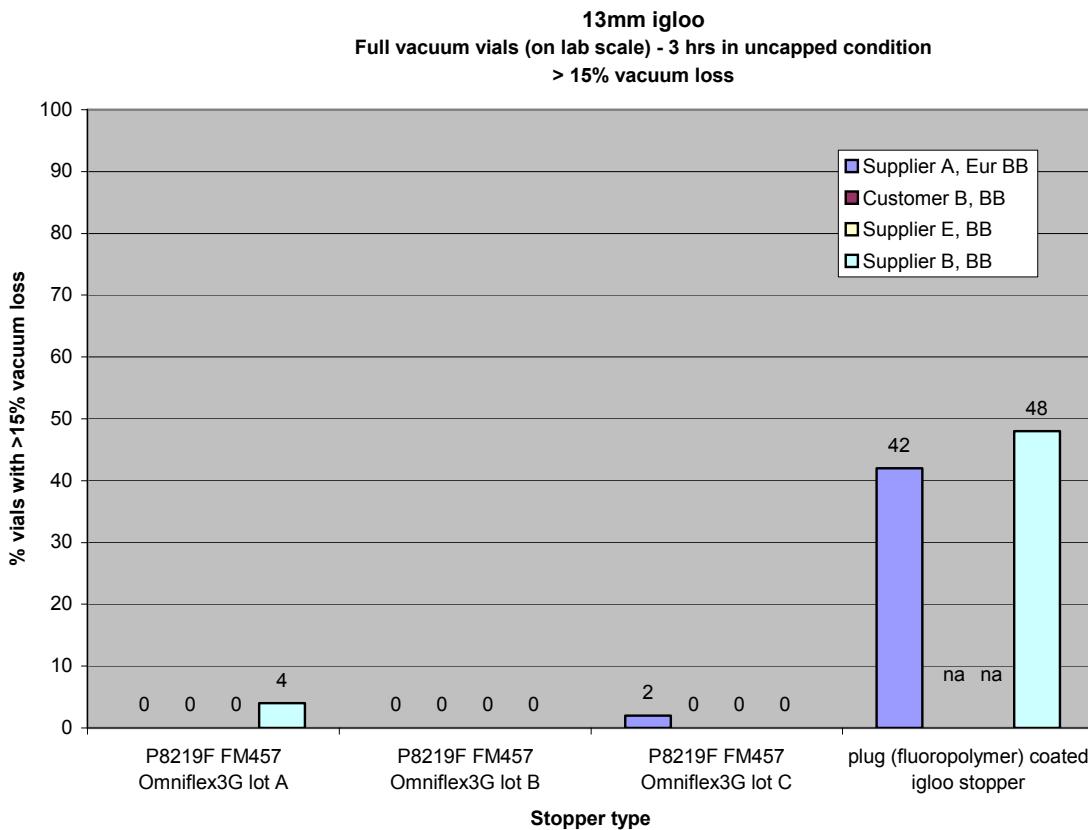
Test method: (same as sub 3.4.1)

- Vials are brought in a lab exsiccator. On the vials freeze-drying stoppers are put in their lyophilization position. The exsiccator is closed.
- Underpressure is created in the vials by use of a vacuum pump that is connected to the exsiccator. The pressure in the vials in the exsiccator is installed at +/- 100 mbara (mbar absolute pressure).
- At that pressure the stoppers are pressed down from their lyophilization to their seating position.
- 100 vials are tested per product sample and per vial type.
- The residual underpressure in the vials is measured after 3 hours storage in uncapped condition by using a pressure gauge with a needle (destructive measurement).

Results

Figures below give for each product and for each vial type the percentage of vials with more than 2%, resp. more than 5% and resp. more than 15% of loss of the originally installed vacuum under the conditions of the test and of the measurement as described above. The plug (fluoropolymer) film coated stopper was only tested on 2 vials.



**Conclusions:**

- FM457/0, Omniflex3G closure/vial seal integrity in uncapped condition is better than that of the plug (fluoropolymer) film coated stopper involved in this test.
- The specific results are depending on the type of vial.

Careful selection by the pharmaceutical manufacturer of a suitable vial in connection with lyophilization closures is highly indicated.

3.4.6. 13mm lyo -igloo design in 4 different vial types – stoppers from industrial mould

In this paragraph the vacuum retention properties of a product V9402, FM457/0, Omniflex3G are reported. The latter product is obtained from an industrial mould

4 different vial types have been used to evaluate the vacuum retention properties of V9402 FM457/0, Omniflex3G.

The plug film coated 13 mm lyo-igloo design was not tested in this case.

Test description

Identification of vials:

1. Supplier A vial with European blow back
2. Supplier C vial with blow back
3. Tubular vial, received from customer A
4. Tubular vial with blow back, received from customer B

Identification of coated lyo stoppers:

1. Production mould product in Omniflex3G :
V9402 FM457/0 Omniflex 3G, batch 30083696
2. Production mould product in Omniflex3G :
V9402 FM457/0 Omniflex 3G, batch 30083697

Test method (same as sub 3.4.2) :

- underpressure in vials with BOC Edwards lyo chamber: first test series with absolute pressure in vials of +/- 100 mbar (+/- 76 Torr) ; second test series with absolute pressure in vials of +/- 500 mbar (+/- 380 Torr).
- 50 vials prepared per product sample and per vial type for each pressure condition
- measurement of underpressure in vials by using the Lighthouse equipment (non-destructive)
- measurement after 3 hrs storage at ambient conditions (stoppered/uncapped)

Results

Full Vacuum, uncapped condition during 3 hrs

Tested for 50 vials per sample,

Result expressed in % vials with more than 5% or more than 15% vacuum loss

Condition: **100 mbara pressure in vials and then further stored in uncapped condition during 3 hrs.**

	Supplier A vial Eur BB Vacuumloss >5% >15%		Supplier C vial with BB Vacuumloss >5% >15%	
13 mm igloo lyo: V9402 FM457/0 Omniflex3G, batch 30083696	0% 0%		0% 0%	
V9402 FM457/0 Omniflex3G, batch 30083697	0% 0%		0% 0%	

	Customer A vial Vacuumloss >5% >15%		Customer B vial with BB Vacuumloss >5% >15%	
13 mm igloo lyo: V9402 FM457/0 Omniflex3G, batch 30083696	0% 0%		0% 0%	
V9402 FM457/0 Omniflex3G, batch 30083697	0% 0%		0% 0%	

Partial Vacuum, uncapped condition during 3 hrs

Tested for 50 vials per sample,

Result expressed in % vials with more than 5% or more than 15% vacuum loss

Condition: **500 mbara pressure in vials and then further stored in uncapped condition during 3 hrs.**

	Supplier A vial Eur BB Vacuumloss >5% >15%		Supplier C vial with BB Vacuumloss >5% >15%	
13 mm igloo lyo: V9402 FM457/0 Omniflex3G, batch 30083696	0% 0%		0% 0%	
V9402 FM457/0 Omniflex3G, batch 30083697	0% 0%		0% 0%	

	Customer A vial Vacuumloss >5% >15%		Customer B vial with BB Vacuumloss >5% >15%	
13 mm igloo lyo: V9402 FM457/0 Omniflex3G, batch 30083696	0% 0%		0% 0%	
V9402 FM457/0 Omniflex3G, batch 30083697	0% 0%		0% 0%	

Conclusions:

The coated 13 mm lyo igloo parts from industrial mould V9402 are in line with the parts from the trial mould P8219F. Results obtained with stoppers manufactured from an industrial tool thus confirm the small scale results.

3.4.7. 13mm lyo 2-leg design in 4 different vial types

In this paragraph the vacuum retention properties of a product HPP079, FM457/0, Omniflex3G are reported. Drawing of this product can be found in attachment 1. Mould HPP079 is an industrial mould.

4 different vial types have been used to evaluate the vacuum retention properties of 3 different production batches of HPP079, FM457/0, Omniflex3G.

Test description

Identification of vials (same as sub 3.3.5):

1. Supplier A tubular vial with European blow back
2. Tubular vial with blow back, received from customer B
3. Supplier E tubular vial with blow back
4. Supplier B tubular vial with blow back

Identification of coated lyo stoppers:

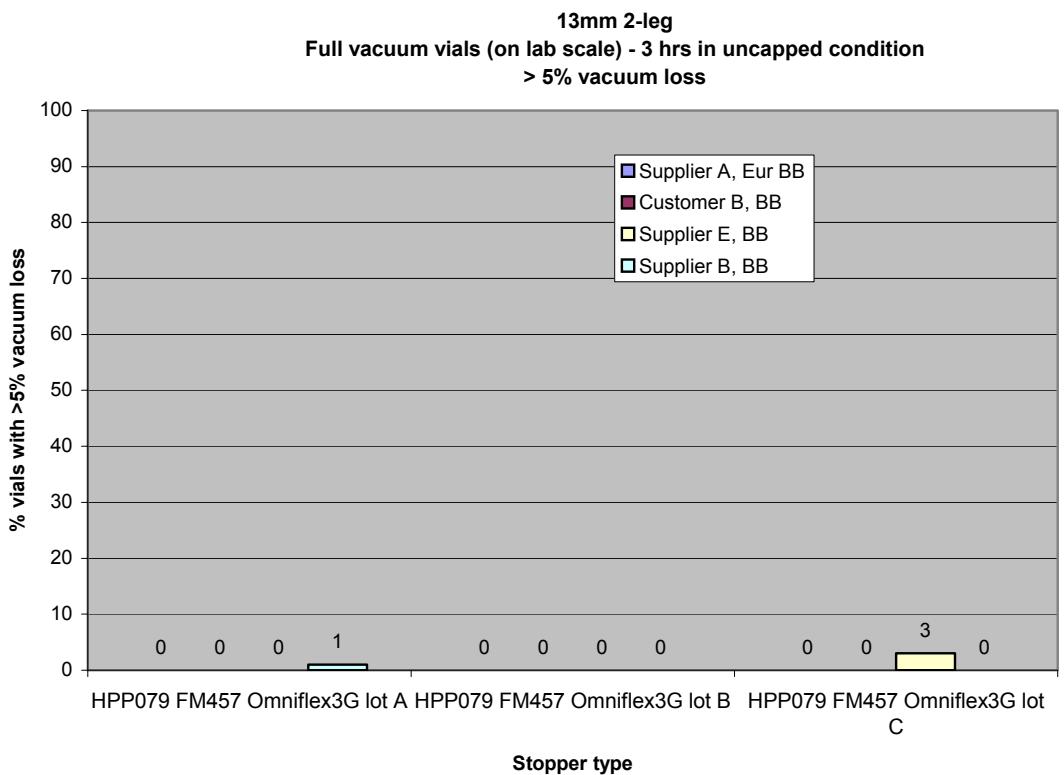
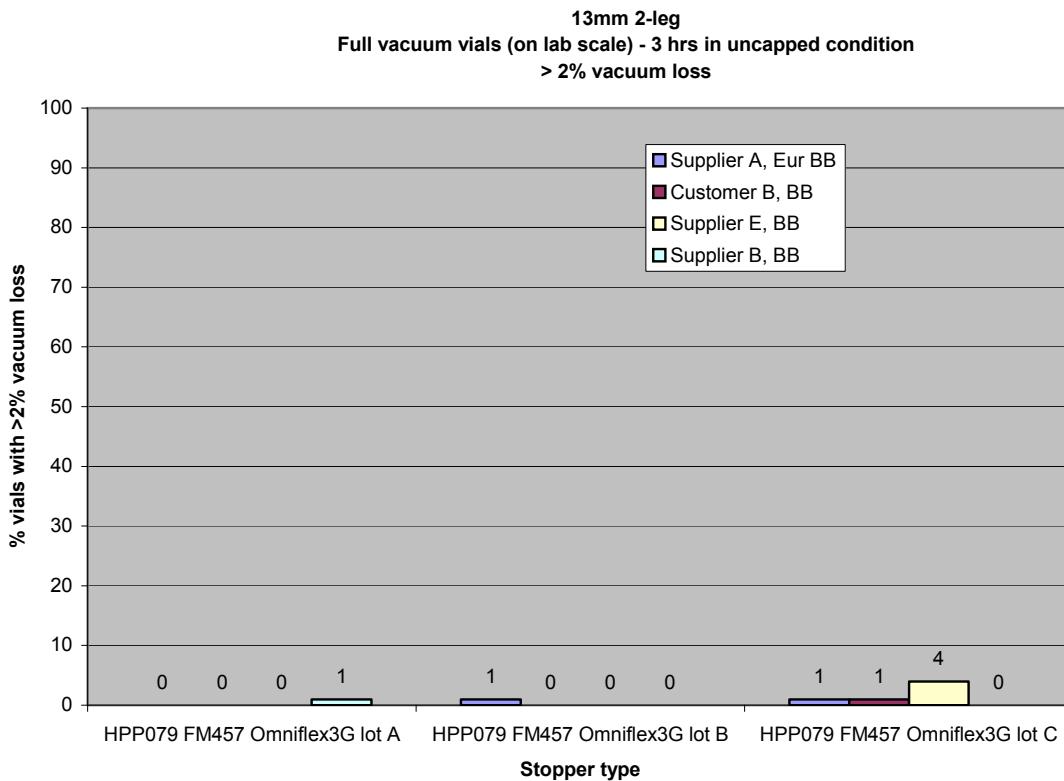
1. Omniflex3G coated product:
FM457/0 HPP079 Omniflex3G, batch 642001 ('lot A' in fig.)
FM457/0 HPP079 Omniflex3G, batch 704003 ('lot B' in fig.)
FM457/0 HPP079 Omniflex3G, batch 704005 ('lot C' in fig.)

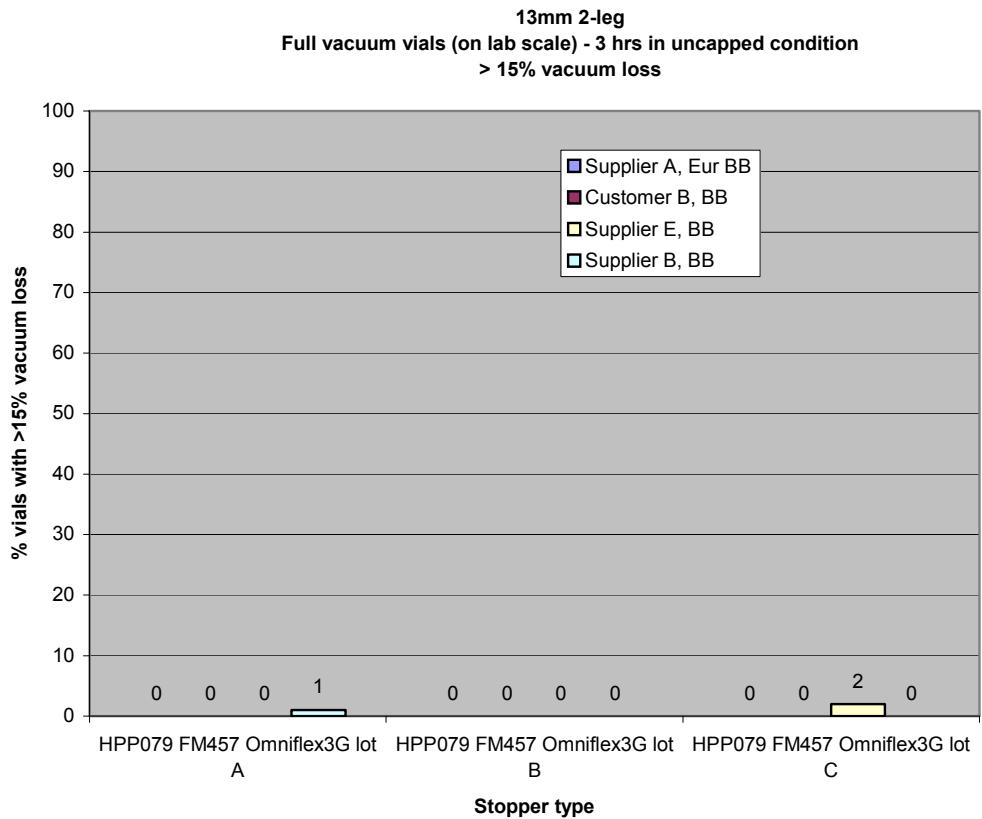
Test method: (same as sub 3.4.1)

- Vials are brought in a lab exsiccator. On the vials freeze-drying stoppers are put in their lyophilization position. The exsiccator is closed.
- Underpressure is created in the vials by use of a vacuum pump that is connected to the exsiccator. The pressure in the vials in the exsiccator is installed at +/- 100 mbara (mbar absolute pressure).
- At that pressure the stoppers are pressed down from their lyophilization to their seating position.
- 100 vials are tested per product sample and per vial type.
- The residual underpressure in the vials is measured after 3 hours storage in uncapped condition by using a pressure gauge with a needle (destructive measurement).

Results

Figures below give for each vial type the percentage of vials with more than 2%, resp. more than 5% and resp. more than 15% of loss of the originally installed vacuum under the conditions of the test and of the measurement as described above.



**Conclusions:**

- Design HPP079 in Omniflex3G is deemed to generate satisfactory results on vacuum retention.
- The specific results are depending on the type of vial.

Careful selection by the pharmaceutical manufacturer of a suitable vial in connection with lyophilization closures is highly indicated.

3.5. Serum closures

Development work was spent on checking whether Omniflex3G in combination with stopper design changes equally gives more comfort in the field of vacuum (or nitrogen) retention for serum stopper applications, even after storage at ultra low temperatures such as cold storage (-78°C/-108,4°F). The results of this work are described in this section.

3.5.1. 20 mm serum closures in 3 different vial types – stoppers from trial mould

In this paragraph the vacuum retention properties before capping of a product P8575A, FM457/0, Omniflex3G are reported. Drawing of this product can be found in attachment 1. The latter product again is obtained from a trial mould. This trial mould allowed to generate enough parts for development purposes, however is not suitable for industrial production. On industrial scale 20 mm serum stoppers are obtained from an industrial mould with number V9407.

3 different vial types have been used to evaluate the vacuum retention properties of P8575A, FM457/0, Omniflex3G.

Test description

Identification of vials:

1. Supplier A tubular vial with European blow back
2. Supplier B tubular vial with US blow back
3. Tubular vial customer C with blow back

Identification of coated lyo stoppers:

1. Omniflex3G coated product :
FM457/0 P8575A Omniflex3G, batch 749004

Test method (same as sub 3.4.2) :

- underpressure in vials by using BOC Edwards lyo chamber (see attachment 3) : one test series with absolute pressure in the vials of +/- 100 mbara (+/- 76 Torr); other test series with absolute pressure in the vials of +/- 500 mbara (+/- 380 Torr).
- 50 vials prepared per product sample and per vial type for each pressure condition
- measurement of headspace pressure in vials by using the Lighthouse equipment (non-destructive pressure measurement) (see attachment 3)
- measurement at 3 different points in time after leaving the lyo chamber:
 - before capping the vials (after 3 hrs storage in uncapped condition)²
 - after capping the vials
 - after storage of capped vials at -80°C/overnight (followed by reconditioning till room temperature)³

Results

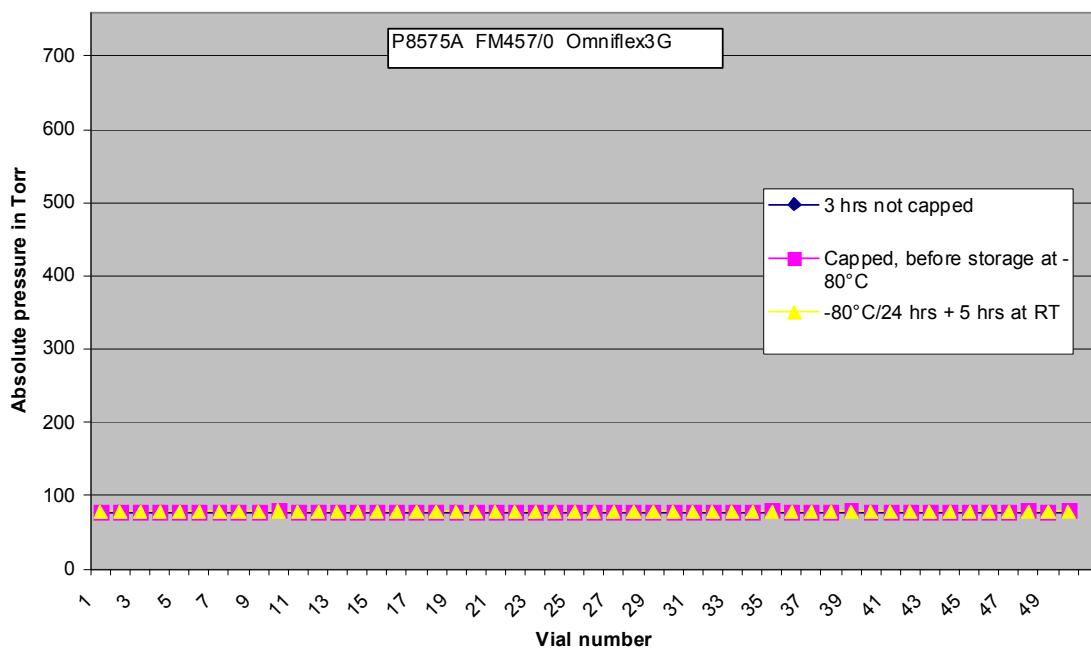
Figures below give for each vial type the individual results of the absolute pressures measured before capping (after 3 hrs storage in uncapped condition), after capping and after storage of capped vials at -80°C/overnight.

² : serum vials are normally capped immediately after stoppering. 3 hours waiting time between stoppering and capping thus represents an extreme worst case.

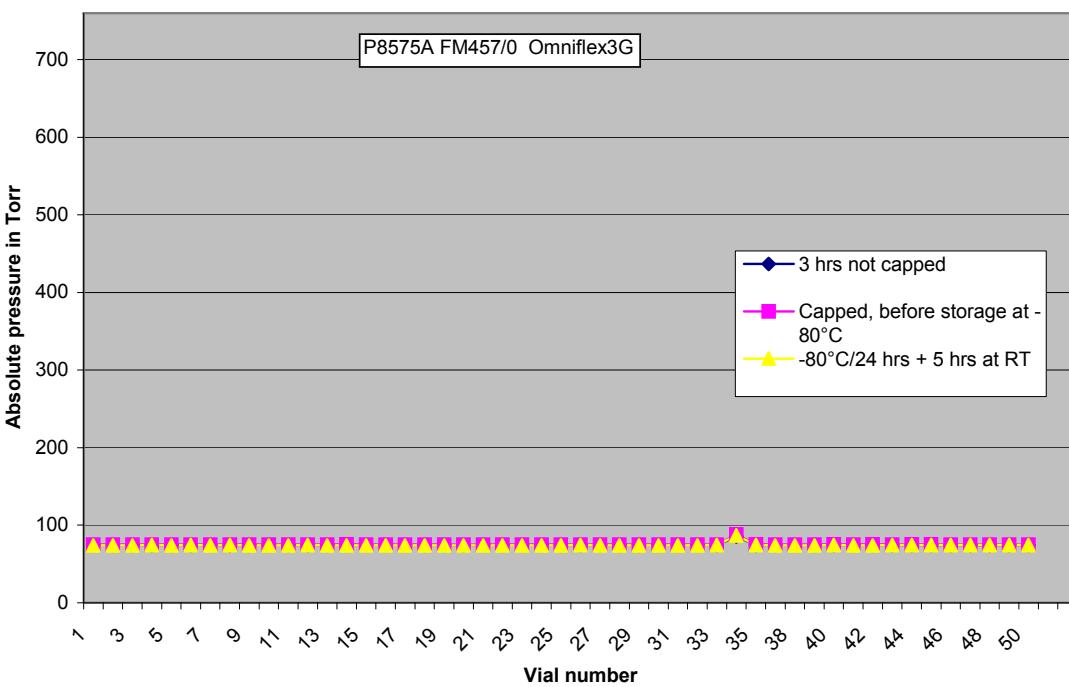
³ : storage at -80°C mimics "cold chain" storage conditions

Full vacuum

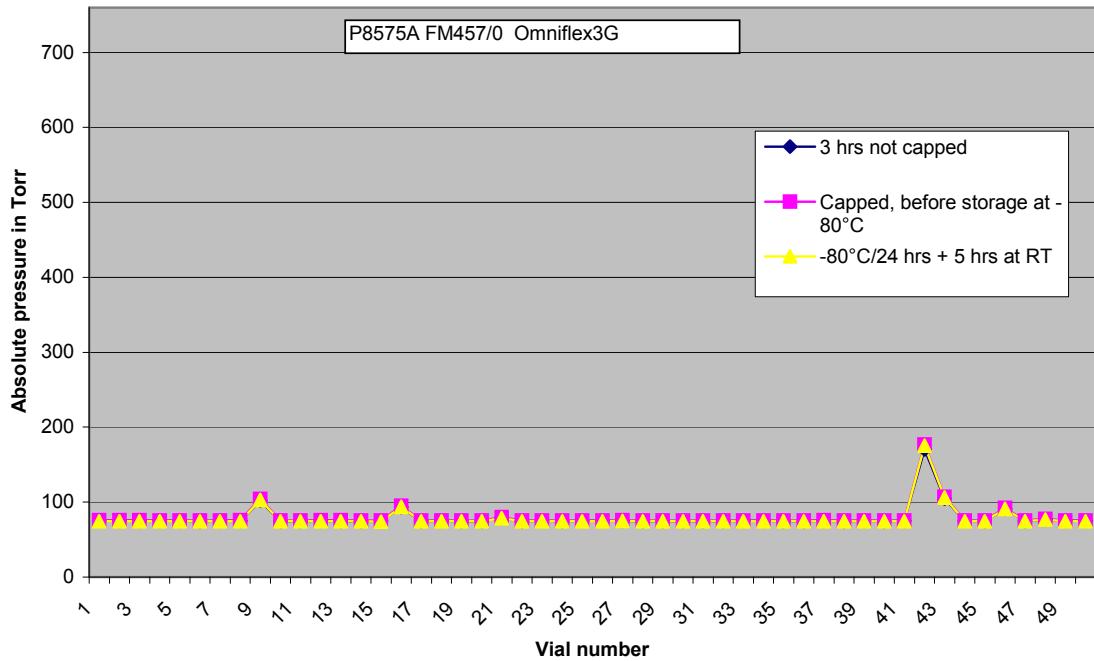
Supplier A vial Eur BB 20 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials



Supplier B vial US BB 20 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials

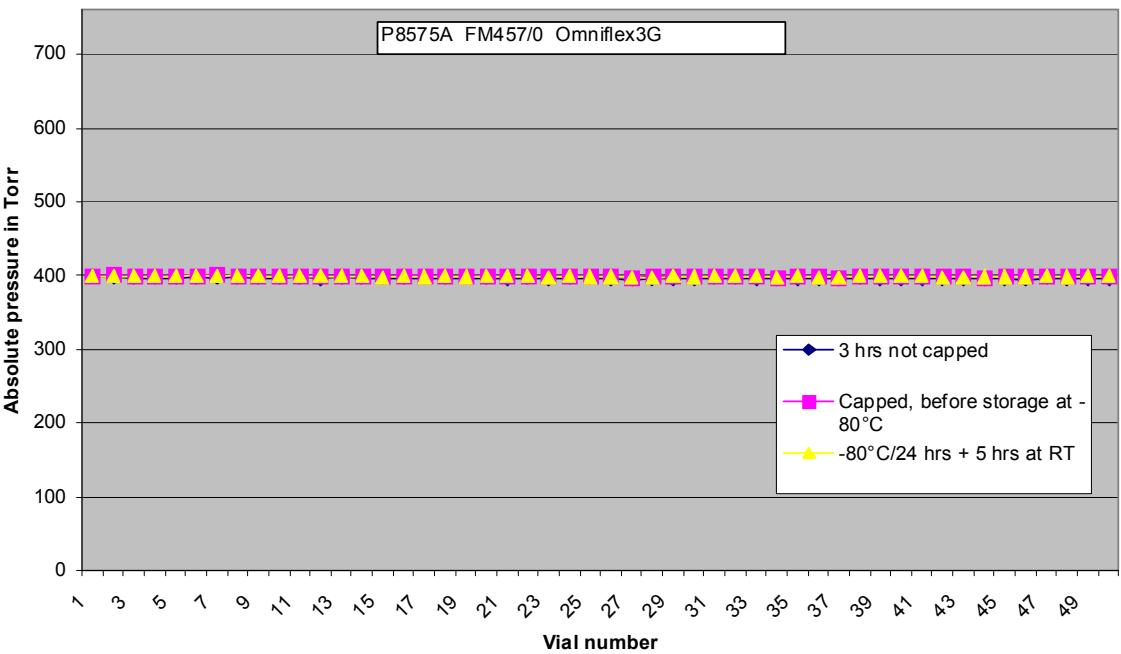


Customer C vial BB 20 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials

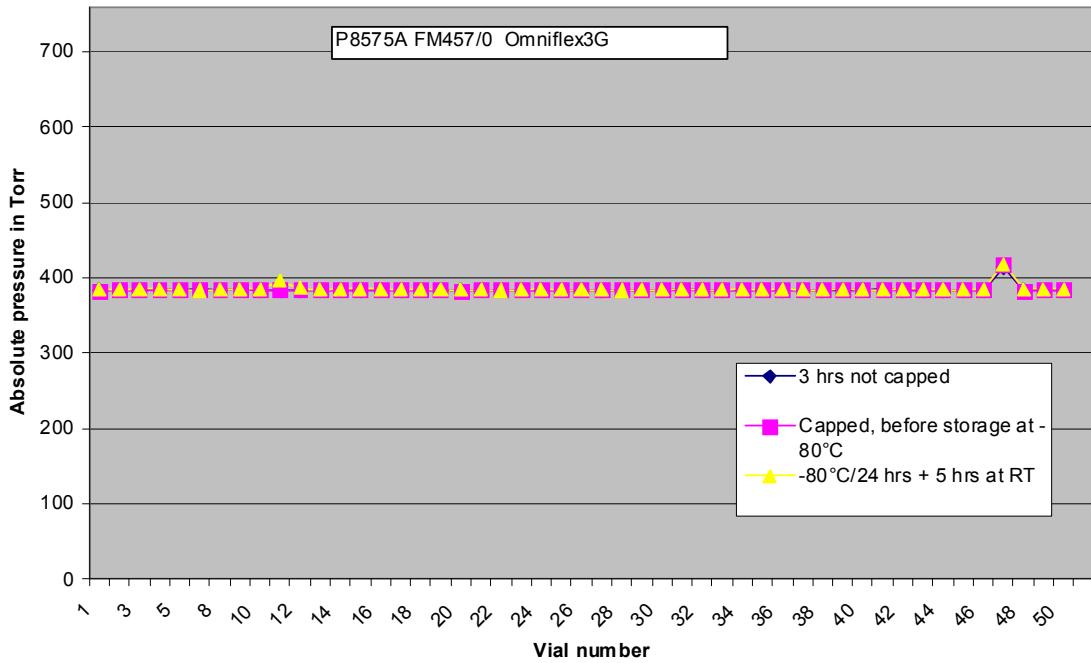


Partial vacuum

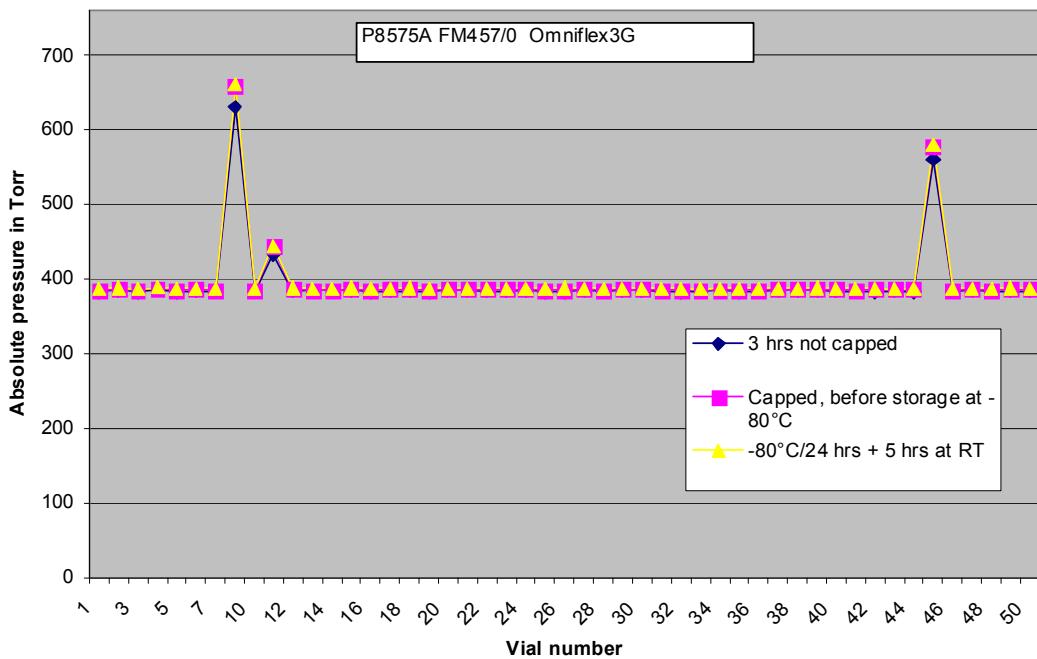
Supplier A vial Eur BB 20 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Supplier B vial US BB 20 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Customer C vial BB 20 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Conclusions:

- P8575A, FM457/0, Omniflex3G generates satisfactory results on vacuum retention.
- The specific results are depending on the type of vial.
- Storage of capped vials at extremely low temperatures as encountered in cold chain applications do not affect vacuum retention.

Careful selection by the pharmaceutical manufacturer of a suitable vial in connection with serum closures is highly indicated.

3.5.2. 20 mm serum closures in 3 different vials – stoppers from industrial mould

In this paragraph the vacuum retention properties of a product V9407, FM457/0, Omniflex3G are reported. The latter product is obtained from an industrial mould

3 different vial types have been used to evaluate the vacuum retention properties of V9407 FM457/0, Omniflex3G.

Test description

Identification of vials:

1. Supplier A tubular vial with European blow back
2. Supplier B tubular vial with US blow back
3. Tubular vial, received from customer C

Identification of coated lyo stoppers:

Production mould product in Omniflex3G : V9407 FM457/0 Omniflex 3G, batch 30099627

Test method (same as sub 3.4.2) :

- underpressure in vials by using BOC Edwards lyo chamber (see attachment 3) : one test series with absolute pressure in the vials of +/- 100 mbara (+/- 76 Torr); other test series with absolute pressure in the vials of +/- 500 mbara (+/- 380 Torr).
- 50 vials prepared per product sample and per vial type for each pressure condition
- measurement of headspace pressure in vials by using the Lighthouse equipment (non-destructive pressure measurement) (see attachment 3)
- measurement at 3 different points in time after leaving the lyo chamber:
 - before capping the vials (after 3 hrs storage in uncapped condition)⁴
 - after capping the vials
 - after storage of capped vials at -80°C/overnight (followed by reconditioning till room temperature)⁵

Results

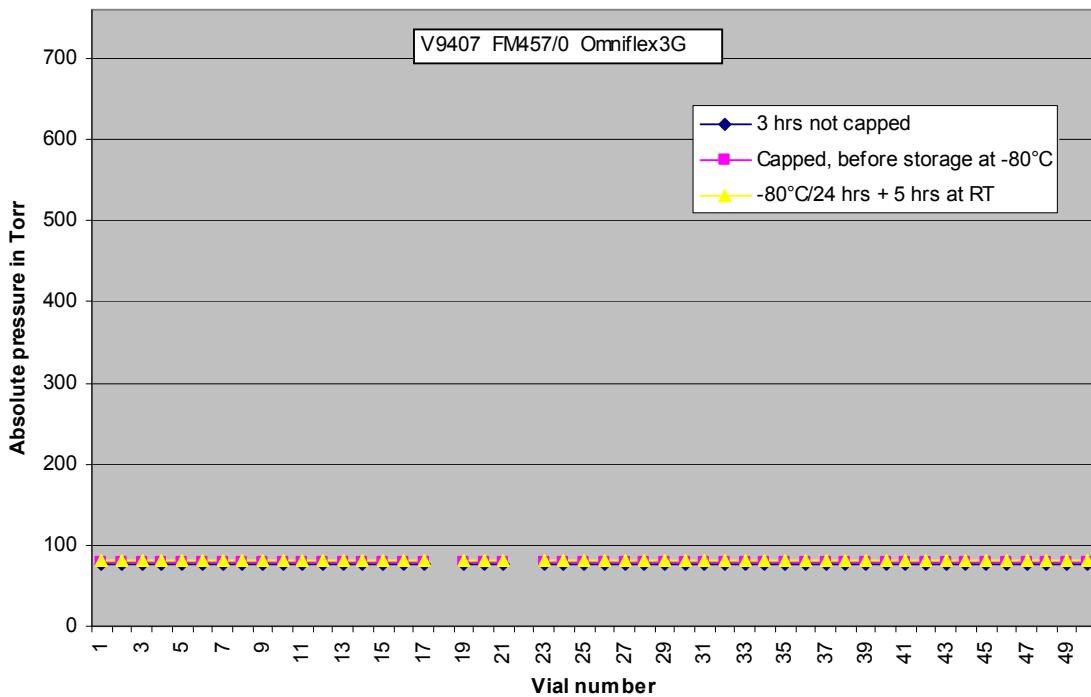
Figures below give for each vial type the individual results of the absolute pressures measured before capping (after 3 hrs storage in uncapped condition), after capping and after storage of capped vials at -80°C/overnight.

⁴ : serum vials are normally capped immediately after stoppering. 3 hours waiting time between stoppering and capping thus represents an extreme worst case.

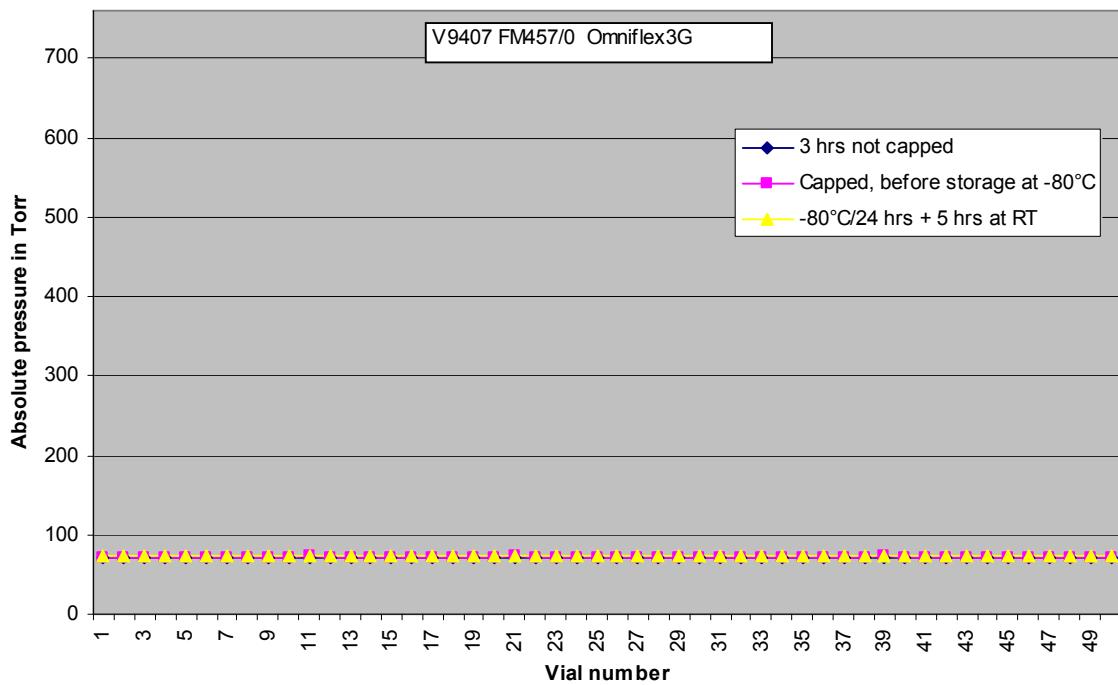
⁵ : storage at -80°C mimics "cold chain" storage conditions

Full vacuum

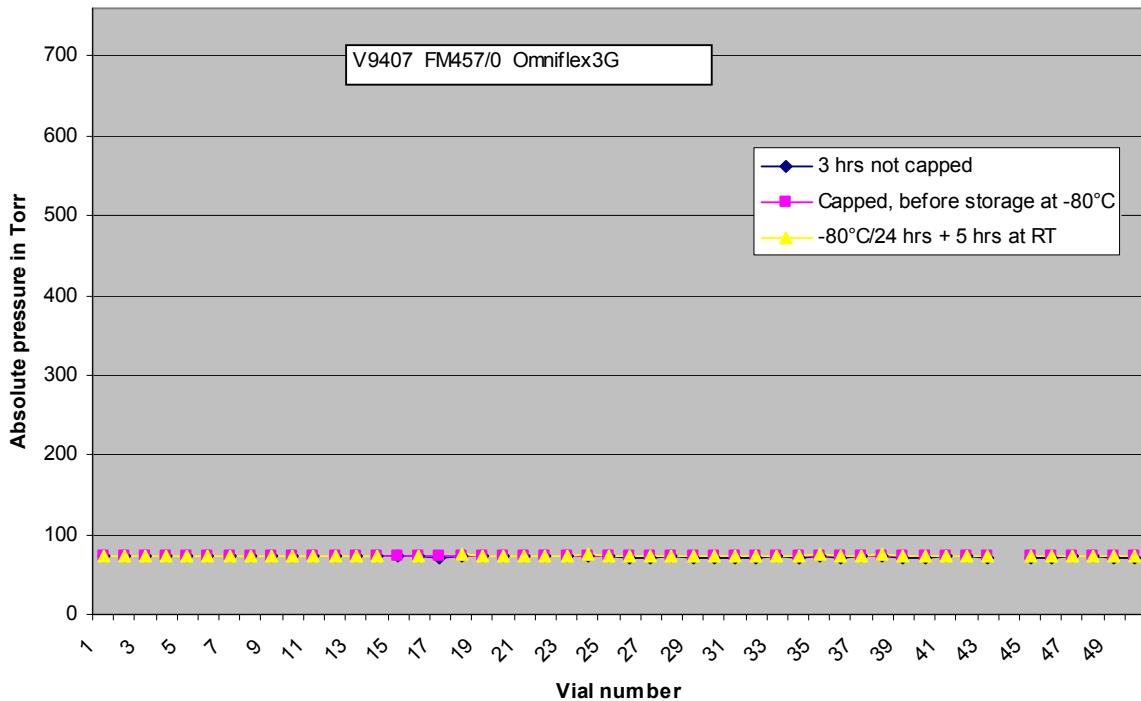
Supplier A Eur BB vial 20 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials



Supplier B vial US BB 20 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials

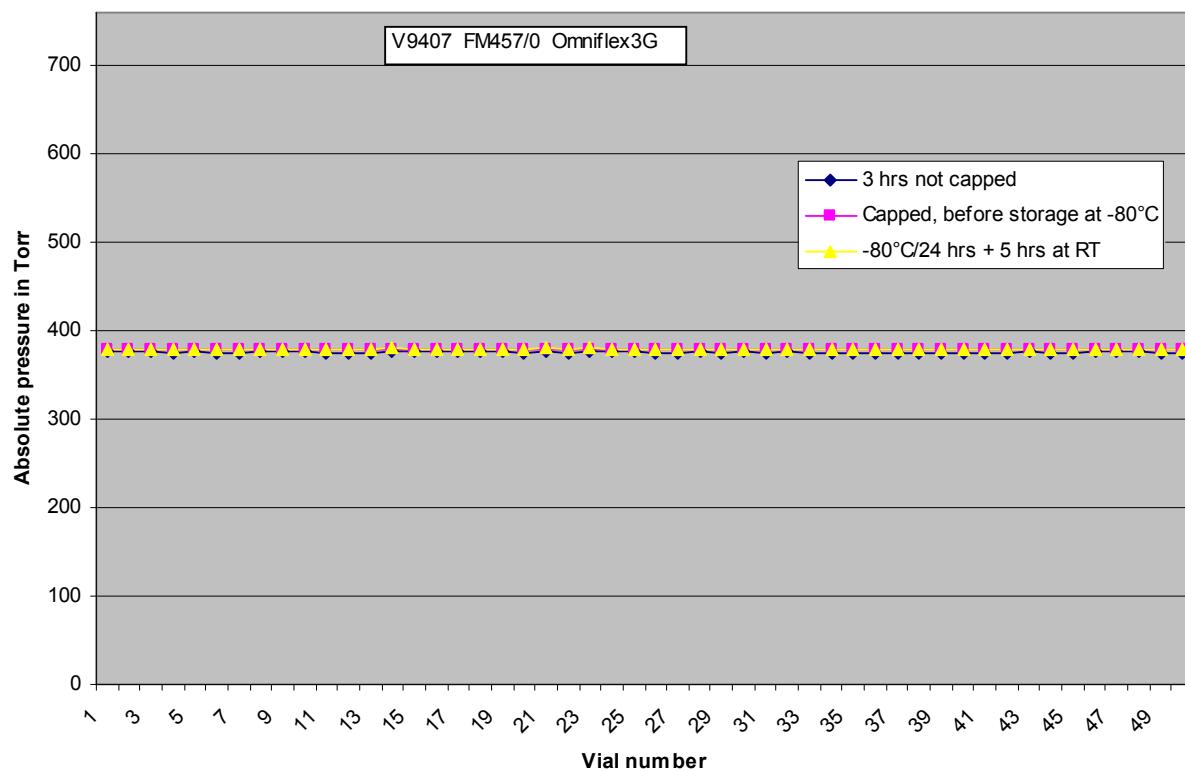


Customer C vial BB 20 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials

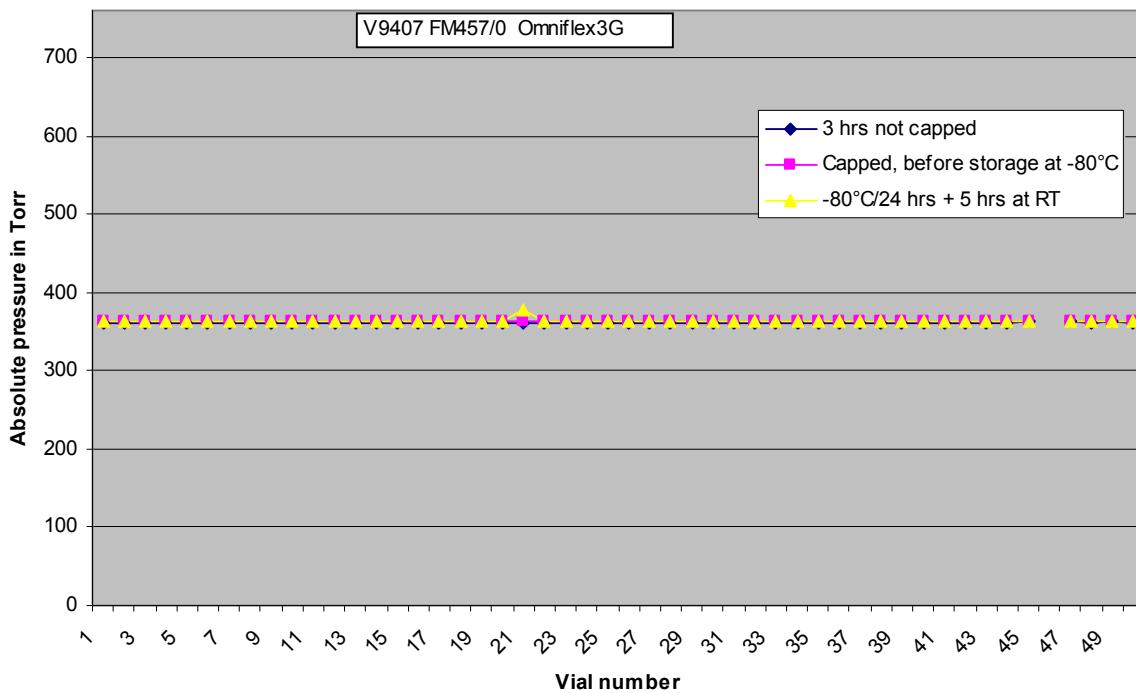


Partial vacuum

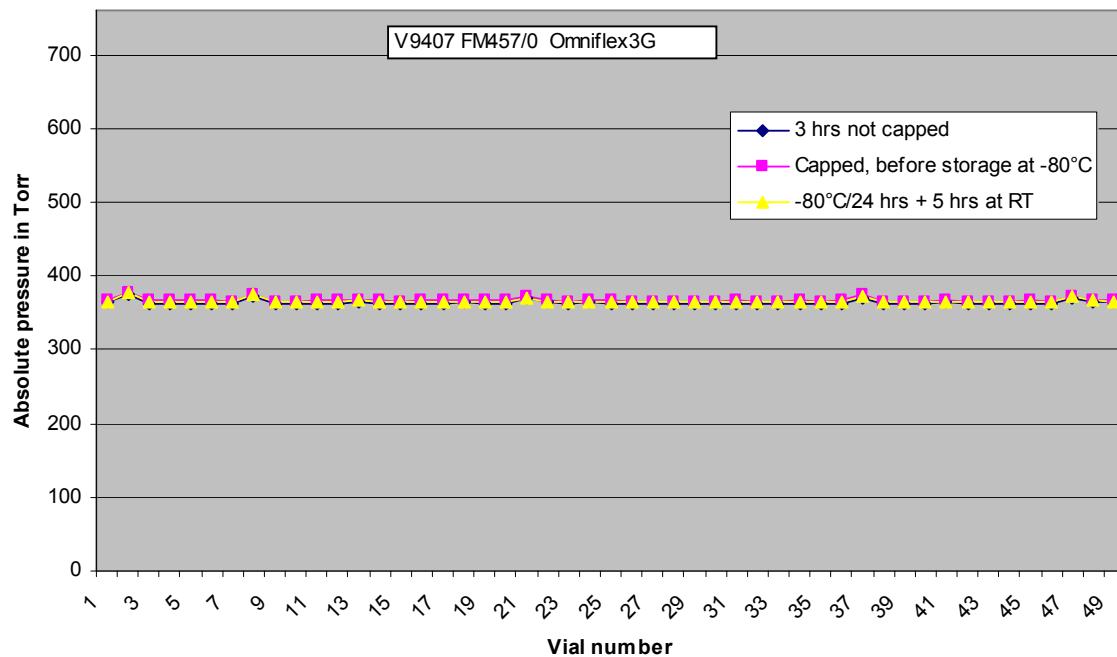
Supplier A Eur BB vial 20 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Supplier B vial US BB 20 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Customer C vial BB 20 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Conclusions:

The coated 20 mm serum closures from industrial mould V9407 are in line with the parts from the trial mould P8575A. Results obtained with stoppers manufactured from an industrial tool thus confirm the small scale results.

3.5.3. 13 mm serum closures in 3 different vial types – stoppers from trial mould

In this paragraph the vacuum retention properties before capping of a product P8576A, FM457/0, Omniflex3G are reported. Drawing of this product can be found in attachment 1. The latter product again is obtained from a trial mould. This trial mould allowed to generate enough parts for development purposes, however is not suitable for industrial production. On industrial scale 13 mm serum stoppers are obtained from an industrial mould with number V9401.

3 different vial types have been used to evaluate the vacuum retention properties of P8576A, FM457/0, Omniflex3G.

Test description

Identification of vials:

1. Supplier A tubular vial with European blow back
2. Supplier B tubular vial with US blow back
3. Supplier F tubular vial with blow back

Identification of coated lyo stoppers:

1. Omniflex3G coated product:
FM457/0 P8576A Omniflex3G, batch 749002

Test method (same as sub 3.4.2):

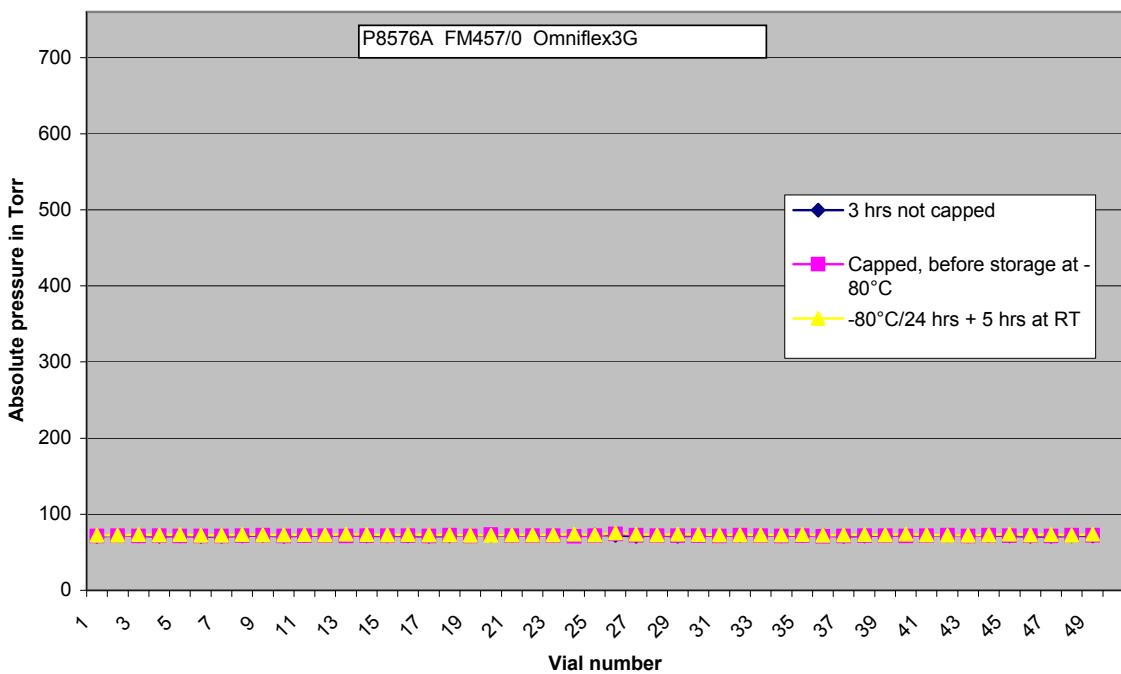
- underpressure in vials by using BOC Edwards lyo chamber (see attachment 3) : one test series with absolute pressure in the vials of +/- 100 mbara (+/- 76 Torr) ; other test series with absolute pressure in the vials of +/- 500 mbara (+/- 380 Torr).
- 50 vials prepared per product sample and per vial type for each pressure condition
- measurement of headspace pressure in vials by using the Lighthouse equipment (non-destructive pressure measurement) (see attachment 3)
- measurement at 3 different points in time after leaving the lyo chamber:
 - before capping the vials (after 3 hrs storage in uncapped condition)
 - after capping the vials
 - after storage of capped vials at -80°C/overnight (followed by reconditioning till room temperature)

Results

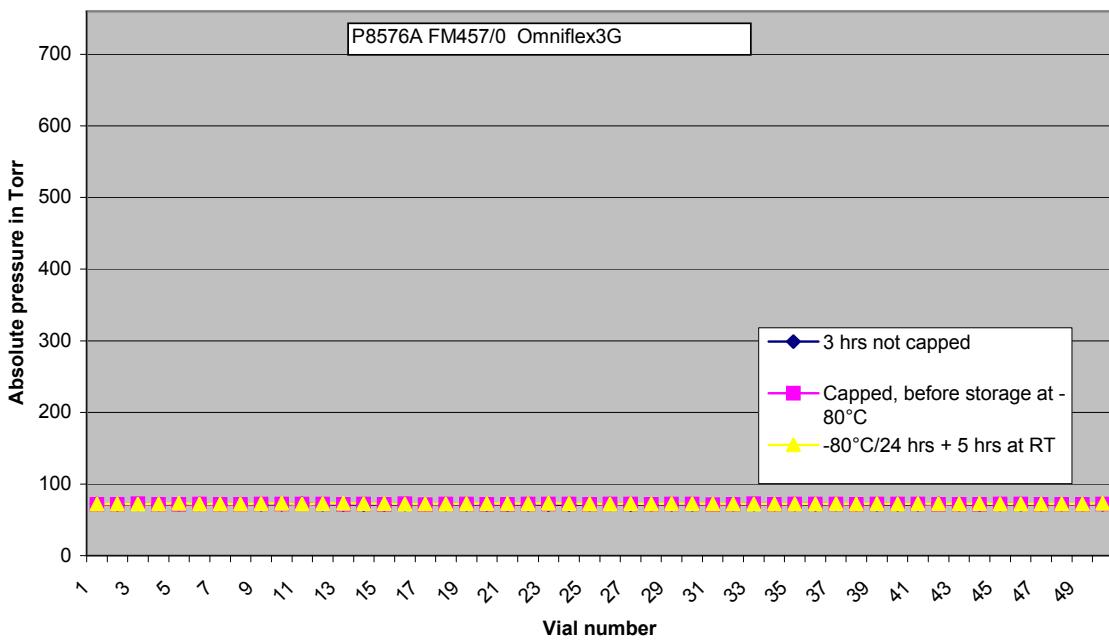
Figures below give for each product and for each vial type the individual results of the pressures measured before capping (after 3 hrs storage in uncapped condition), after capping and after storage of capped vials at -80°C/overnight.

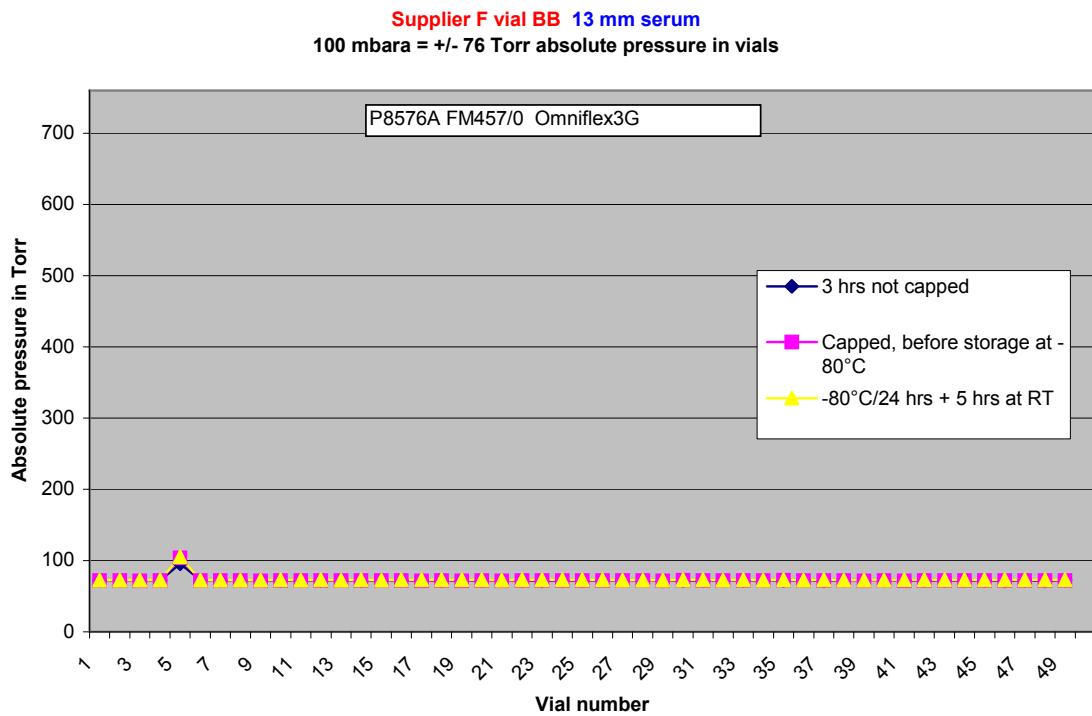
Full vacuum

Supplier A vial Eur BB 13 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials

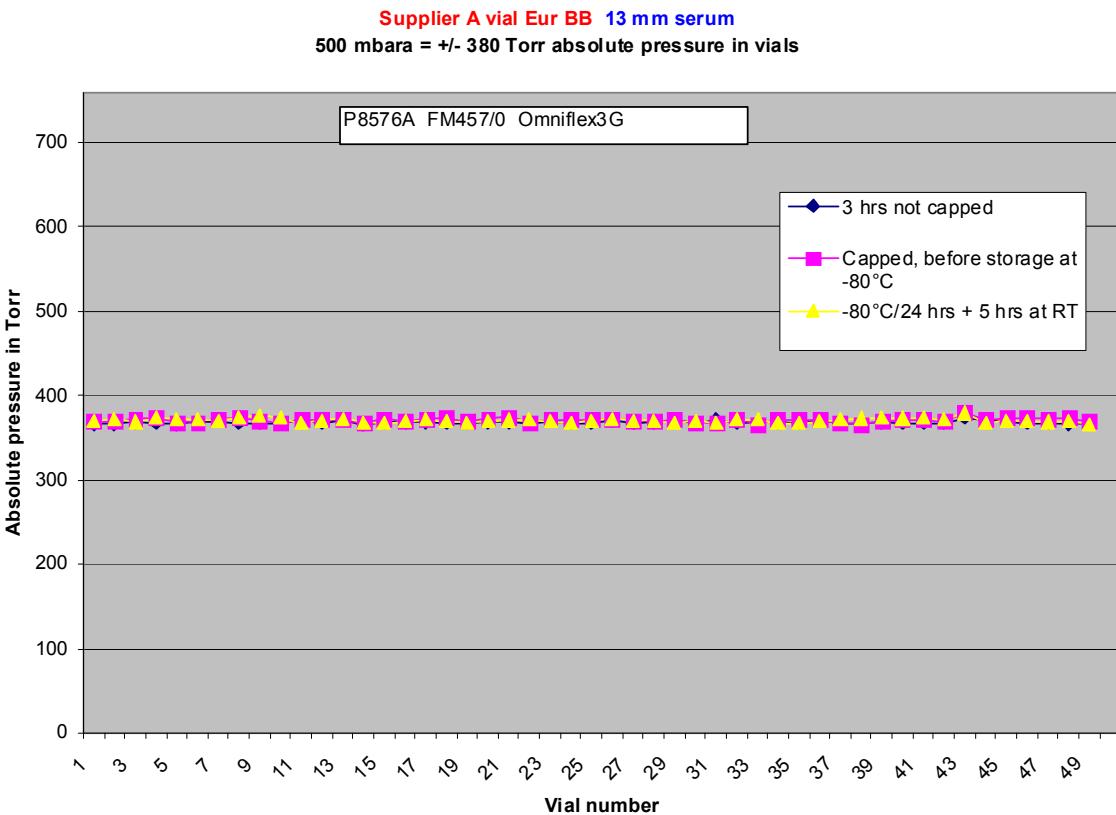


Supplier B vial US BB 13 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials

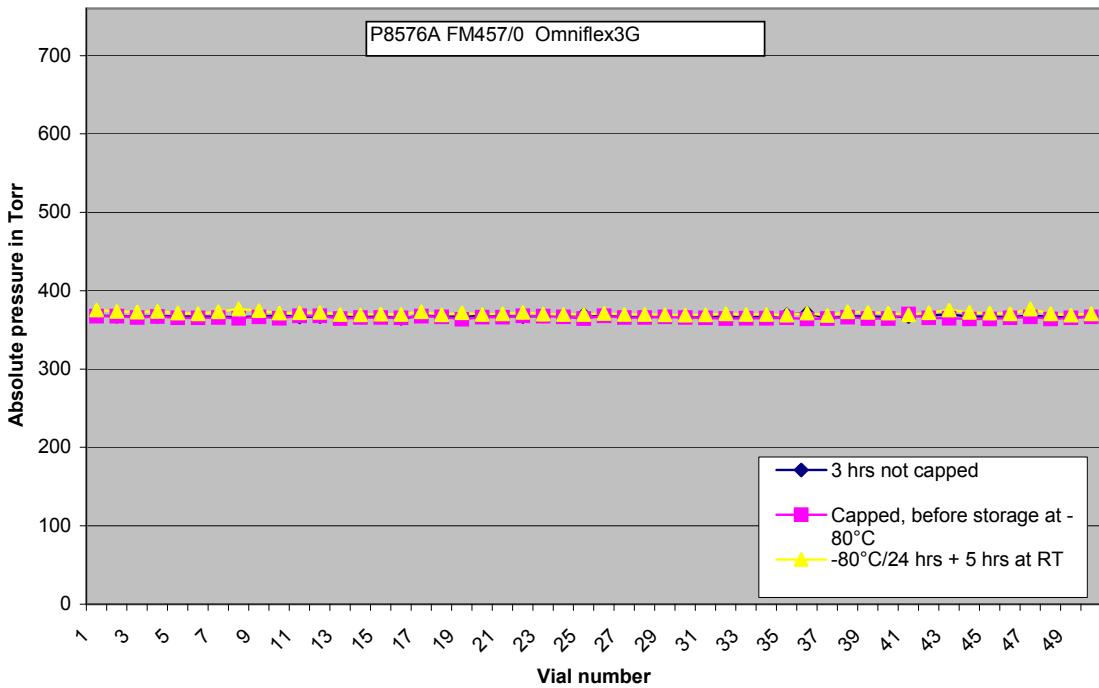




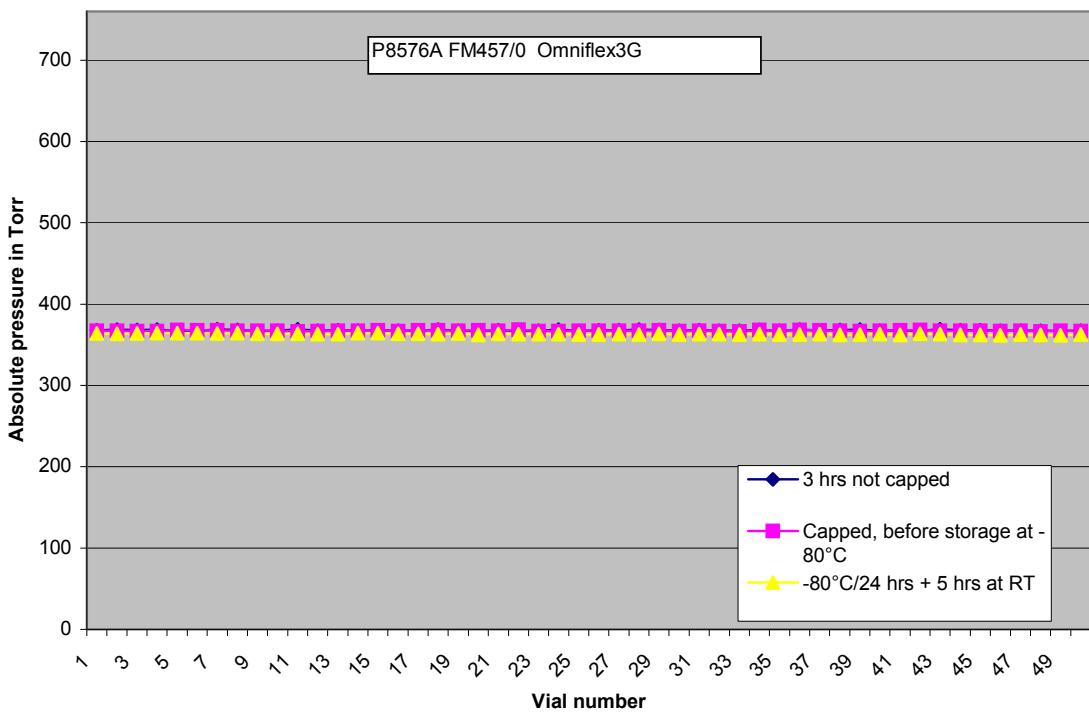
Partial vacuum



Supplier B vial US BB 13 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Supplier F vial BB 13 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Conclusions:

- P8576A, FM457/0, Omniflex3G generates satisfactory results on vacuum retention.
- The specific results are depending on the type of vial.
- Storage of capped vials at extremely low temperatures as encountered in cold chain applications do not affect vacuum retention.

Careful selection by the pharmaceutical manufacturer of a suitable vial in connection with serum closures is highly indicated.

3.5.4. 13 mm serum closures in 3 different vials – stoppers from industrial mould

In this paragraph the vacuum retention properties of a product V9401, FM457/0, Omniflex3G are reported. The latter product is obtained from an industrial mould.

3 different vial types have been used to evaluate the vacuum retention properties of V9401 FM457/0, Omniflex3G.

Test description

Identification of vials:

1. Supplier A tubular vial with European blow back
2. Supplier B tubular vial with US blow back
3. Supplier F tubular vial with blow back

Identification of coated lyo stoppers:

Production mould product in Omniflex3G : V9401 FM457/0 Omniflex 3G, batch 30100412

Test method (same as sub 3.4.2) :

- underpressure in vials by using BOC Edwards lyo chamber (see attachment 3) : one test series with absolute pressure in the vials of +/- 100 mbara (+/- 76 Torr); other test series with absolute pressure in the vials of +/- 500 mbara (+/- 380 Torr).
- 50 vials prepared per product sample and per vial type for each pressure condition
- measurement of headspace pressure in vials by using the Lighthouse equipment (non-destructive pressure measurement) (see attachment 3)
- measurement at 3 different points in time after leaving the lyo chamber:
 - before capping the vials (after 3 hrs storage in uncapped condition)⁶
 - after capping the vials
 - after storage of capped vials at -80°C/overnight (followed by reconditioning till room temperature)⁷

Results

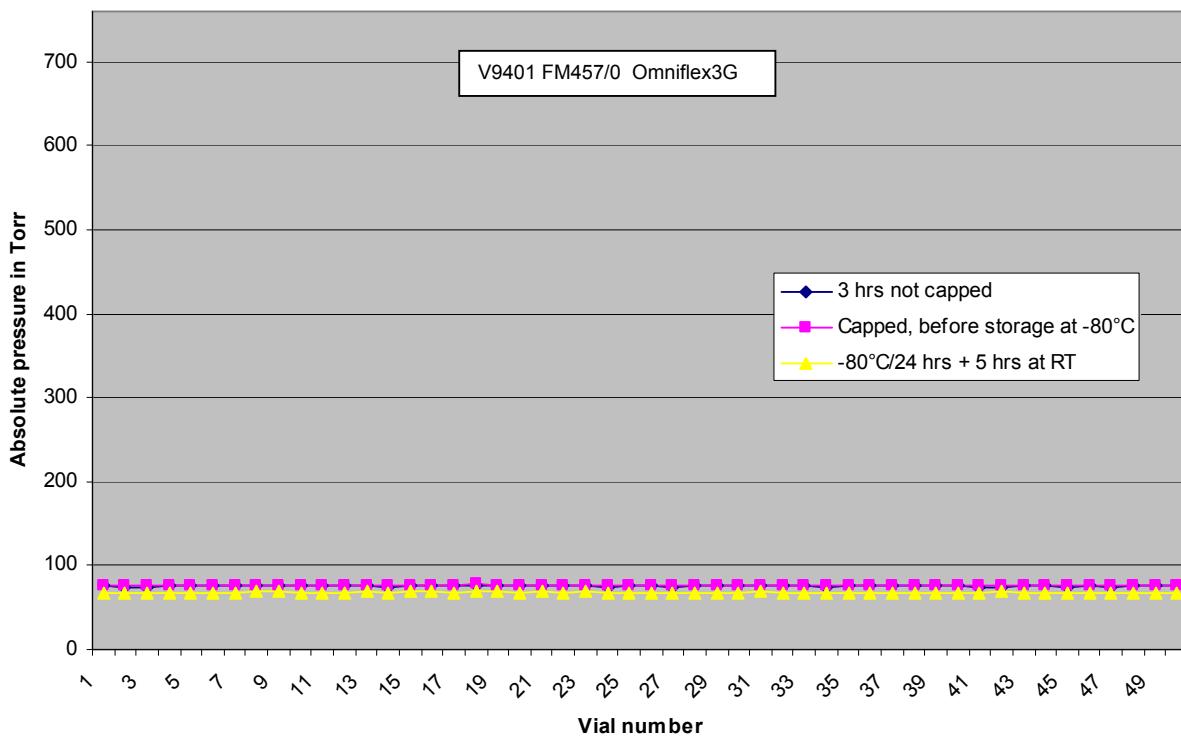
Figures below give for each vial type the individual results of the absolute pressures measured before capping (after 3 hrs storage in uncapped condition), after capping and after storage of capped vials at -80°C/overnight.

⁶ : serum vials are normally capped immediately after stoppering. 3 hours waiting time between stoppering and capping thus represents an extreme worst case.

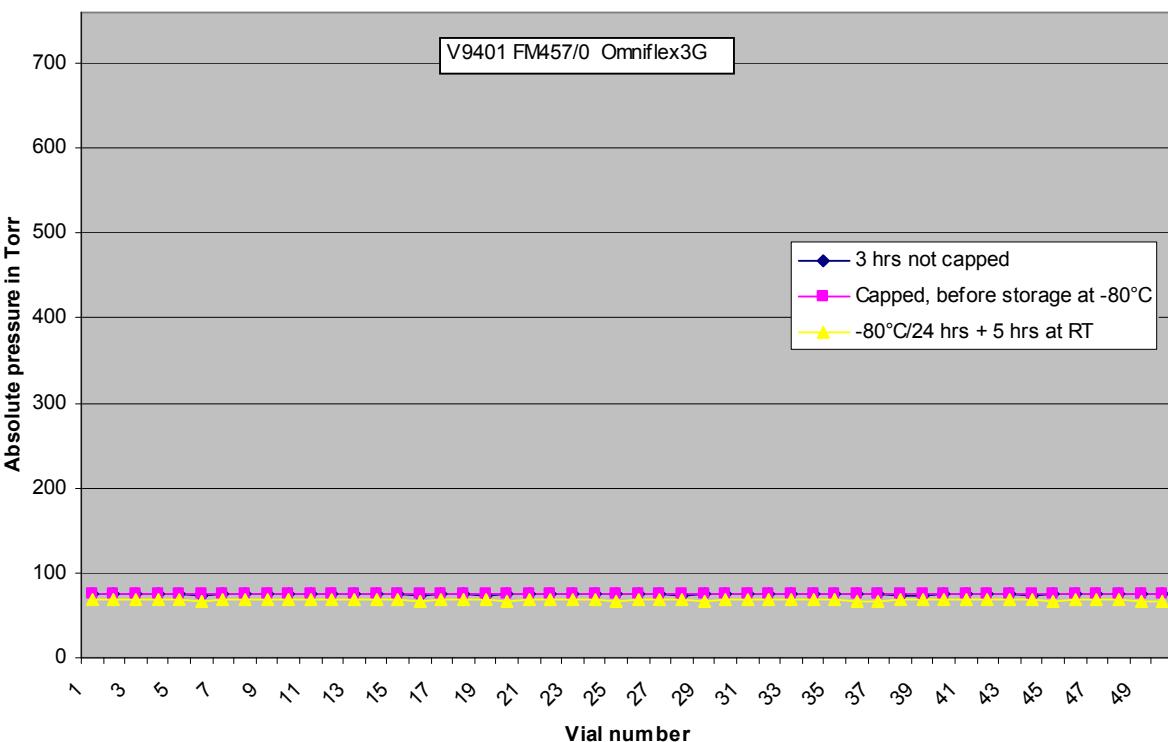
⁷ : storage at -80°C mimics "cold chain" storage conditions

Full vacuum

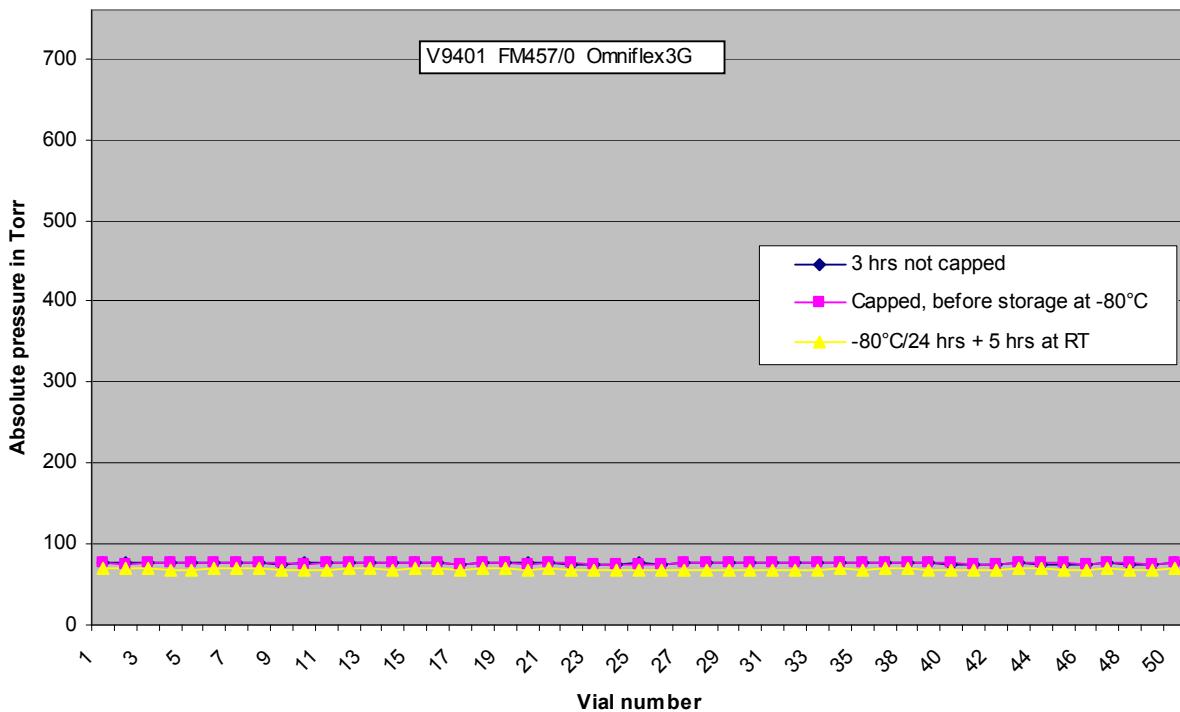
Supplier A Eur BB vial 13 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials



Supplier B vial US BB 13 mm serum
100 mbara= +/- 76 Torr absolute pressure in vials

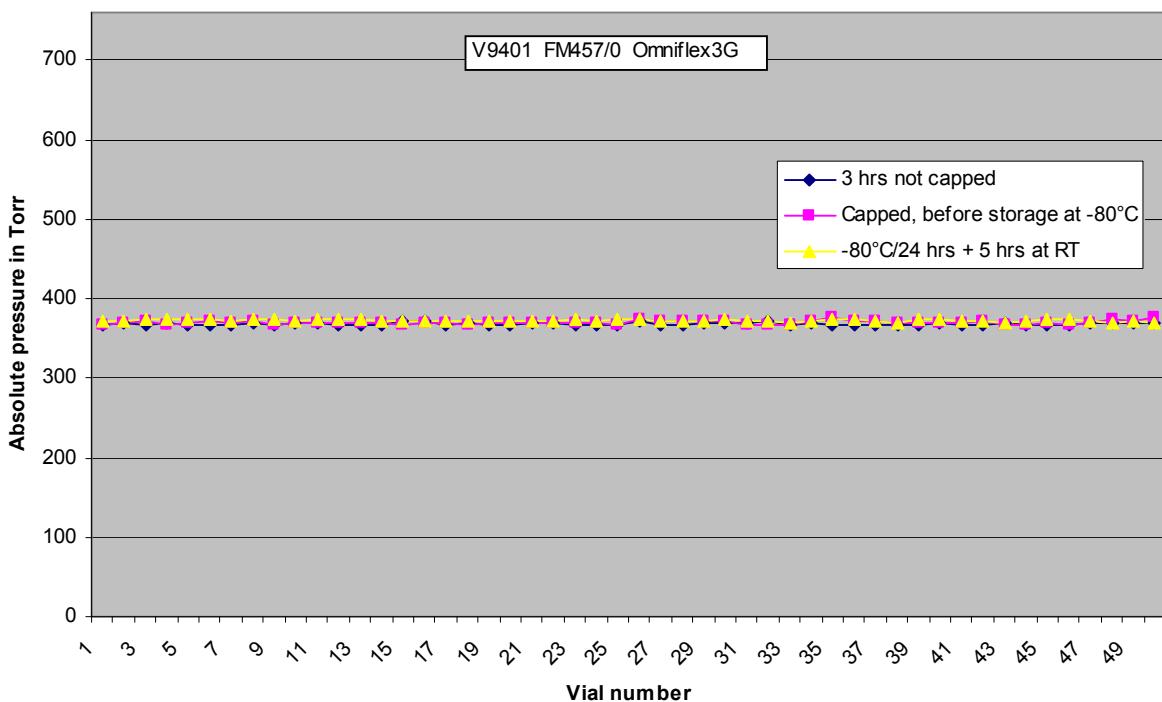


Supplier F vial BB 13 mm serum
100 mbara = +/- 76 Torr absolute pressure in vials

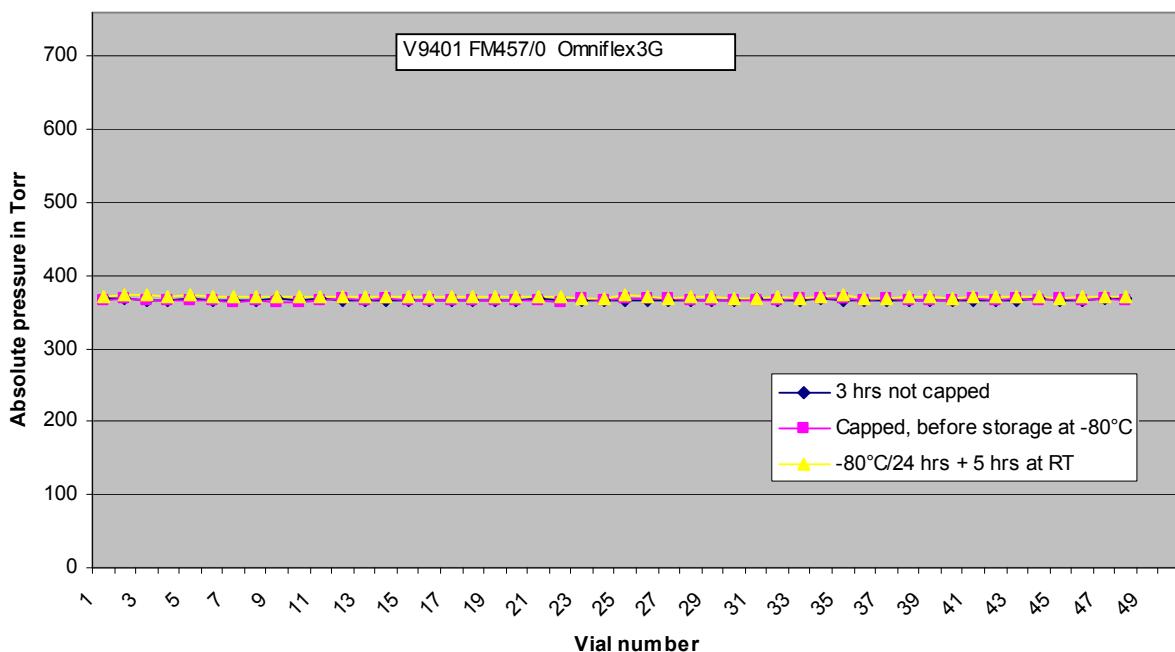


Partial vacuum

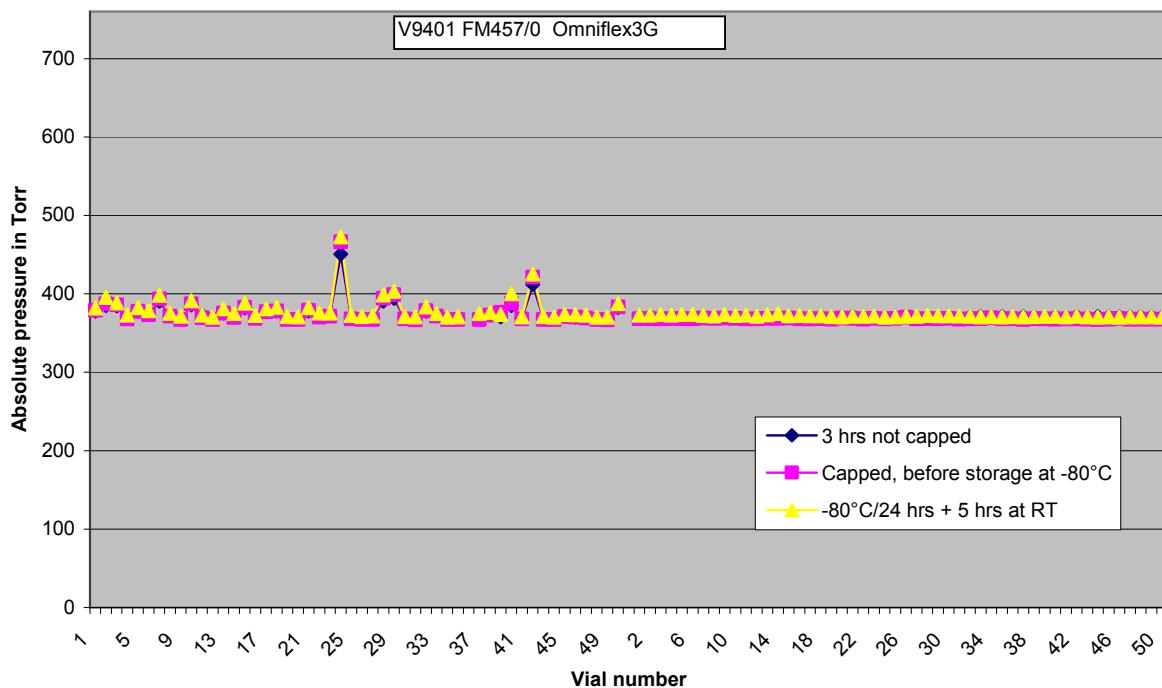
Supplier A Eur BB vial 13 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Supplier B vial US BB 13 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Supplier F vial BB 13 mm serum
500 mbara = +/- 380 Torr absolute pressure in vials



Conclusions:

The coated 13 mm serum closures from industrial mould V9401 are in line with the parts from the trial mould P8576A. Results obtained with stoppers manufactured from an industrial tool thus confirm the small scale results.

4. Pharmaceutical properties

4.1. Compatibility with different antibiotic powders

Antibiotic powders are known to be sensitive to contact with rubber closures. Upon dissolution of the drug with the drug diluent usually a certain level of turbidity develops. This in many cases can be attributed to long-term interaction between the rubber product and the drug.

With fluoropolymer coated closures turbidity levels in reconstituted solutions are lower and nearly independent of the contact time between the drug and the closure.

In this paragraph compatibility studies of Omniflex3G with 6 different antibiotic powders are reported.

Results are presented in comparison with results for non-coated FM457/0 closures. The latter are known already to lead to the lowest possible turbidity level for non-coated closures.

4.1.1. Test method

- Injection vials are filled with a specified amount of antibiotic powder, closed with steam sterilized and dried closures and secured with an alu cap.
- The vials are kept on storage in inverted position and under accelerated conditions of test.
- After 1, 2 and 3 months of storage the powder is reconstituted and the turbidity of the resulting solution is measured. Turbidity is expressed in NTU (Nephelos Turbidity Units).

4.1.2. Identification of rubber stoppers and antibiotic powders

Rubber stoppers

1. FM457/0 V9154 Omniflex3G
batches 628001, 638006 and 639001
2. FM457/0 V9154 non-coated, siliconized
batches 613353, 605412 and 505928

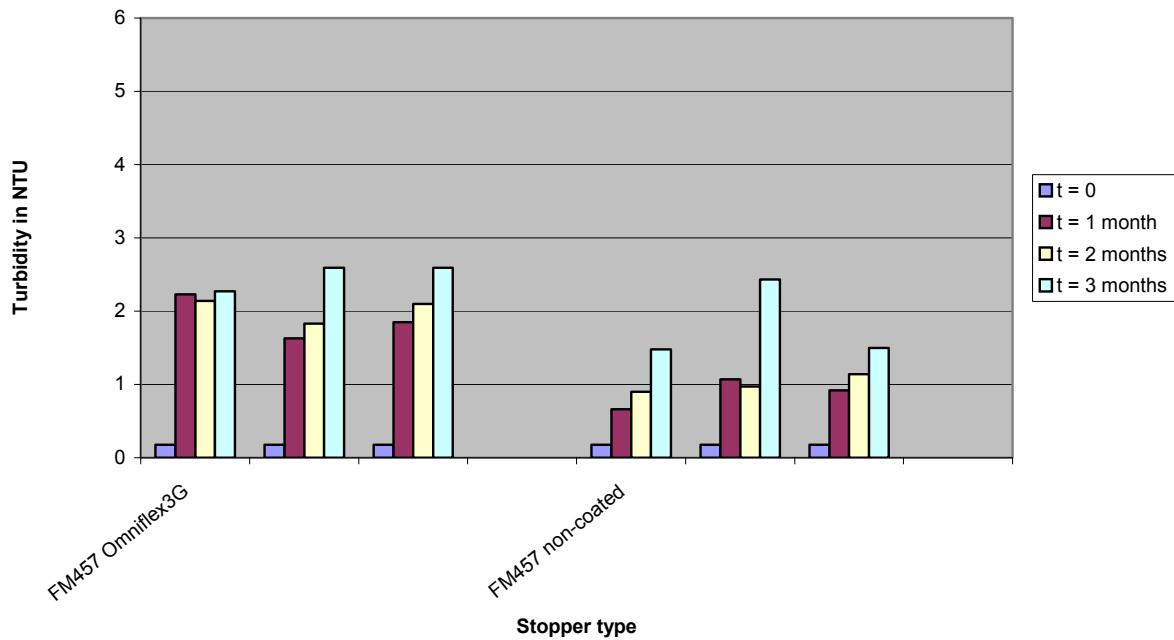
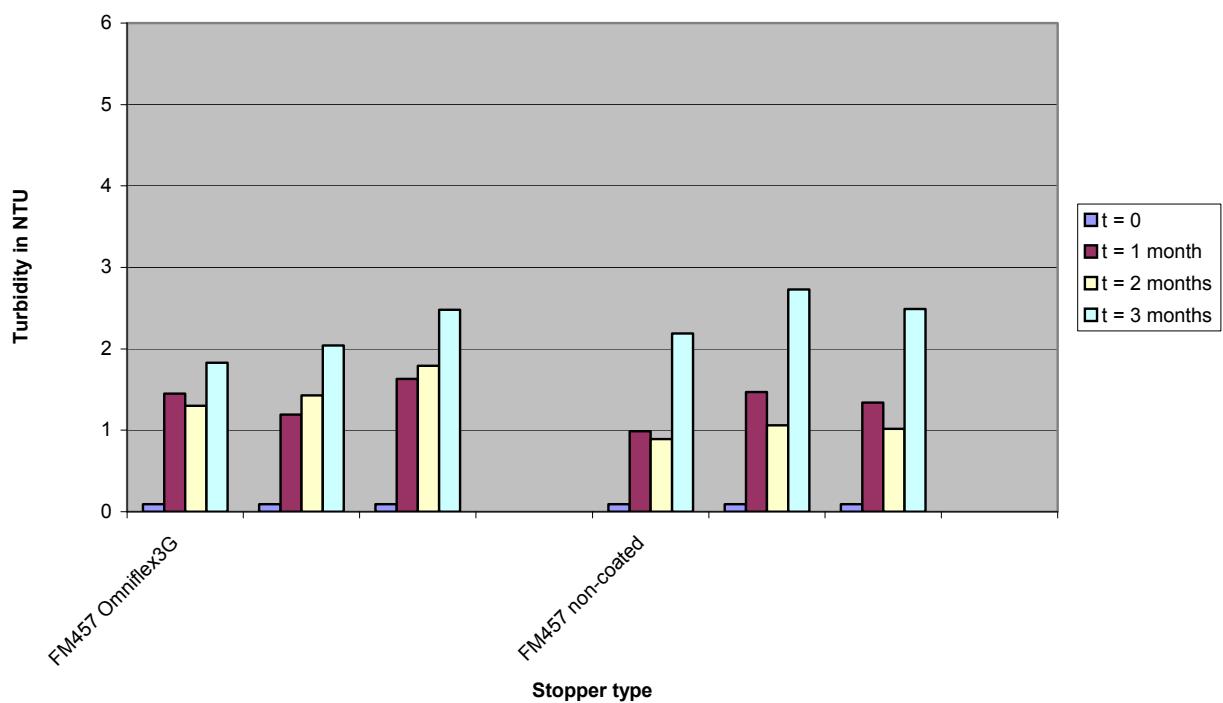
Antibiotic powders

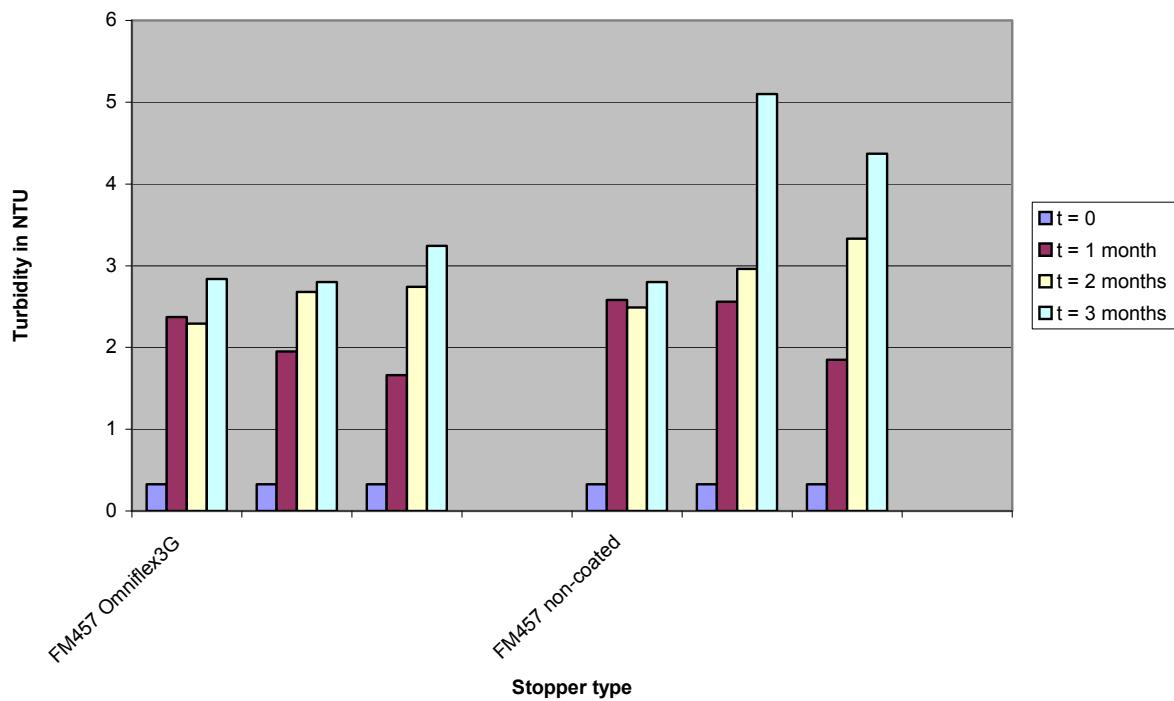
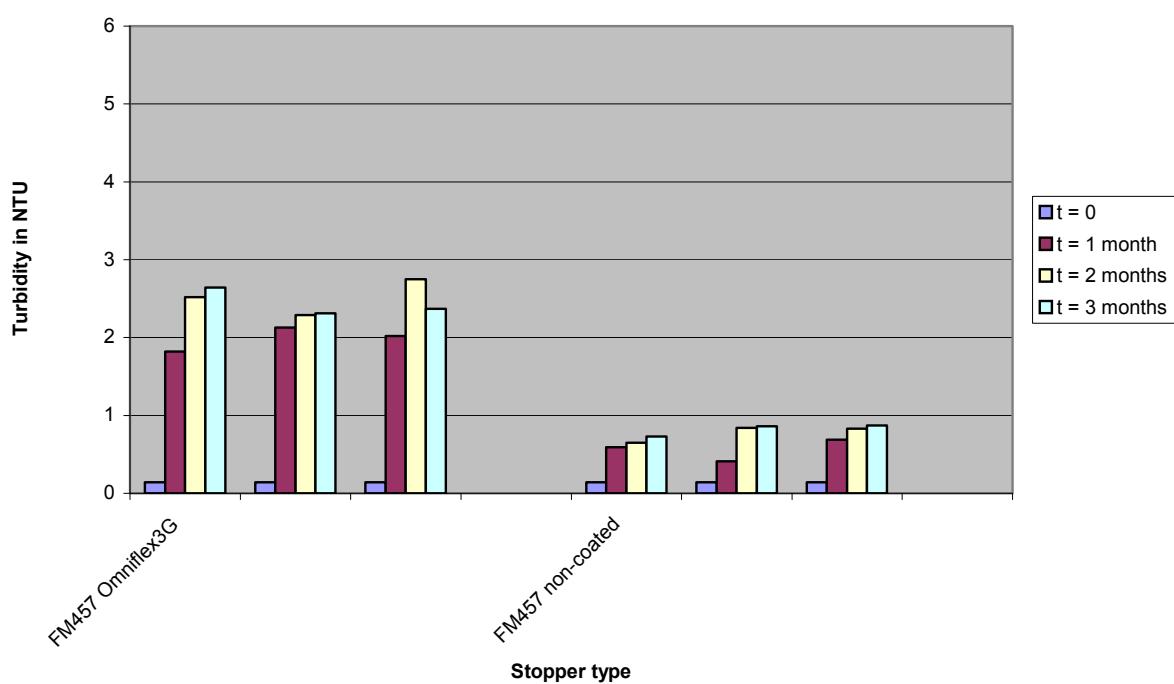
1. Cefuroxime sodium
2. Cefazolin sodium
3. Cefotaxim sodium
4. Ceftriaxon sodium
5. Amoxicillin sodium
6. Ampicillin sodium

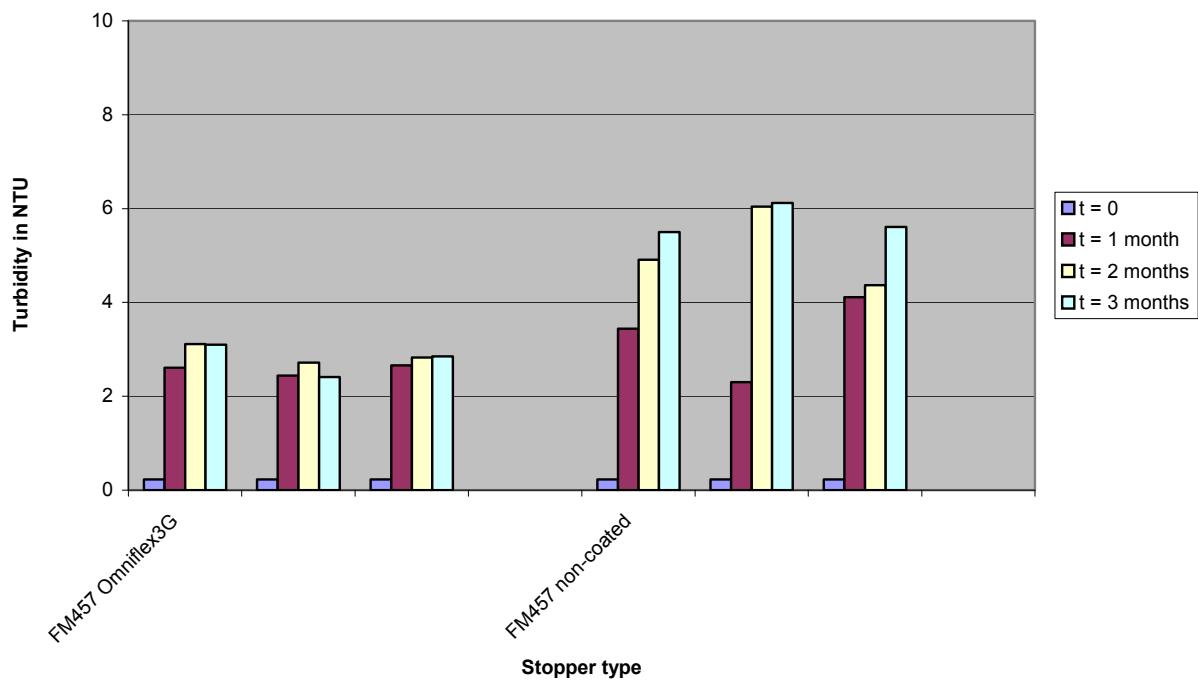
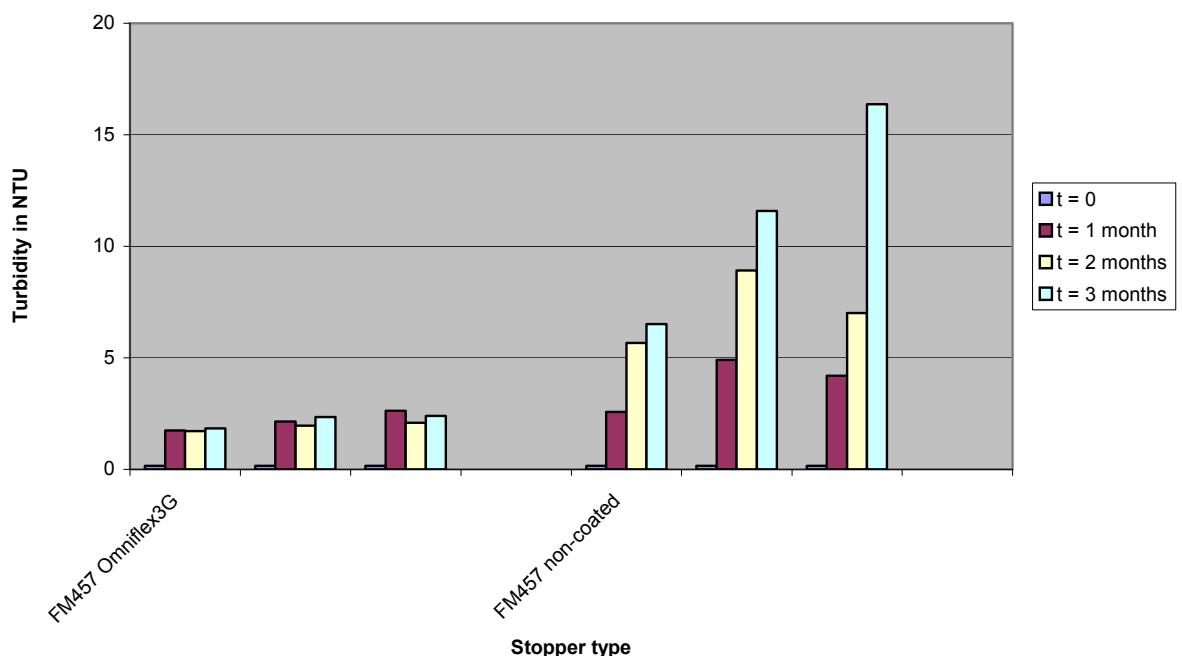
Origin and batch numbers of the antibiotic powders tested are on file.

Results

The results for each individual antibiotic powder are given in the following figures.
Each result gives the average value of 3 different vials.

Cefuroxime sodiumCefazoline sodium

Cefotaxim sodium*Ceftriaxon sodium*

Amoxycillin*Ampicillin*

4.1.3. Conclusion

All measured turbidity values of FM457/0 Omniflex3G are low (below 3 NTU). Turbidity at this level is measurable, however not visible to the naked eye.

4.2. Compatibility with oils

Mineral oil and vegetable oil in contact with uncoated halobutyl rubber are known to be absorbed. Absorption is a function of a.o. the type of oil and the type of rubber.

This paragraph reports the compatibility results of Omniflex3G in contact with mineral oil respectively vegetable oil.

The present FM457/0 non-coated has been tested as reference. Also plug (fluoropolymer) film coated stoppers have been tested.

4.2.1. Test method

- Vials are filled with a specified amount of oil, closed with sterilized and dried closures of which the weight is precisely known and capped with an aluminum cap.
- After storage of the vials in inverted position stoppers are removed from the vials. The compatibility of the closures is determined by determining their weight increase.

4.2.2. Identification of rubber stoppers and oils

Rubber stoppers

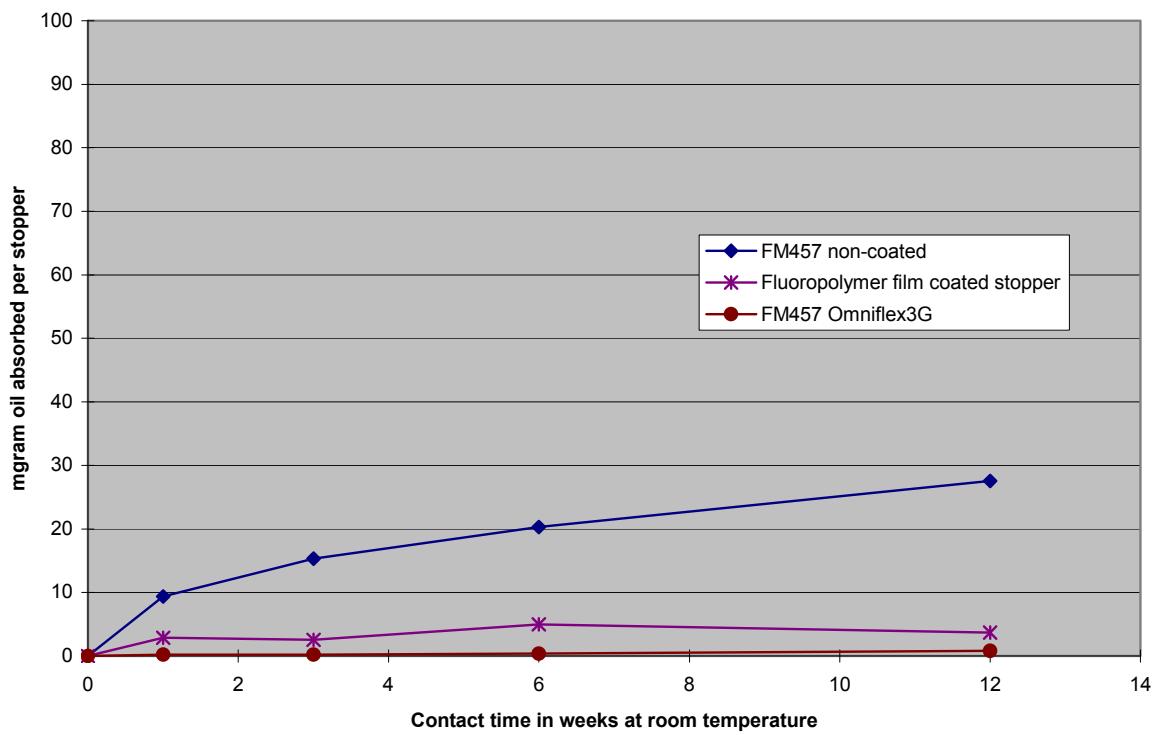
1. FM457/0 V9048 Omniflex3G, batch 707005
2. FM457/0 V9048 non-coated, batch 642903
3. plug (fluoropolymer) film coated stopper

Oils

1. Vegetable oil: arachidic oil lot A0229247
2. Mineral oil: Primol 352 lot GV130200101

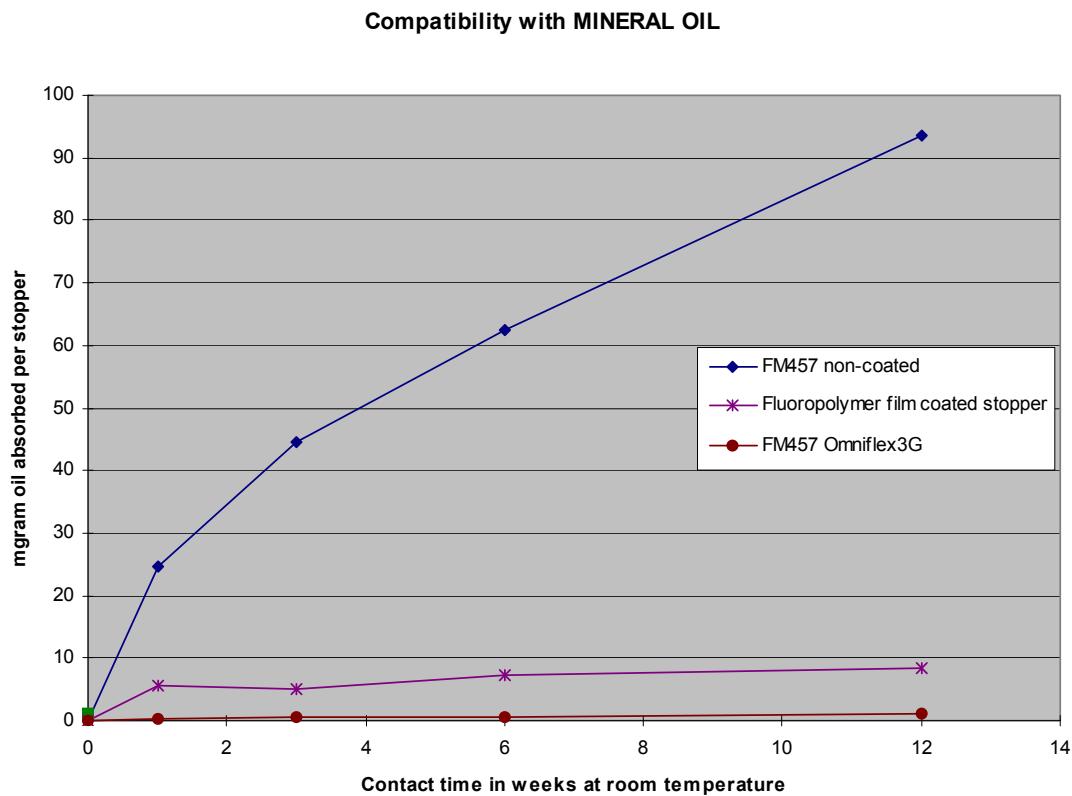
4.2.3. Results

The results for each individual oil are given in the following figures.
Each result represents the average value for 5 different vials that were measured.

Vegetable oil**Compatibility with VEGETABLE OIL**

(*) fluoropolymer film coating on major part of the plug only; no total coating as with Omniflex3G

Mineral oil



(*) fluoropolymer film coating on major part of the plug only; no total coating as with Omniflex3G.

4.2.4. Conclusion

FM457 Omniflex3G closures show considerably less swelling (measured as a weight increase) in contact with mineral oil and vegetable oil than uncoated FM457 closures.

Absorbance of mineral oil for Omniflex3G closures is less than for fluoropolymer film coated plugs. This is ascribed to the presence of a small ring of uncoated rubber on the plug part of the film coated stopper that is accessible to the mineral oil when the vial is in inverted position. The total coating on Omniflex3G precludes that this happens with this type of stoppers.

4.3. Compatibility with preservatives

Rubber closures have the tendency to absorb some drug formulation components, to a variable extent depending on their composition. If such preservatives are originally present in only small quantities, this absorption phenomenon might pose a problem.

In this paragraph, the absorption of 5 common preservatives is reported as measured over time in solutions in contact with FM457 Omniflex3G.
Also FM457/0 non-coated has been tested as reference.

4.3.1. Compatibility with parabens

Test method

- Vials are filled with a specified amount of an aqueous paraben solution at a known concentration (0.06 % w/v for methyl paraben, 0.012 % for propyl paraben).
- After stoppering with steam sterilized and dried closures and capping the vials are stored in inverted position.
- As a function of time the paraben concentration in the vials is followed up by UV spectrophotometry.

Identification of rubber stoppers and parabens

Rubber stoppers:

1. FM457/0 V9048 Omniflex3G, batch 707005
2. FM457/0 V9048 non-coated, batch 642903

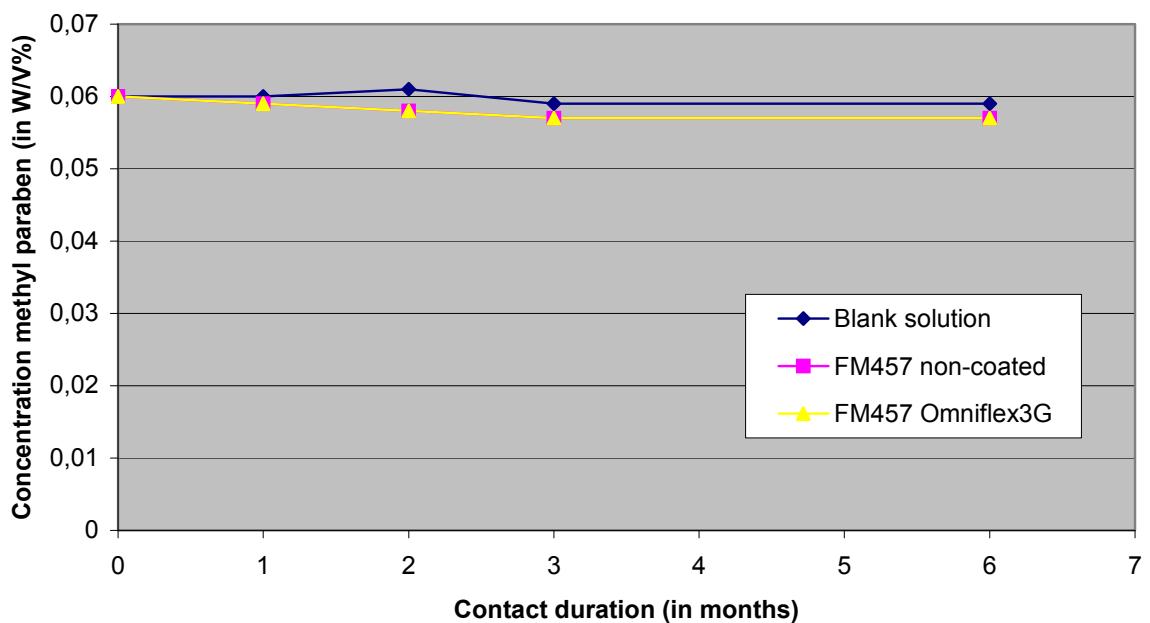
Parabens:

1. Methyl paraben (metargin) Acros Organics lot number A0230039
2. Propyl paraben (propagin) Acros Organics lot number A0237275

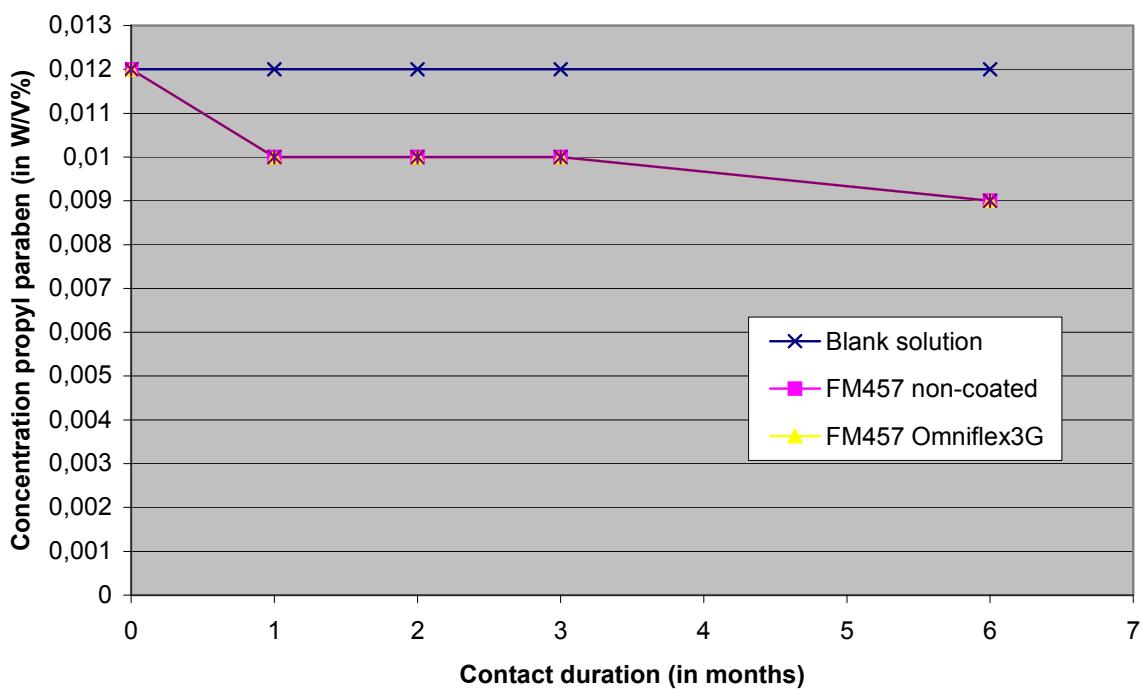
Results

The results for each individual paraben are given in the following figures.
Each result represents the average value for 5 different vials that were measured.

Follow up concentration of methyl paraben (0.06W/V%) after contact with different stoppers



Follow up concentration of propyl paraben (0.012W/V%) after contact with different stoppers



Conclusion

FM457/0 Omniflex3G displays an equal tendency to absorb methyl paraben respectively propyl paraben from a 0.06 respectively 0.012 W/V% aqueous solution in comparison with the current FM457/0 non coated. Absorption is low for both stopper types.

4.3.2. Compatibility with metacresol

Test method

- Vials are filled with a specified amount of an 0.3 % (w/v) aqueous metacresol solution.
- After stoppering with steam sterilized and dried closures and capping the vials are stored in inverted position.
- As a function of time the metacresol concentration in the vials is followed up by UV spectrophotometry.

Identification of rubber stoppers and metacresol

Rubber stoppers:

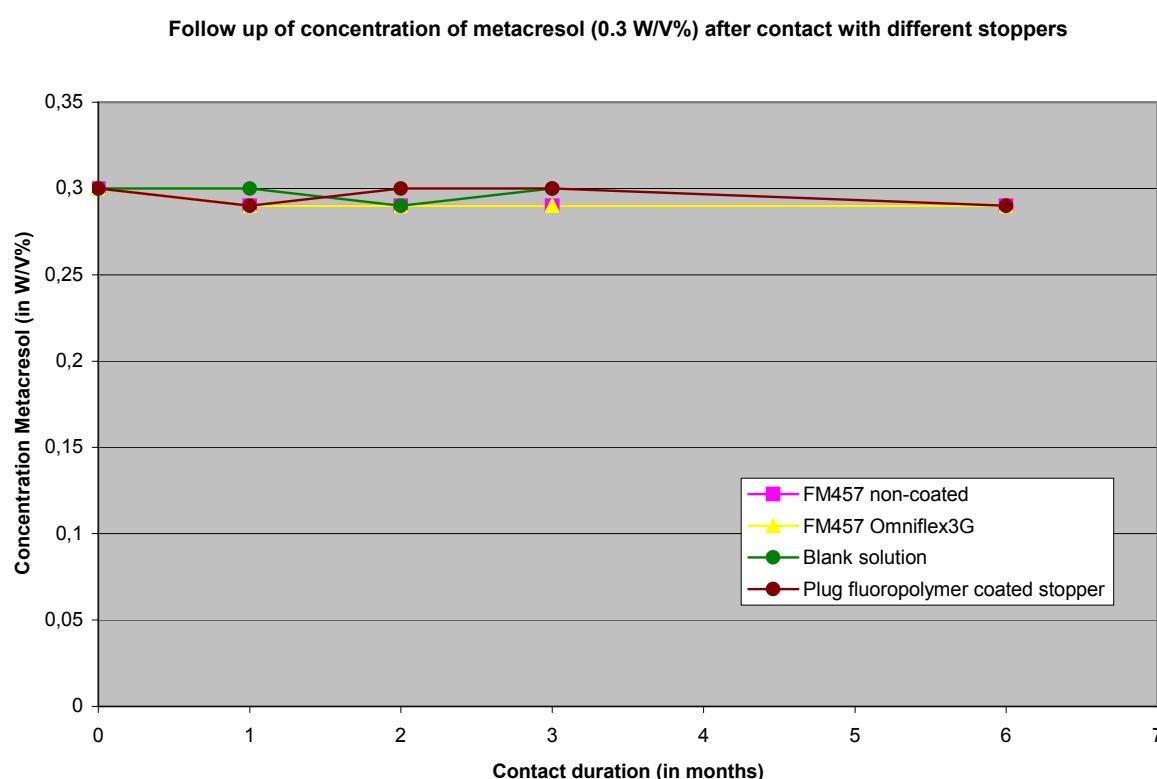
1. FM457/0 V9048 Omniflex3G, batch 707005
2. FM457/0 V9048 non-coated, batch 642903

Metacresol Acros Organics lot number A0221460

Results

The results for metacresol are given in the following figure.

Each result represents the average value for 5 different vials that were measured.



Conclusion

Omniflex3G does not show a tendency to absorb metacresol from a 0.3 W/V% aqueous solution.

4.3.3. Compatibility with benzyl alcohol

Test method

- Vials are filled with a specified amount of a 1 % (w/v) aqueous benzyl alcohol solution.
- After stoppering with steam sterilized and dried closures and capping the vials are stored in inverted position.
- As a function of time the benzyl alcohol concentration in the vials is followed up by UV spectrophotometry.

Identification of rubber stoppers and benzyl alcohol

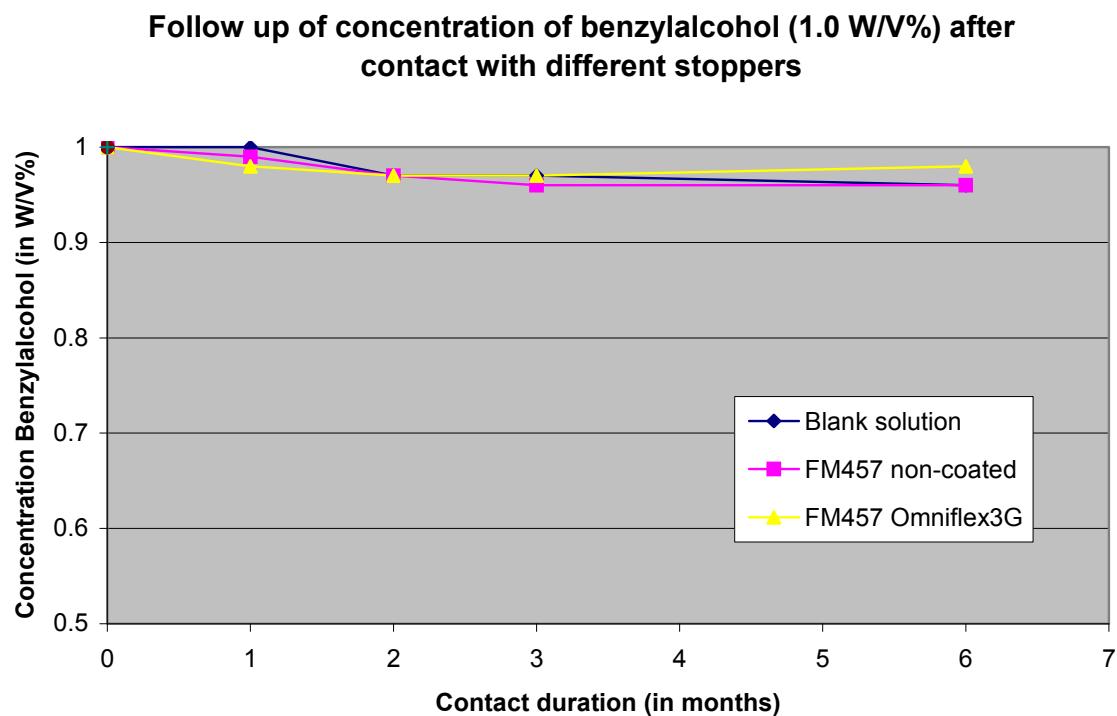
Rubber stoppers:

1. FM457/0 V9048 Omniflex3G, batch 707005
2. FM457/0 V9048 non-coated, batch 642903

Benzyl alcohol VWR lot number 03L120022

Results

The results for benzyl alcohol are given in the following figure.
Each result represents the average value for 5 different vials that were measured.



Conclusion

Omniflex3G does not show a tendency to absorb benzylalcohol from a 1.0 W/V% aqueous solution.

4.3.4. Compatibility with benzalkonium chloride

Test method

- Vials are filled with a specified amount of a 0.01 % (w/v) aqueous benzalkonium chloride solution.
- After stoppering with steam sterilized and dried closures and capping the vials are stored in inverted position.
- As a function of time the benzalkonium chloride concentration in the vials is followed up by UV spectrophotometry.

Identification of rubber stoppers and benzalkonium chloride

Rubber stoppers:

1. FM457/0 V9048 Omniflex3G batch 707005
2. FM457/0 V9048 non-coated batch 642903

Benzalkonium chloride VWR lotnumber 07D060018

Results

The results for benzalkoniumchloride are given in the following table.
Each result represents the average value for 5 different vials that were measured.

%W/V benzalkoniumchloride	At start	1 month	2 months	3 months	6 months
Blank solution	0.010	0.010	0.010	0.010	0.009
FM457 non-coated	0.010	0.010	0.010	0.010	0.009
FM457 Omniflex3G	0.010	0.010	0.010	0.010	0.009

Conclusion

FM457 Omniflex3G does not show any tendency to absorb benzalkonium chloride from a 0.010 W/V% aqueous solution.

5. Particulate cleanliness

The level of subvisible and visible particles on Omniflex3G coated closures was measured for 3 production batches of 20mm 2-leg lyo Omniflex3G. The particulate cleanliness was determined using the method described in ISO 8871-3.

5.1. Subvisible particulate cleanliness

Test method

Datwyler procedure QA-021 "Determination of subvisible particle count" was followed. This group procedure is based on ISO 8871-3.

Results

The table below shows the subvisible particulate cleanliness results for the different product designs in FM457/0 Omniflex3G. The reported value is the average of a certain number of batches.

	# subvisible particles per 10 cm ² rubber surface area		
	2-5µ	5-10µ	10-25µ
FM457/0 V9396 Omniflex3G 8 production batches	308	62	5
FM457/0 V9397 Omniflex3G 8 production batches	272	55	4
FM457/0 V9402 Omniflex3G 2 production batches	238	72	6
FM457/0 V9401 Omniflex3G 4 production batches	298	72	9

Typical subvisible counts for non-coated closures in three different rubber compounds are given as reference in the underneath table.

	# subvisible particles per 10 cm ² rubber surface area		
	2-5µ	5-10µ	10-25µ
FM140 20 mm lyo siliconized ISAF1 101 production batches	1350	340	40
FM157 13 mm serum siliconized ISAF1 112 production batches	1850	470	51
FM257 13 mm lyo siliconized ISAF1 118 production batches	1400	380	42

Conclusion

Subvisible particulate cleanliness for FM457/0 Omniflex3G stoppers is better than other non-coated rubber compounds.

5.2. Visible particulate cleanliness

Test method

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

Results

The table below shows the subvisible particulate cleanliness results for the different product designs in FM457/0 Omniflex3G. The reported value is the average of a certain number of batches.

	# visible particles per 10 cm ² rubber surface area		
	25-50µ	50-100µ	>100µ
FM457/0 V9396 Omniflex3G 8 production batches	2.7	0.9	0.3
FM457/0 V9397 Omniflex3G 8 production batches	2.2	1.0	0.3
FM457/0 V9402 Omniflex3G 2 production batches	2.3	1.7	0.4
FM457/0 V9401 Omniflex3G 4 production batches	2.8	1.9	0.5

Typical subvisible counts for non-coated closures in three different rubber compounds are given as reference in the underneath table.

	# visible particles per 10 cm ² rubber surface area		
	25-50µ	50-100µ	>100µ
FM140 20 mm lyo siliconized ISAF1 101 production batches	12.0	7.5	1.9
FM157 13 mm serum siliconized ISAF1 112 production batches	22	10.5	2.6
FM257 13 mm lyo siliconized ISAF1 118 production batches	9.0	6.0	2.2

Conclusion

Visible particulate cleanliness FM457/0 Omniflex3G stoppers is better than other non-coated rubber compounds.

6. Application tests

6.1. Steam sterilization resistance

6.1.1. Standard lab autoclave test

Test method

100 Omniflex3G 20mm lyo closures are loaded in a glass beaker with internal diameter 75mm.

The closures are rinsed 3 times with distilled water at room temperature and subsequently autoclaved at 121°C for 30 minutes.

The beaker with the autoclaved closures is stored for 24 hours at room temperature whereby the closures are kept immobile. After this time the beaker is inverted and the closures are dumped on a flat surface.

The number of closures sticking together is recorded.

Identification of rubber closures

The test was done on various designs and various batches.

Results

The autoclaved Omniflex3G closures were found not to stick together.

6.1.2. Autoclave test in Steam Sterilizable bags

Test method

6 medium size steam sterilizable bags are filled with 1800 FM457/0 V9154 Omniflex3G closures.

These 6 filled bags are subjected to an autoclave cycle at 121°C during 1 hour followed by 90 minutes vacuum drying.

Thereafter, 5 bags are stacked 5-high to cool to room temperature, outside the autoclave. 1 bag is left separate and is cooled down to room temperature outside the autoclave in this condition.

The closures are transferred to a hopper and are checked for twinning and sticking which prohibits passage through the hopper.

Identification of rubber closures

The test was done on various designs and various batches.

Results

FM457/0 Omniflex3G 20mm lyo closures were found not to stick together. The number of sticking products in the hopper was < 0.1%.

6.2. Closure insertion force

In this test, the force required to insert an Omniflex3G closure in a vial is measured.
This test has been performed for :

- the new 20mm 2-leg design : P8345B
- the new 20mm igloo design: P8506M

(both in Omniflex3G coated version).

FM457/0 V9154 and V9172 non-coated siliconized closures were tested in comparison.

Closure insertion force is not only influenced by the rubber closure (compound hardness, product design, surface treatment) but also by the vial type (design of vial neck).

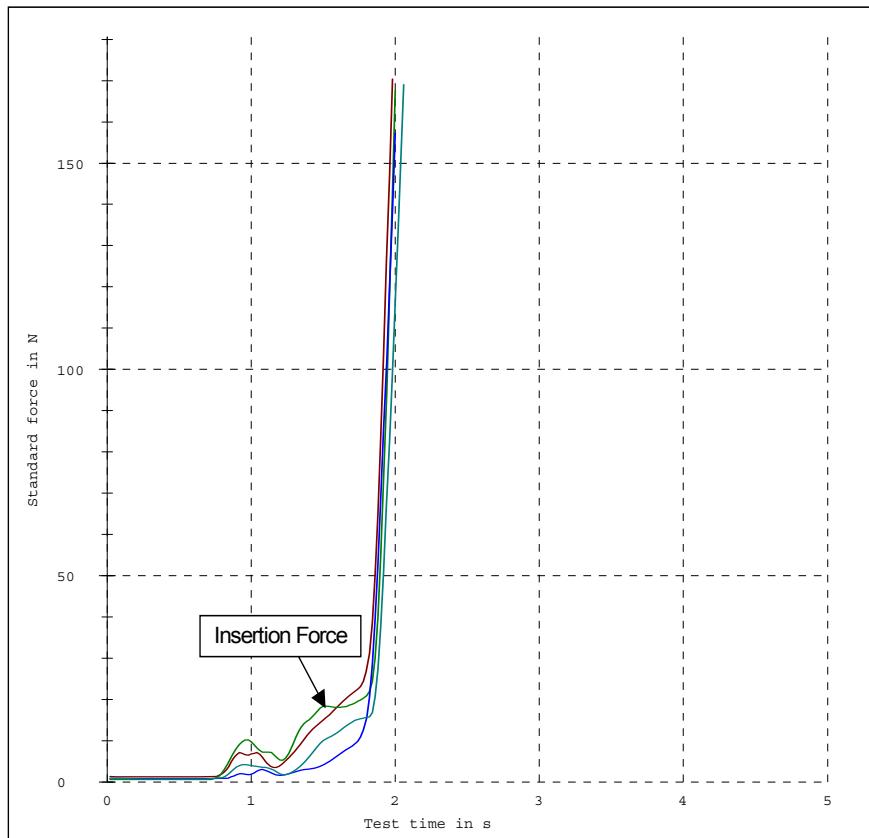
Different vial types have been used for this closure insertion force testing.

In two test series also fluoropolymer film coated stoppers were tested as reference.

6.2.1. Test description

Test method

- A glass vial (one single vial for the entire test) with a well known diameter is used.
- Before putting on every individual stopper the vial neck each time is degreased.
- Closures are steam sterilized and dried.
- The closure is put on the vial and the insertion force is measured with a tensile bench.



Identification of rubber closures and vials

Identification of vials:

1. Supplier C moulded vial
2. Supplier A tubular vial with European blow back
3. Supplier A tubular vial with US blow back
4. Supplier D tubular vial without blow back

Identification of stoppers:

20mm lyo 2-leg:

1. V9154 FM457/0 siliconized, batch 522959
2. P8345B FM457/0 Omniplex3G, batch 707004
3. plug (fluoropolymer) film coated stopper

20mm lyo igloo:

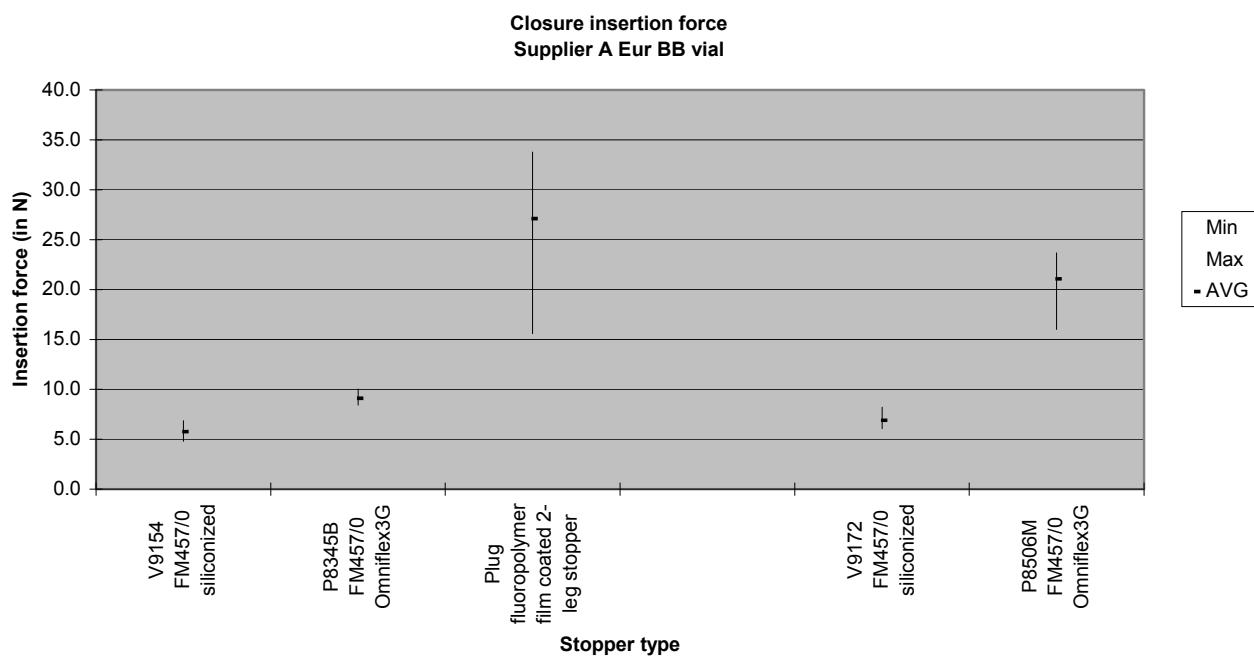
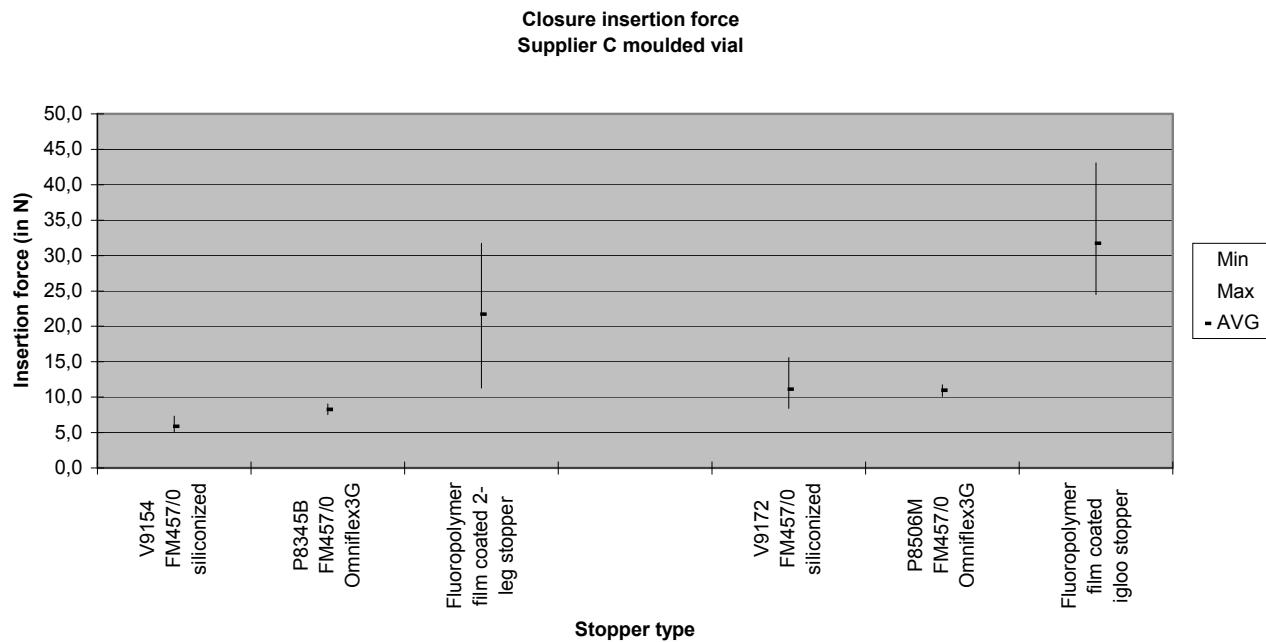
1. V9172 FM457/0 SAF1 (siliconized) batch 505929
2. P8506M Omniplex3G batch 707003
3. plug (fluoropolymer) film coated stopper

6.2.2. Results

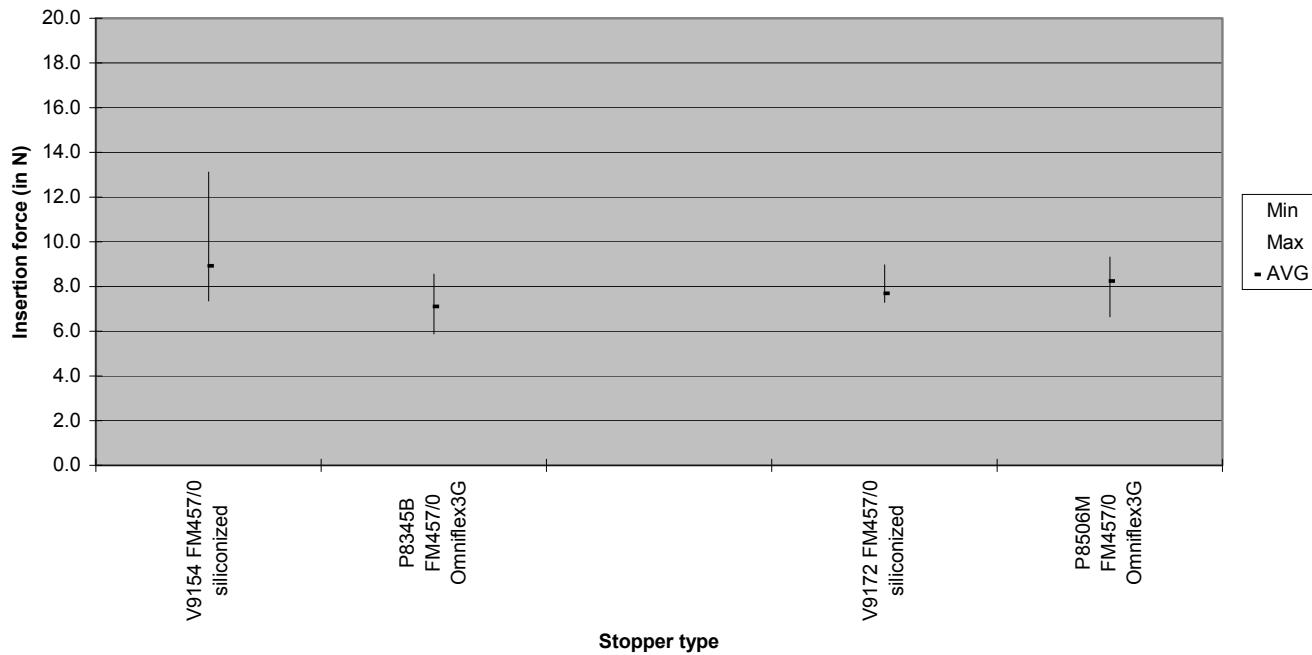
Results are given in the figures and tables below.

6.2.3. Conclusions

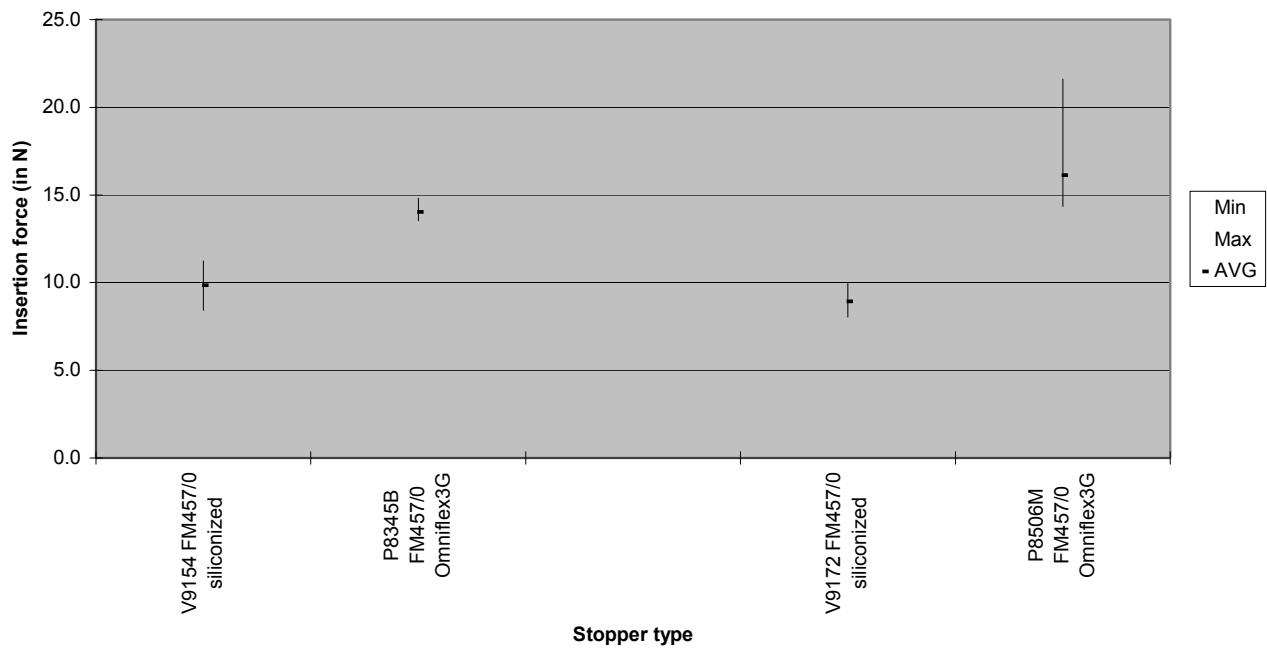
Insertion forces for FM457/0 Omniplex3G and for FM457/0 siliconized closures are in the same order of magnitude.



**Closure insertion force
Supplier A vial US BB**



**Closure insertion force
Supplier D vial without BB**



7. Regulatory status

Omniflex3G is recorded in Datwyler's US FDA Drug Master File and in Datwyler's file with the Canadian Health Protection Branch.

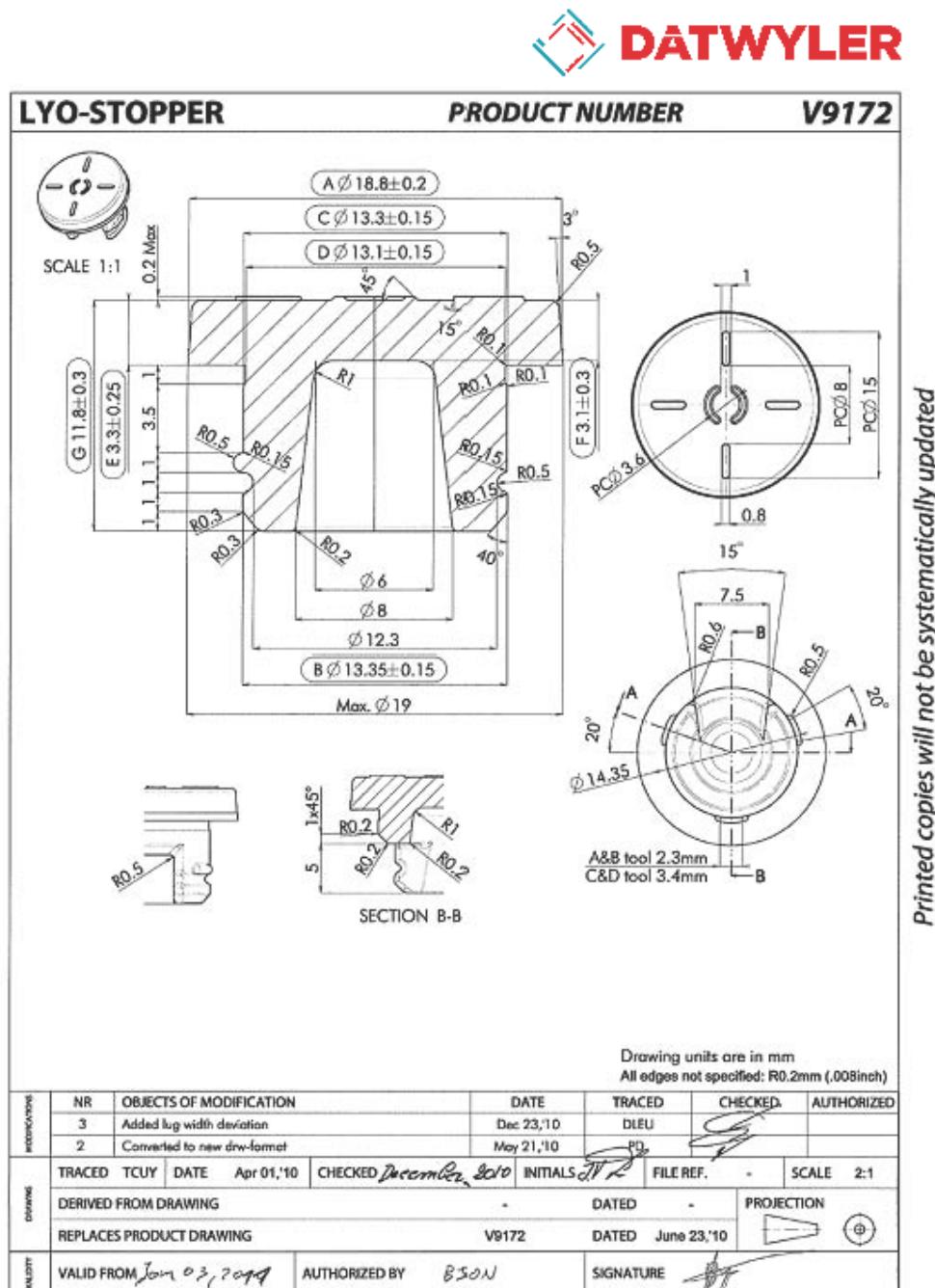
On customer request Letters of Authorization can be addressed to FDA or the Canadian HPB. Your Datwyler Sales or Technical Support representative will be glad to give you support in this.

8. History

<i>Edition (Issue Date)</i>	<i>Change (chapter + change)</i>	<i>Comment (Rationale)</i>
2 (October 23, 2008)		
3 (February 28, 2011)	<ul style="list-style-type: none"> • Omitted paragraph on particulate cleanliness and surface silicone in introductory section 'Omniflex3G – Description' • Added 'History' section to document 	<ul style="list-style-type: none"> • Too little supportive evidence • Update to current format of CS document
4 (April 28, 2011)	<ul style="list-style-type: none"> • Updated with new drawings of V9172, V9397, V9154, V9396, V9402, HPP079, V9048, V9407 and V9401 in attachment 1 • Updated with new Compound Data Sheet FM457 in attachment 2 	<ul style="list-style-type: none"> • New drawings of V9172, V9397, V9154, V9396, V9402, HPP079, V9048, V9407 and V9401 available • New Compound Data Sheet of FM457 available

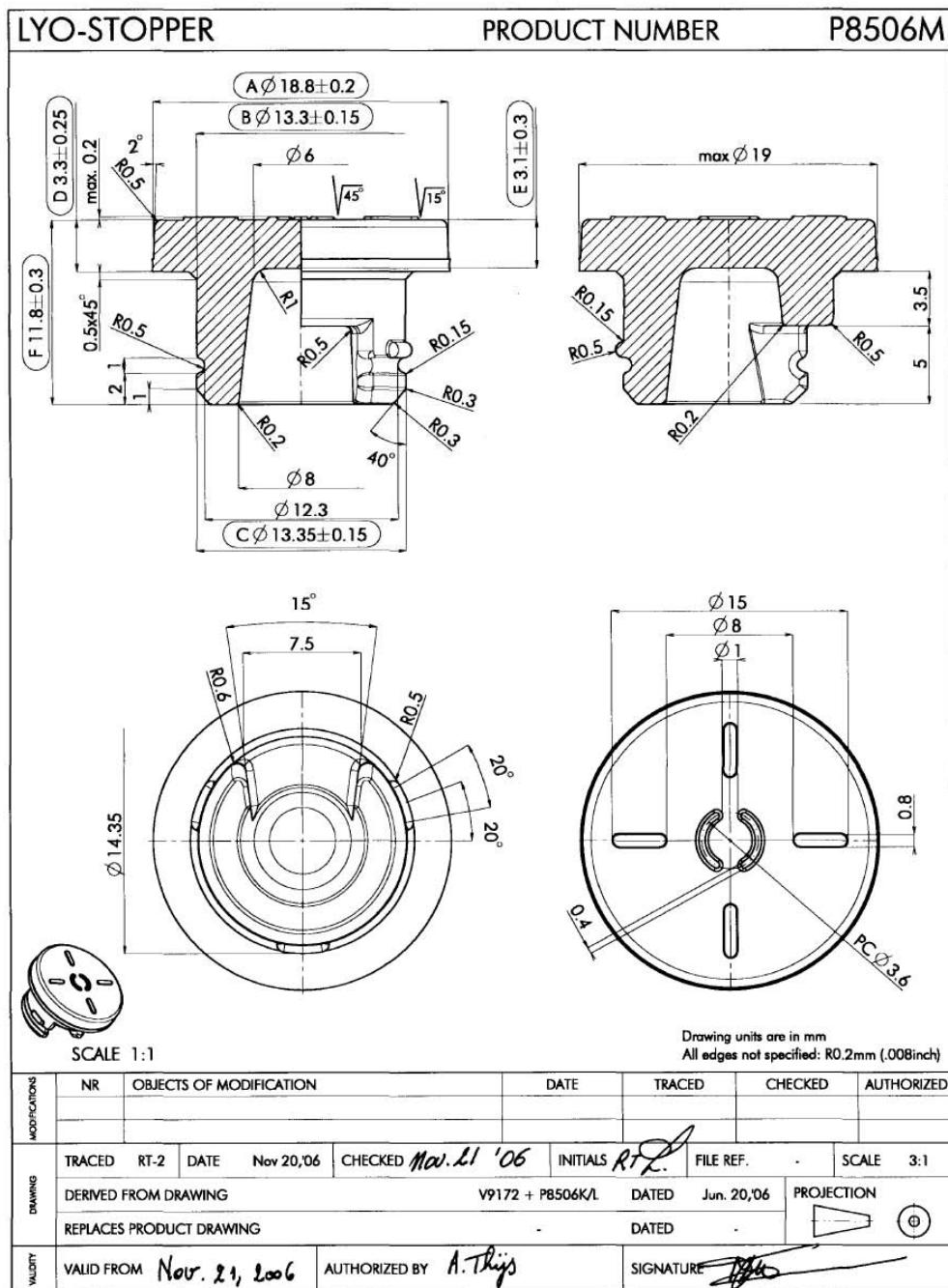
Attachment 1: Product drawings

- 20 mm lyo igloo - Current design : V9172



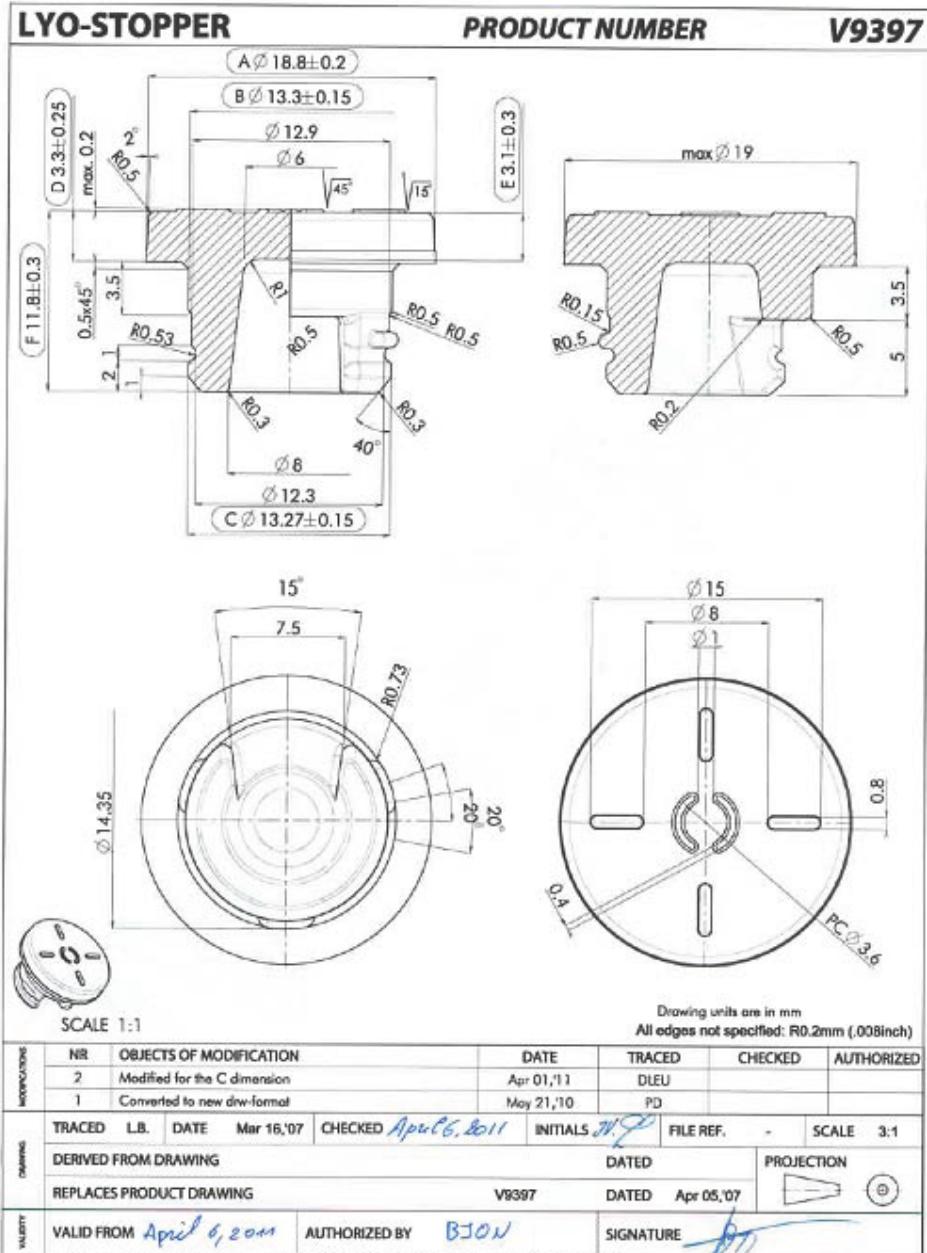
Printed copies will not be systematically updated

- 20 mm lyo igloo - sample mould design : P8506M



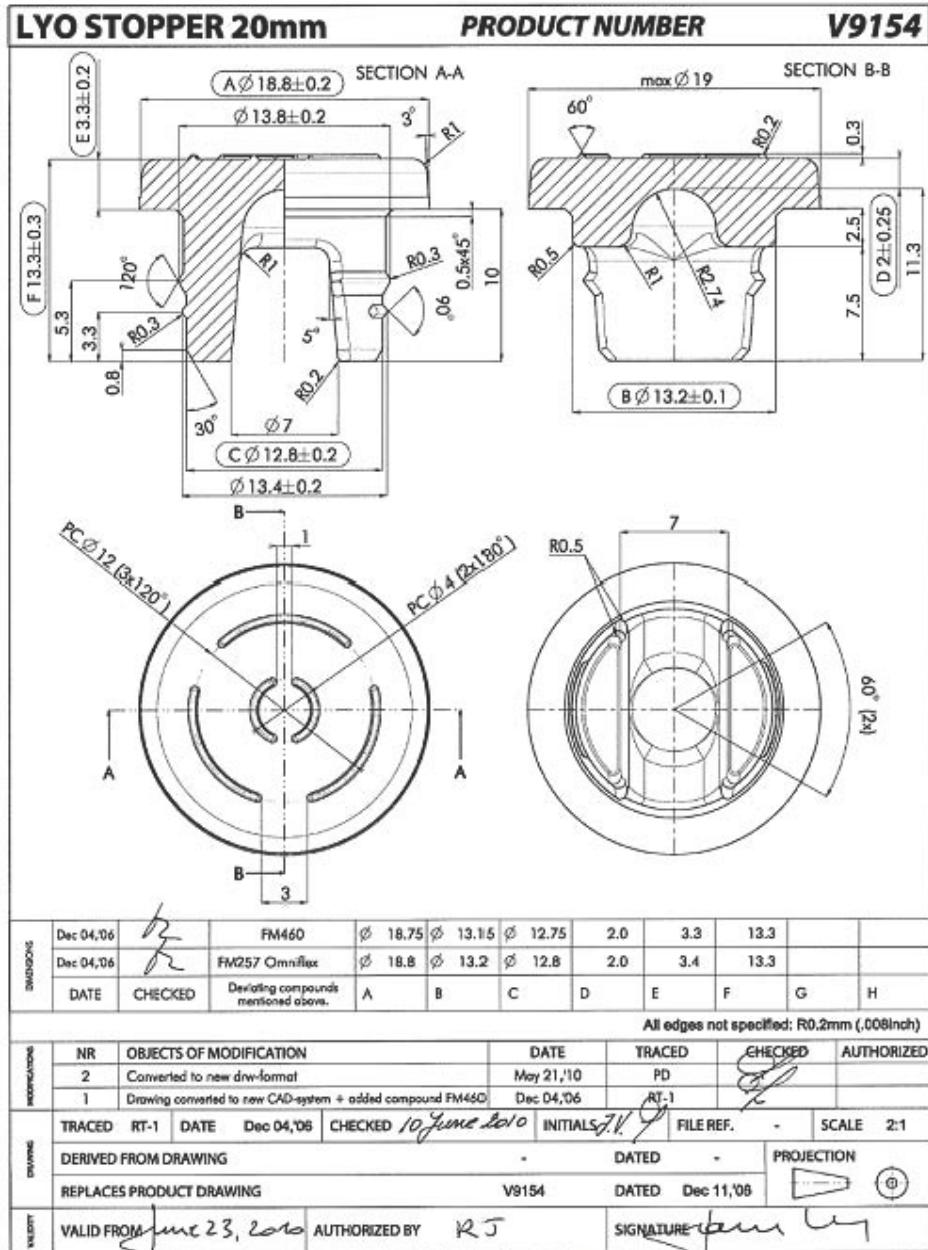
Printed copies will not be systematically updated

- 20 mm igloo – new design - industrial mould : V9397



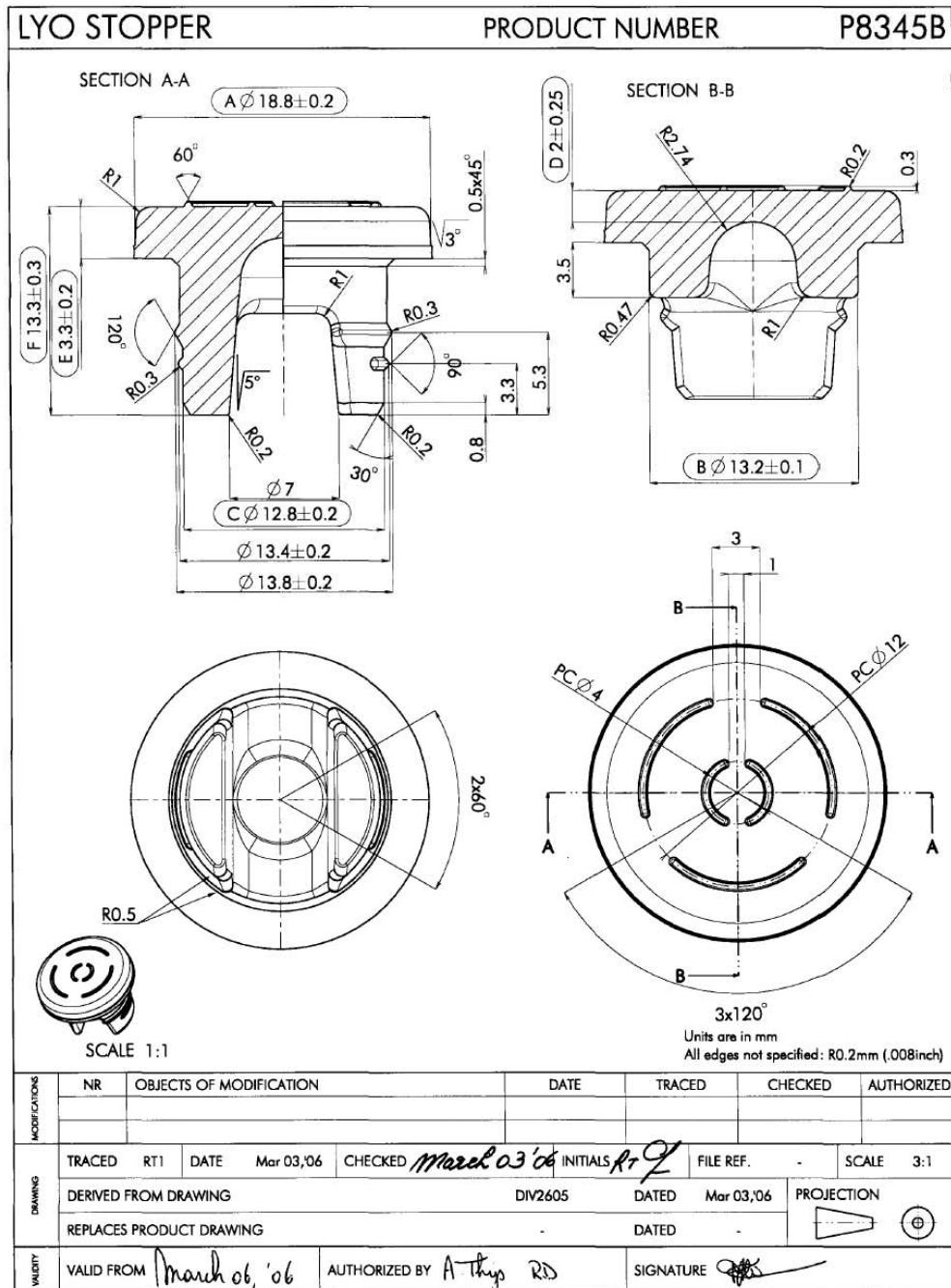
Printed copies will not be systematically updated

- 20 mm lyo 2-leg - Current design: V9154



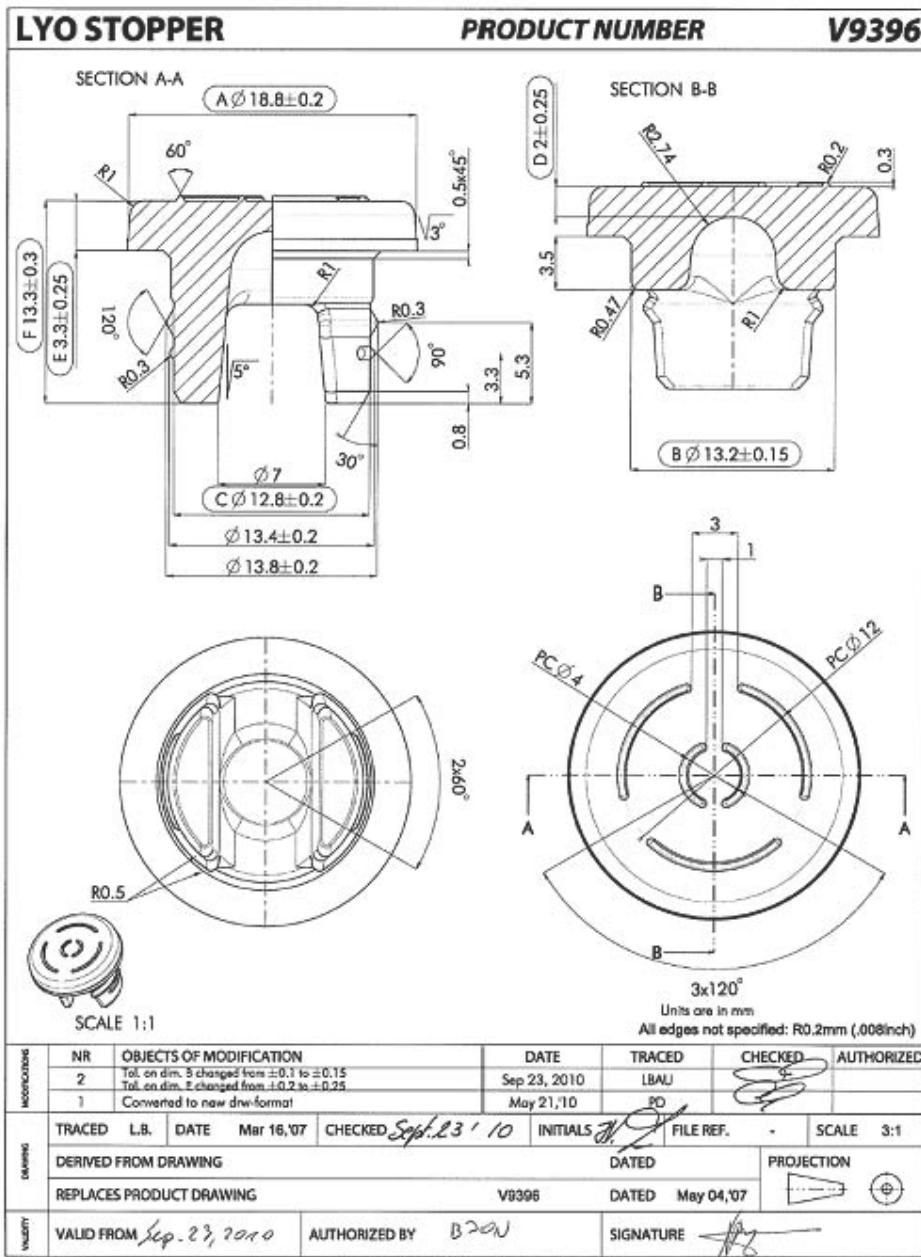
Printed copies will not be systematically updated

- 20 mm lyo 2-leg - sample mould design P8345B



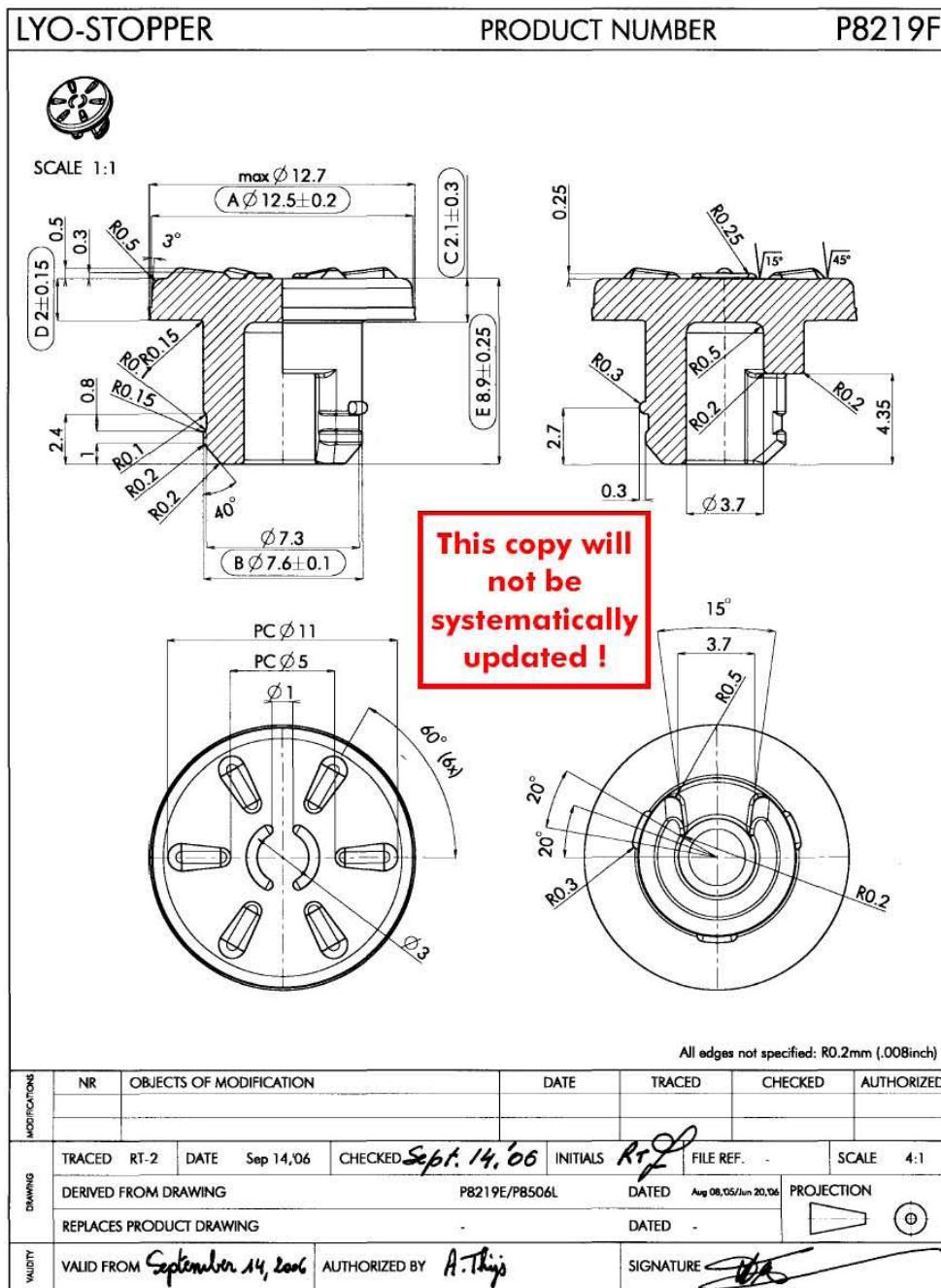
Printed copies will not be systematically updated

- 20 mm lyo 2-leg – new design - industrial mould V9396

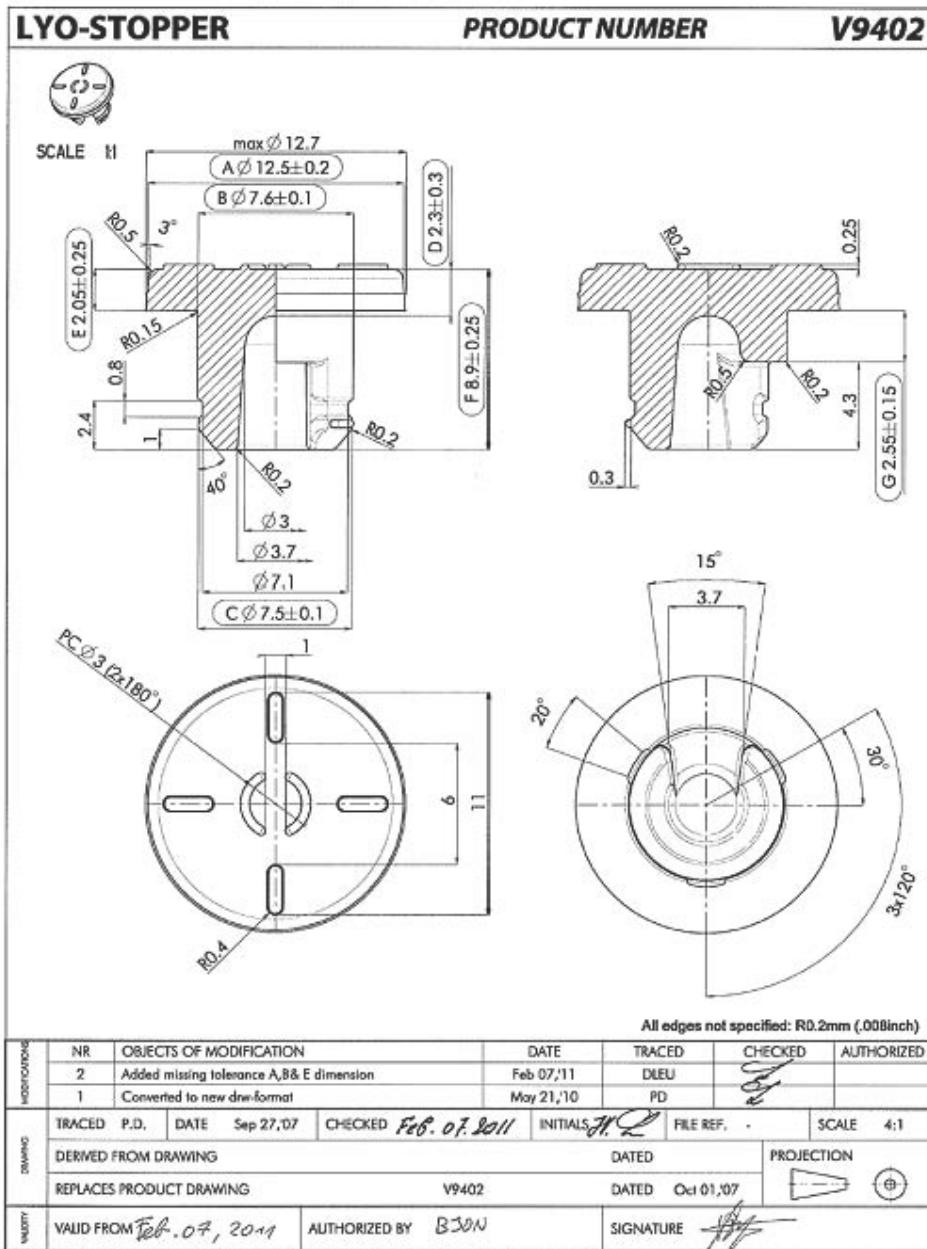


Printed copies will not be systematically updated

- 13mm lyo igloo - sample mould design P8219F

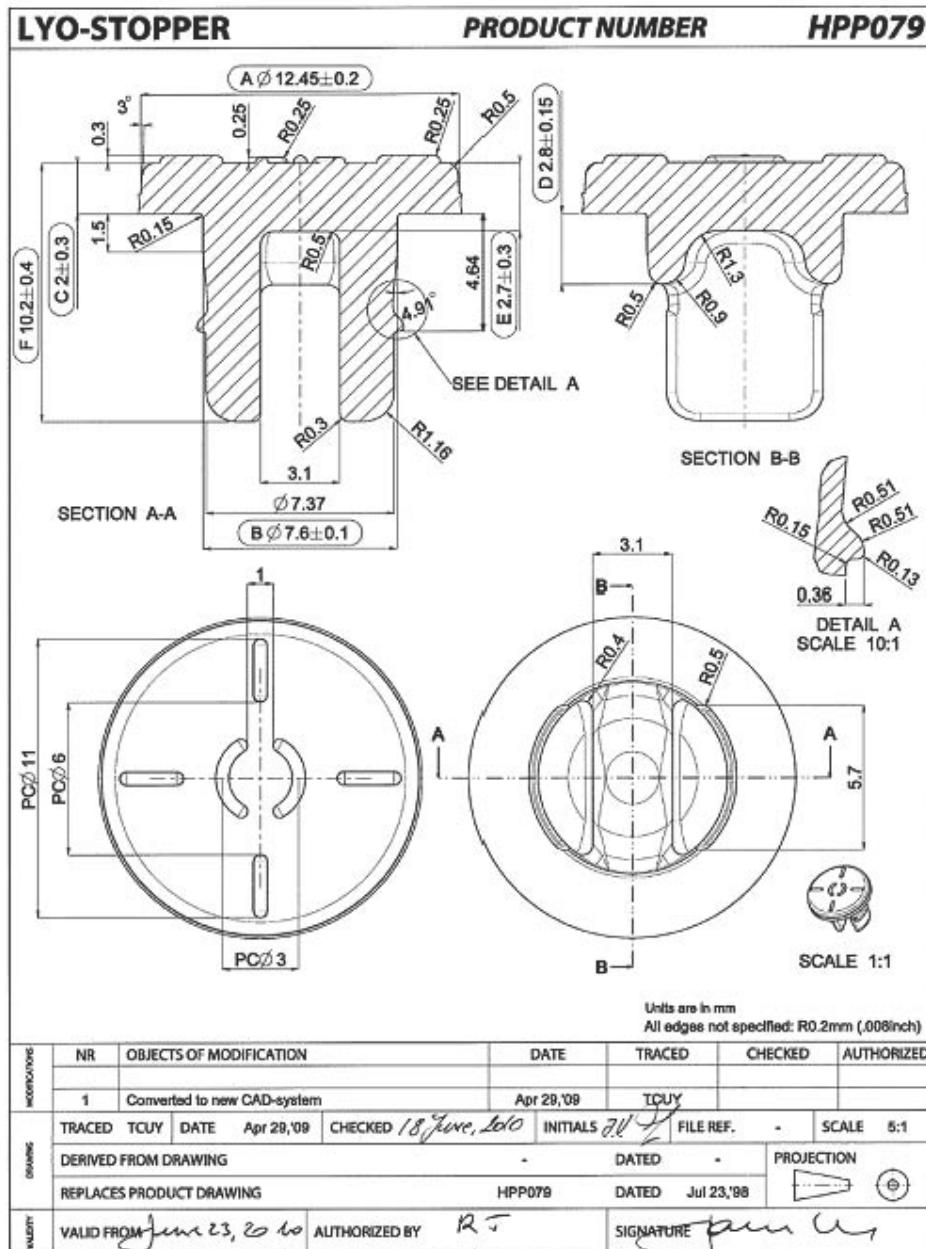


- 13 mm lyo igloo – new design - industrial mould V9402



Printed copies will not be systematically updated

- 13 mm lyo 2-leg: HPP079 (industrial mould)



Printed copies will not be systematically updated

20 mm serum – Current design : V9048

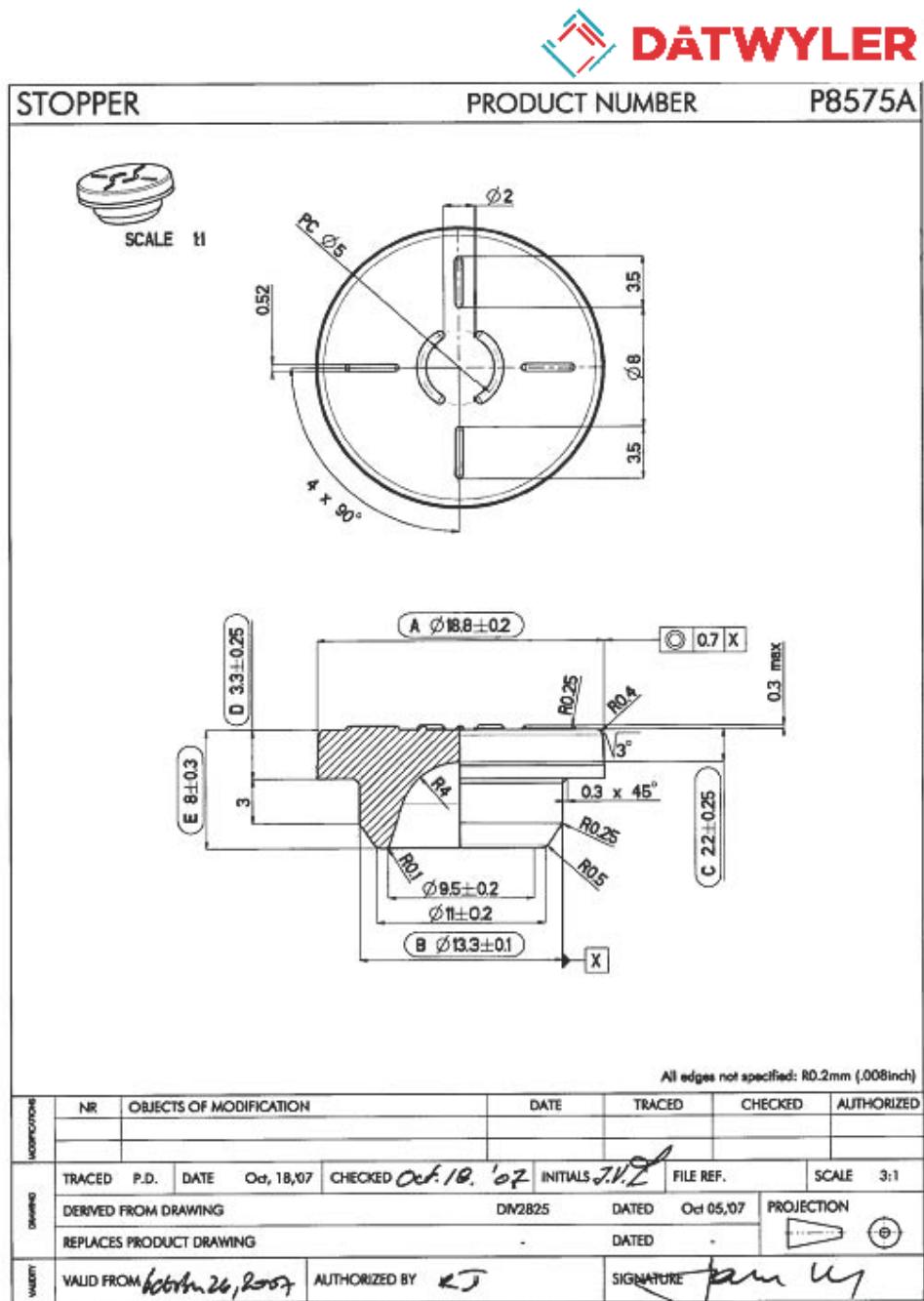


STOPPER		PRODUCT NUMBER		V9048																																																					
SCALE 1:1																																																									
<table border="1"> <thead> <tr> <th>DATE</th> <th>CHECKED</th> <th colspan="6">All compounds except above mentioned</th> </tr> <tr> <th>A</th> <th>B</th> <th>C</th> <th>D</th> <th>E</th> <th>F</th> <th>G</th> <th>H</th> </tr> </thead> <tbody> <tr> <td>May 07, '96</td> <td><i>✓</i></td> <td>FM240</td> <td>Ø 18.7</td> <td>Ø 13.15</td> <td>Ø 13.0</td> <td>2.2</td> <td>3.3</td> <td>8.0</td> </tr> <tr> <td></td> <td></td> <td></td> <td>±0.2</td> <td>±0.1</td> <td>±0.1</td> <td>±0.25</td> <td>±0.25</td> <td>±0.3</td> </tr> <tr> <td>Nov 10, '06</td> <td><i>✓</i></td> <td>FM259OmniflexPlus</td> <td>Ø 18.7</td> <td>Ø 13.15</td> <td>Ø 12.95</td> <td>2.2</td> <td>3.3</td> <td>8.0</td> </tr> <tr> <td></td> <td></td> <td></td> <td>±0.2</td> <td>±0.15</td> <td>±0.15</td> <td>±0.25</td> <td>±0.25</td> <td>±0.3</td> </tr> </tbody> </table>						DATE	CHECKED	All compounds except above mentioned						A	B	C	D	E	F	G	H	May 07, '96	<i>✓</i>	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	<i>✓</i>	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																																																							
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May 07, '96	<i>✓</i>	FM240	Ø 18.7	Ø 13.15	Ø 13.0	2.2	3.3	8.0																																																	
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Nov 10, '06	<i>✓</i>	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																																																	
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	<i>[Signature]</i>																																																		
	3	Converted to new dwg-format			May 21, '10	PD																																																			
DRAWING	TRACED	KV-2	DATE	Oct 30, '03	CHECKED <i>JK, Nov, 2010</i>	INITIALS <i>JV</i>	FILE REF.	SCALE 3:1																																																	
	DERIVED FROM DRAWING					DATED	PROJECTION																																																		
	REPLACES PRODUCT DRAWING V9048					DATED Nov 14, '06																																																			
VALIDITY	VALID FROM <i>June 23, 2010</i>		AUTHORIZED BY <i>RJ</i>			SIGNATURE <i>[Signature]</i>																																																			

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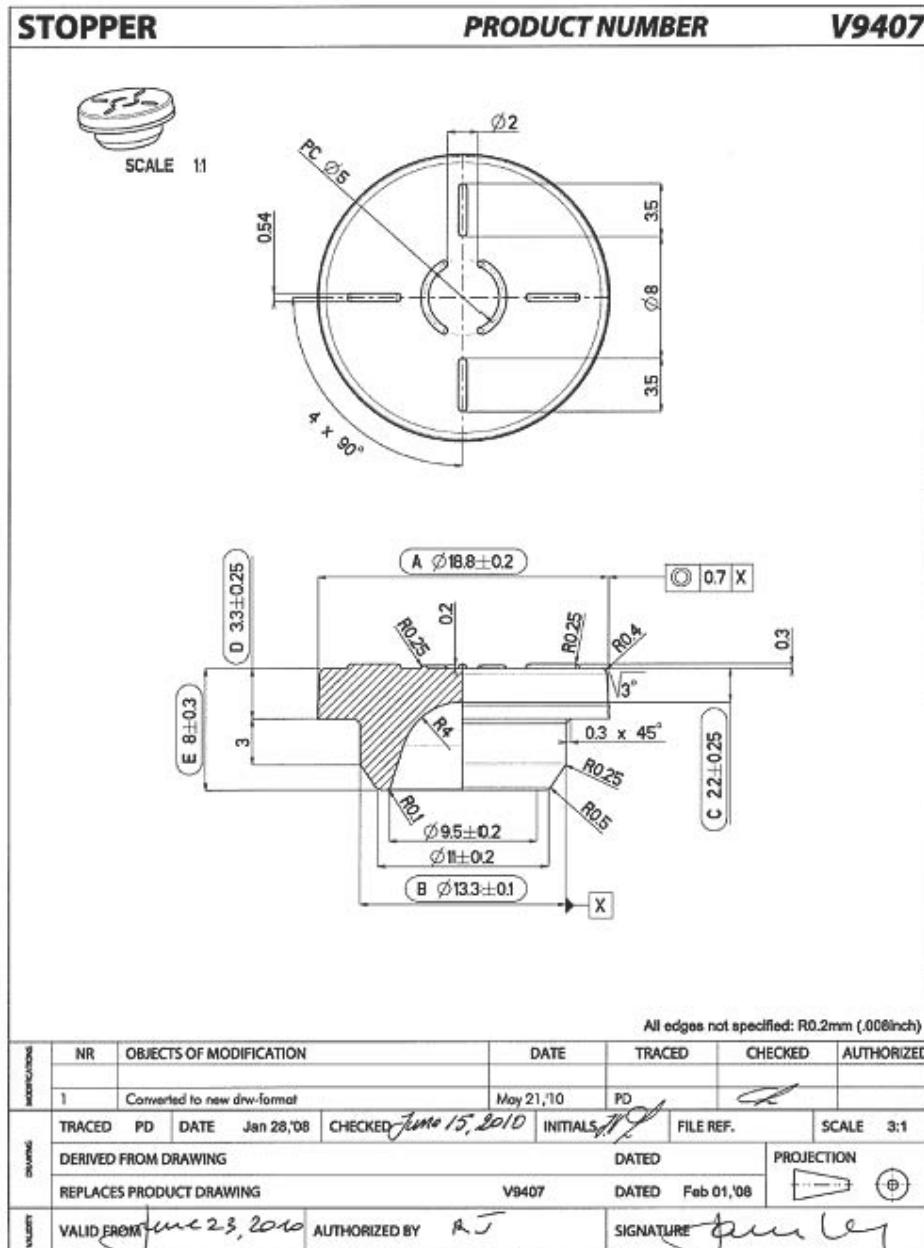
This drawing is the property of Datwyler and may not be copied nor disclosed to third parties without our written consent.
Dimensions without tolerance indication correspond to DIN-ISO 3302 Class M9. Cut or punched edges can be slightly conical, eccentric and/or variable.

- 20 mm serum – sample mould design P8575A



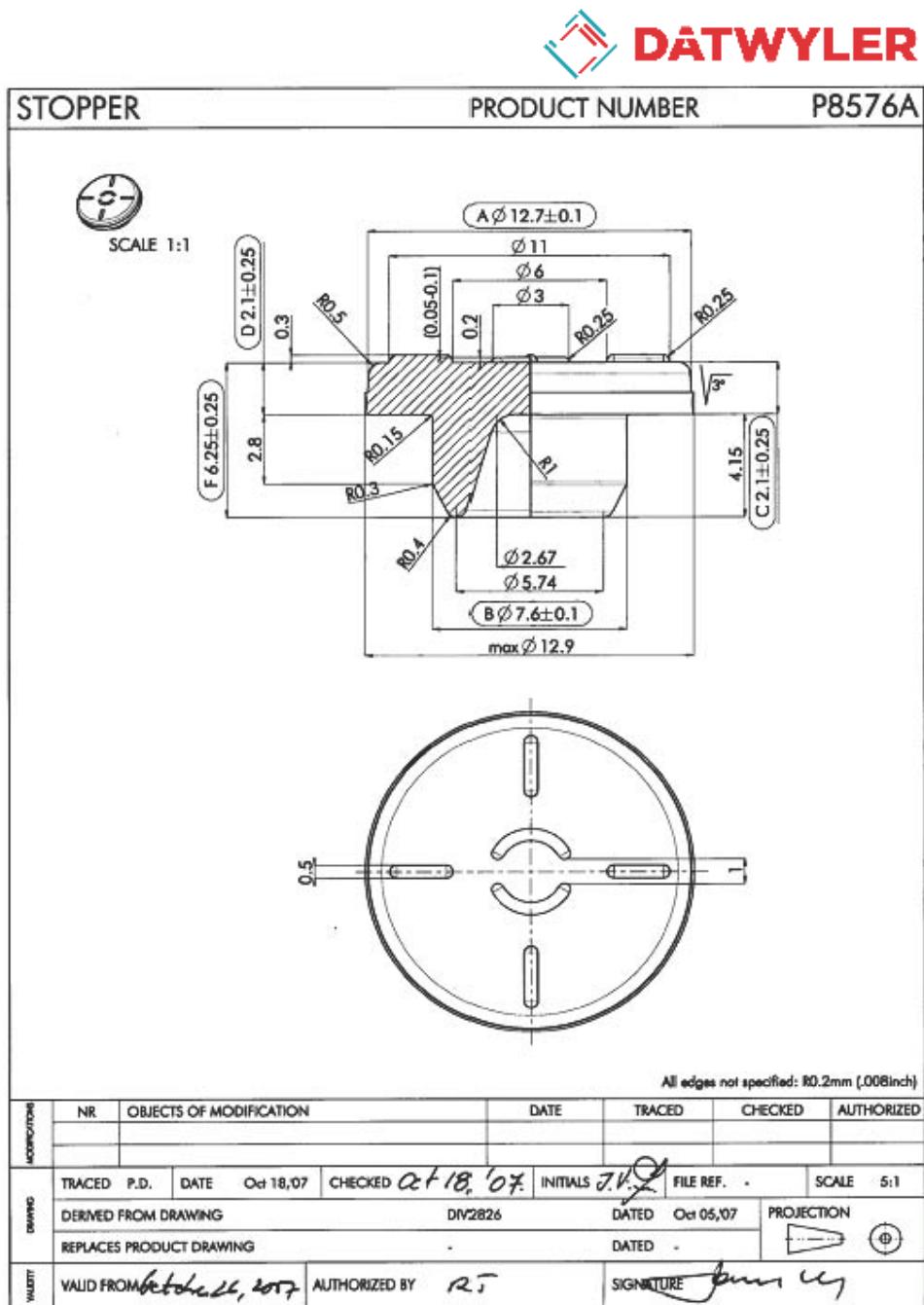
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- 20 mm serum – new design - industrial mould V9407



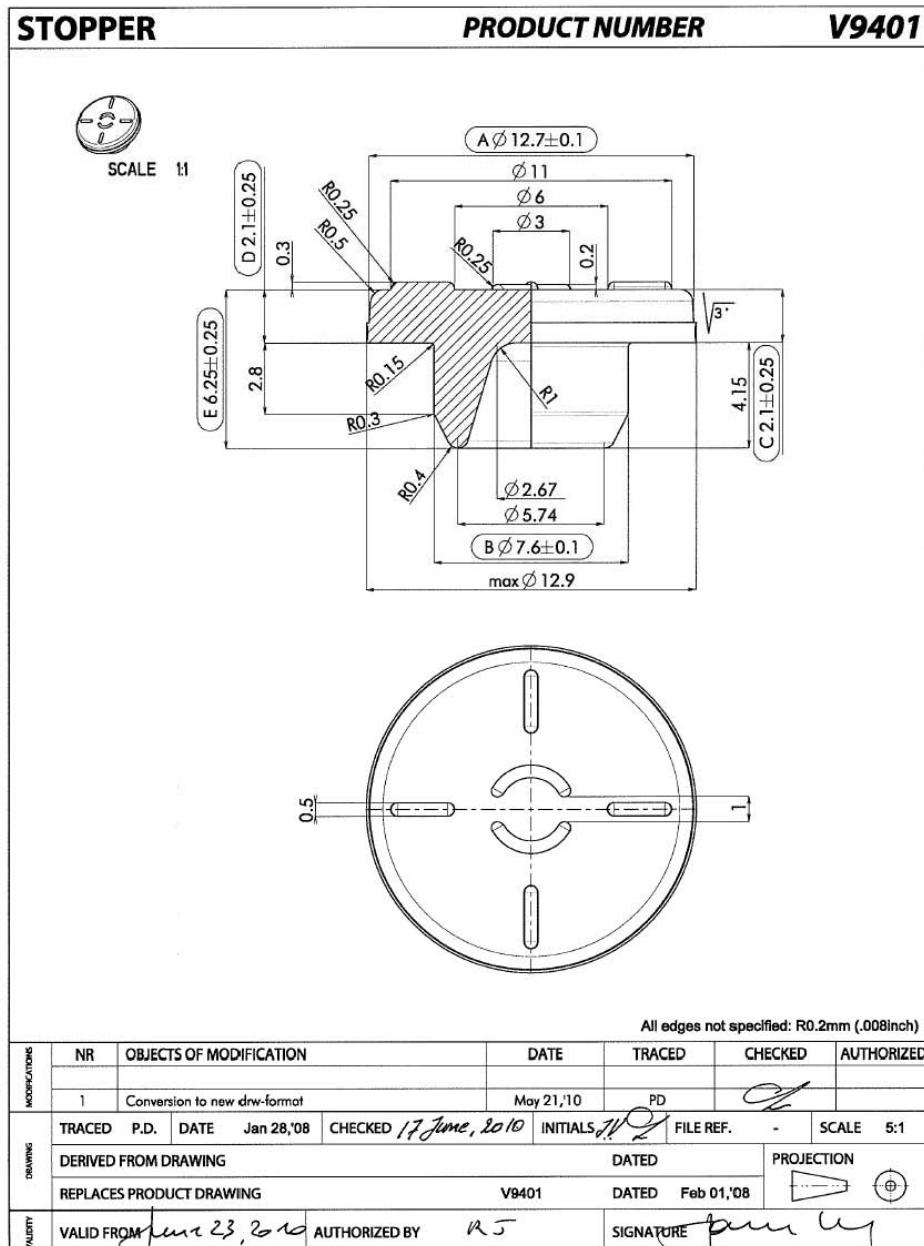
Printed copies will not be systematically updated

- 13 mm serum – sample mould design P8576A



Printed copies will not be systematically updated

- 13 mm serum – new design - industrial mould V9401



Printed copies will not be systematically updated

Attachment 2: Compound data sheet FM457



Compound Data Sheet

FM457/0 **Grey**

General description

Bromobutyl compound, unconventionally cured. Latex free and free from MBT.
Extremely low extractables level.

Application range: universal; especially suitable for WFI applications.

Physical properties

	<i>Unit</i>	<i>Method</i>	<i>Target</i>	<i>Range</i>
Hardness	"Shore A	ISO 7619-1 (1 sec. Indentation) Avg of 3 measurements	47	± 5
Density	g/cm ³	ISO 2781	1.265	± 0.025
Ash	%	Internal Method(s): Calc. 4h @ 700° C	41.0	± 2.0
Compression Set	%	ISO 815	30	max.
Tensile Strength	N/mm ²	ISO 37	4	min.

Chemical properties

FM457(**) meets the chemical requirements for Type I Closures specified in General Chapter 3.2.9. of the European Pharmacopoeia and specified in General Chapter <381> of the United States Pharmacopoeia.
Typical USP <381> / EP 3.2.9. data for FM457(**) are presented in the table on page 2.
A typical UV spectrum of the USP <381> / EP 3.2.9. extract of FM457(**) is presented in the figure on page 3.

Biological properties

FM457(**) is non-cytotoxic and meets the requirements of the Elution Test as described in General Chapter <87> of the United States Pharmacopoeia.
A typical USP <87> Elution Test Certificate is enclosed on page 4.

Pyrolylate

An infrared spectrum of the pyrolylate of FM457(**) is enclosed on page 5.

Compound statement

A statement about compound FM457(**) in respect to natural rubber latex, nitrosamines, MCBT, Heavy metals, TSE/BSE and GMO is enclosed on page 6.

(**) Note: FM457 refers to the type of compound, the extension "0", "1", ... refers to the colour of the said compound.
Differently coloured compounds might be used for testing throughout this document. It is generally accepted that the colour is irrelevant for the properties discussed in this document.

Prepared by:  R&D Laboratory Date: 10 Oct 2010

Reviewed by:  Material Development Date: 12 Oct 2010

Approved by:  Quality Assurance Date: 14 Oct 2010

Valid from: October 11, 2010
(Replaces CDS of January 2, 2002)

CDS FM457/0

Page 1/6



Typical USP <381> / EP 3.2.9. chemical properties of FM457()**

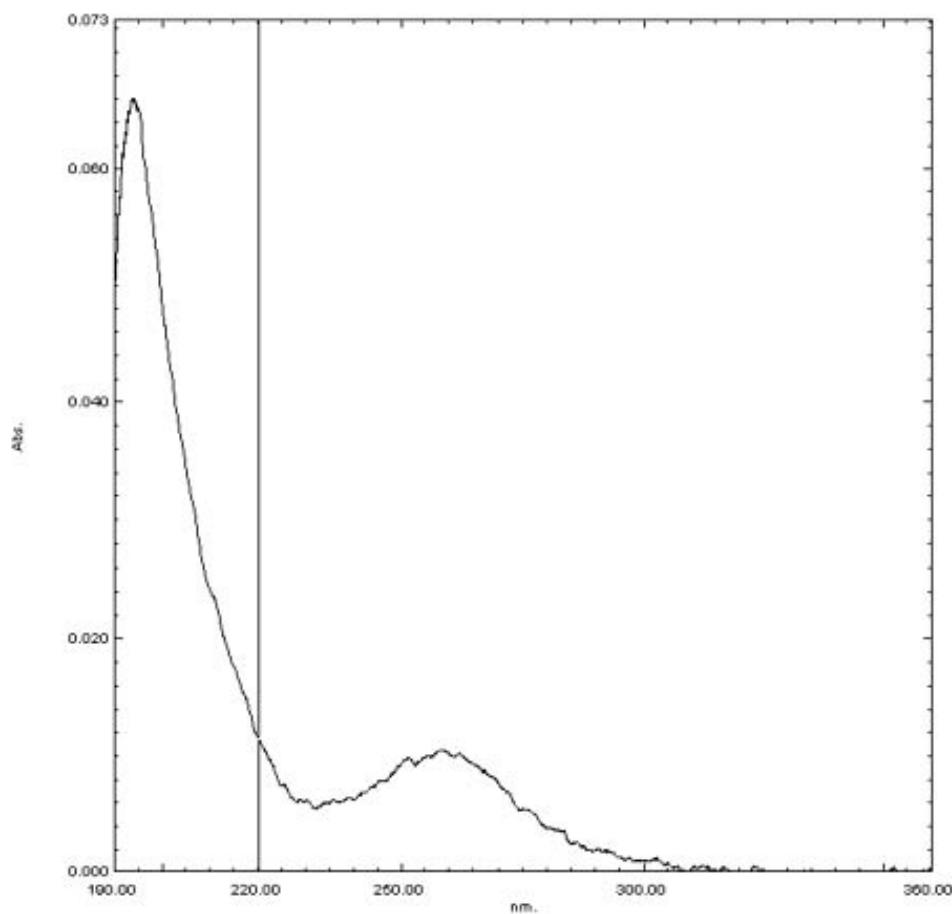
Characteristic		Amount tested	Units	Limit	Typical Values	
Appearance of solution	Turbidity	Sol. S	NTU	Type I: ≤ 6.0 (*)		0.1
	Colour	Sol. S		See test procedure		pass
Acidity or alkalinity		Sol. S (20 ml)	ml 0.01M HCl	≤ 0.8	Blank	
					0.06	0.06
			ml 0.01M NaOH	≤ 0.3	EP	0.06
					USP	0.00
Absorbance		Sol. S	A _{max} 220-360nm	Type I: ≤ 0.2		0.01
Reducing substances		Sol. S (20 ml)	ml 0.002M KMnO ₄	Type I: ≤ 3.0		0.2
Extractable heavy metals		Sol. S	ppm Pb	≤ 2	EP	<2
					USP	<2
Extractable zinc		Sol. S	ppm Zn	≤ 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		0.2
Volatile sulphides		20 cm ²	mg S	≤ 0.02		<0.02

(*) By definition corresponding with reference suspension II.

(**) Note: FM457 refers to the type of compound, the extension "0", "1", ... refers to the colour of the said compound.
Differently coloured compounds might be used for testing throughout this document. It is generally accepted that the colour is irrelevant for the properties discussed in this document.



Typical UV-spectrum of USP <381> / EP 3.2.9. extract of FM457(**)



(**) Note: FM457 refers to the type of compound, the extension '0', '71', ... refers to the colour of the said compound.
Differently coloured compounds might be used for testing throughout this document. It is generally accepted that the colour is irrelevant for the properties discussed in this document.


Typical USP <87> Elution Test Certificate of FM457(**)


► 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 Abou		
Address:	Industrieterrein Kolmen 1519	Date Sample Arrival:	12/05/2010
	3570 Aken, Belgium	Technical Initiation:	17/05/2010
PO.Number:	PB1001706	Technical Completion:	20/05/2010

Study	Elution Test - ISO	Temp/Time	37°C/24 hours
Test Item	V9341 FM457/0 0 kGy Gamma t=24h	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

The test results on the enclosed report are only referring to the tested articles. Partly reproduction of this report can only be allowed after written permission of Toxikon. Toxikon guarantees that all results are acquired by testing according to officially accepted scientific methodology.

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(**) Note: FM457 refers to the type of compound, the extension "0", "1", ... refers to the colour of the said compound.
Differently coloured compounds might be used for testing throughout this document. It is generally accepted that the colour is irrelevant for the properties discussed in this document.

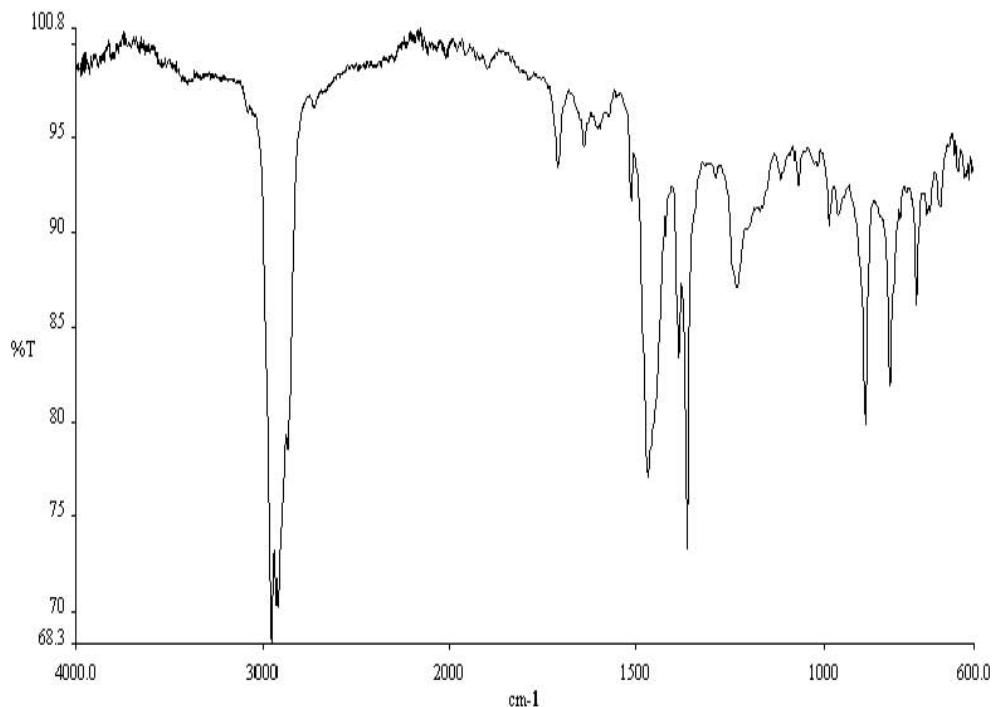
Valid from: October 11, 2010
(Replaces CDS of January 2, 2002)

CDS FM457/0

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Typical infrared spectrum of a pyrolysate (4000-600 cm⁻¹) of FM457()**



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Differently coloured compounds might be used for testing throughout this document. It is generally accepted that the colour is irrelevant for the properties discussed in this document.



Compound statement for FM457()**

Natural rubber latex

Compound FM457(**) is free from natural rubber and natural rubber latex.

Nitrosamines

Compound FM457(**) does not use rubber chemicals that are associated with hazardous nitrosamines formation.

MCBT

Compound FM457(**) does not contain 2-mercaptobenzothiazole (MCBT, also named MBT), or any of its derivatives.

Heavy Metals

- Compound FM457(**) fulfils the European Community Guideline 94/62/EC for heavy metals in packaging materials.
- Compound FM457(**) fulfils the CONEG regulation on reduction of toxics in Packaging Law.

Both directives state that packaging components should not contain more than 100 ppm of Lead (Pb), Cadmium (Cd), Mercury (Hg) and Hexavalent Chromium (VI) (Cr). Where the regulated metals are present at levels below the values stated above, they were not intentionally added during the manufacturing process.

TSE/BSE

Compound FM457(**) does not contain material of animal origin and hence is not associated with TSE/BSE risks.

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

GMO

Compound FM457(**) does not contain ingredients made from GMO's (Genetically Modified Organisms).

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

Attachment 3: Equipment for vacuum retention studies

- Picture of lab exsiccator and pressure gauge



- Lyo chamber



- Lighthouse equipment for non-destructive measurement of headspace pressure in vials

