CUSTOMER SERVICE REPORT
CS0147

Technical Documentation
FM257/2 Omniflex Coated Plunger (OCP)
- Edition 3 –

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www.datwyler.com

Edition 3, February 3, 2012

Table of contents

1. Description

Datwyler's Omniflex Coated Plungers, in short OCP, are bromobutyl rubber plungers that are covered with a fluorinated polymer coating, applied via a proprietary spray-coating process. The rubber substrate used is FM257/2, colour dark gray, a bromobutyl rubber formulation with silicate filler and an unconventional curing system.

The fluorinated polymer coating has a barrier function and provides chemical inertness comparable with that of PTFE (Poly-TetraFluoroEthylene or Teflon®), ensuring a high degree of compatibility with a broad range of pharmaceutical products.

Since products are totally coated, the trimming edge is covered as well and additional siliconization during the final treatment becomes redundant. Both these features and the fact that OCP products are uniquely manufactured in Datwyler's FirstLine™ ([1]) production facility result in a clearly reduced particle burden.

FM257/2, the substrate rubber for OCP products is a modern formulated bromobutyl with a high chemical purity. Combined with the barrier coating, an extremely low extractables and leachables profile is guaranteed. OCP products are not made with natural rubber latex, dry natural rubber or any of its derivatives. They are not made using ingredients of animal origin and do not generate known suspicious chemicals like nitrosamines and 2-mercaptobenzothiazole (MCBT).
Obviously, these products comply with all major pharmacopeia for pharmaceutical rubber.

OCP itself, the fluoropolymer coating process and the relevant washing process are filed with the FDA in a US Drug Master File (#10953) and with the Health Protection Branch in Canada (#1994-027).

Note: OCP = FM257/2 + "fluoropolymer coating"

[1] FirstLine™ is a brand-new state-of-the-art production unit within the Datwyler group where the strictest product specifications for microbiological and particulate cleanliness can be guaranteed.

2. Typical compound ingredients

2.1. Natural Rubber Latex

In line with current market expectations, OCP (Omniflex Coated Plunger) is not made with any natural rubber or natural rubber latex.

2.2. Nitrosamines

Nitrosamines are residues of specific curing systems. These residues are in a number of cases known to be carcinogenic.
OCP is formulated without making use of ingredients that potentially give rise to the formation of nitrosamines.

2.3. MCBT

2-mercaptobenzothiazole (2-MBT, 2-MCBT, MCBT) is a rubber chemical that is associated with a health risk.
OCP does not contain 2-mercaptobenzothiazole (MCBT) or any of its derivatives.

2.4. BSE/TSE

Rubber compounds may contain components that are of animal origin. Most frequently it concerns fatty acids, fatty acid salts or esters that are either present as active components or as additives to active components.
OCP does not use components of animal origin. OCP is in full compliance with the European Pharmacopoeia 5.2.8., "Minimizing the risk of transmitting Animal Spongiform Encephalopathy Agents via medicinal products".
(TSE = Transmissible Spongiform Encephalopathy; BSE = Bovine Spongiform Encephalopathy)

2.5. Heavy Metals

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

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

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

2.6. GMO (Genetically Modified Organisms)

OCP is not made with ingredients that are derived from Genetically Modified Organisms (GMO).

2.7. Bisphenol A (BPA)

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

Datwyler confirms that OCP does not use Bisphenol A or the following BPA related substances in its composition:

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

3. Shelf Life

The shelf life of Omniflex Coated Plungers, intended for use in parenteral applications, stored in the original packaging under the ambient storage conditions as described in the ISO 2230, “Rubber Products – Guideline for storage”, is 2 years after packing date.

Hereafter, based on the indications given in the ISO 2230, an additional shelf life of 5 years can be considered.
Compatibility with the drug must be ascertained by the user.

4. Physical properties

4.1. Identification properties

The following tests are used to identify the rubber formulation following typical rubber technology standards. The physical properties shown in the table below are taken for the rubber substrate compound FM257/2 without the additional fluoropolymer coating.
For technical reasons, these properties are not determined on OCP (FM257/2 in its coated version).

Table : Physical properties – FM257/2

Hardness	°Shore A	ISO 7619	52 ± 5
Density	g/cm³	ISO 2781	1.355 ± 0.025
Ash	%	Internal Method(s): Calcination 4h@700°C	46.0 ± 2.0
Compression Set	%	ISO 815	max. 17
Tensile Strength	N/mm²	ISO 37	min. 3

4.2. ATR-FTIR scans

To distinguish between coated and non-coated rubber, one can make use of an ATR-FTIR (Attenuated Total Reflection -FTIR) scan from the product surface and that of a cut product. The next figures show a reference spectrum of both surfaces.

Figure : FTIR surface scan of OCP (coated rubber)

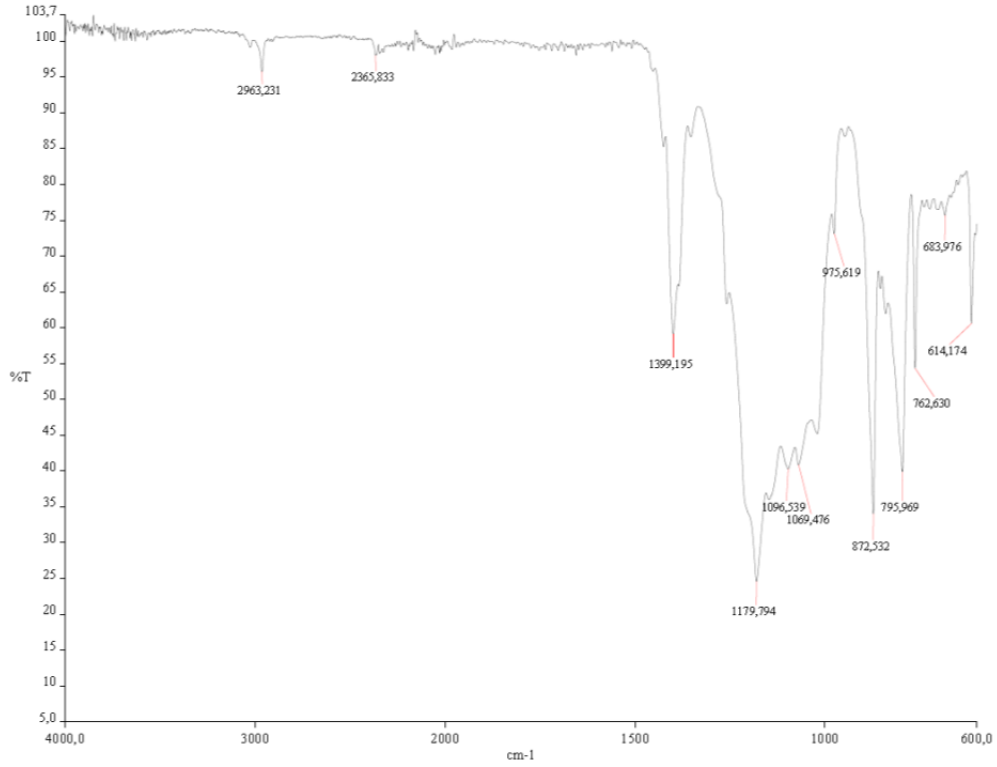
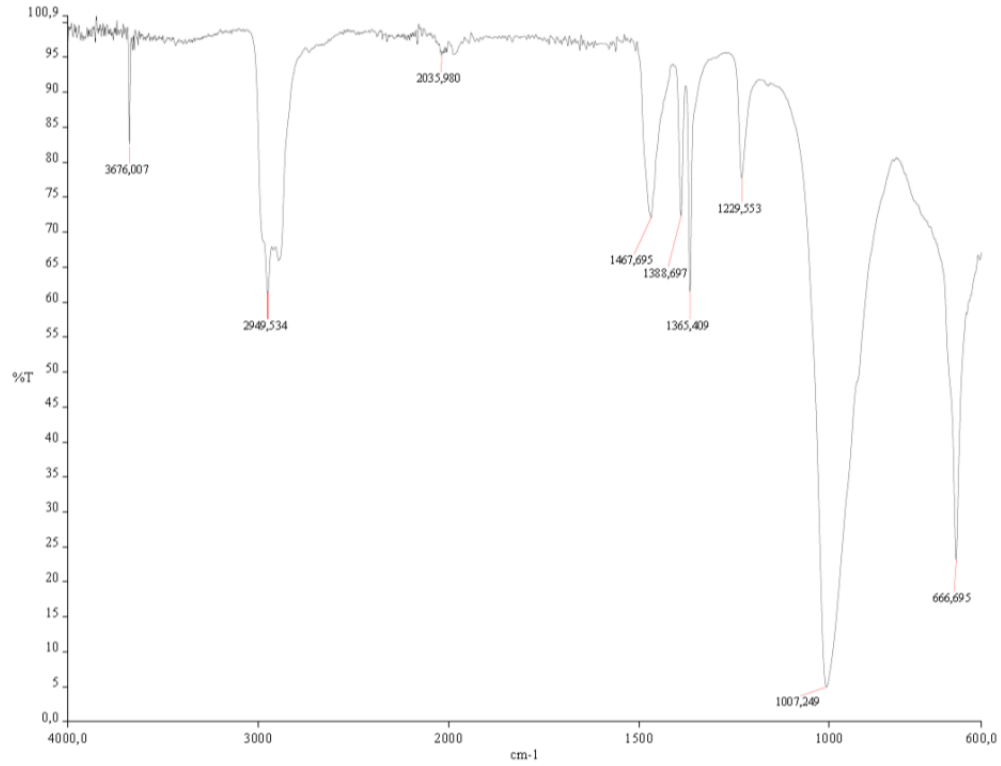


Figure : FTIR surface scan of FM257/2 (uncoated rubber – cut edge)



4.3. Permeability

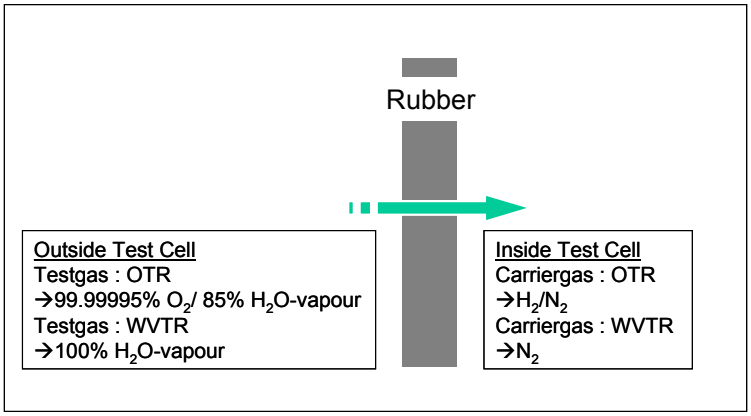
Oxygen and water vapour transmission rates are measured as per ASTM D-3985 (oxygen) and ASTM F-1249 (water vapour). They measure the permeability of a material to oxygen viz. water vapour.
To be able to obtain permeability data on rubber compounds, a special mould, yielding a thin rubber slab, is used to prepare test pieces.
These rubber slabs, with a certain thickness (±1.3mm), are preconditioned at 23°C and 50% RH prior to the actual measurement.

For the test itself, a rubber slab in FM257/2 without coating is cut matching 50 cm² and clamped in a double chamber test cell, acting as a barrier between both chambers (see figure below).

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

Permeability on OCP is not determined for technical reasons. The coating itself does not act as a barrier to O_2 and H_2O and hence the below given properties for FM257/2 are to be considered relevant for OCP as well.

Figure : Schematic principle of a transmission rate measurement



4.3.1. Water Vapour Transmission Rate (WVTR)

Tested slabs: FM257/2 slabs with thickness 1.33mm
Equipment: MOCON, Permatran-W 3/31 MG-module
Conditions: 38 °C ; 100% relative humidity ; 100% flow N_2

Table : WVTR

	WVTR in g/m².24h, 100% RH / 38°C
FM257/2	0.03

4.3.2. Oxygen Transmission Rate (OTR)

Tested slabs: FM257/2 slabs with thickness 1.39mm
Equipment: MOCON, Oxtran 2/20 ML-module
Conditions: 38 °C ; 85 % relative humidity ; 99.99995% O_2

Table : OTR

	OTR in cc/m².24h, 85% RH / 38°C, 99.99995% O_2
FM257/2	48

5. Chemical Properties

5.1. Pharmacopeial data

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

A revised version of USP <381>, has come into force on May 1, 2009. Sample preparation, test description and the 2-tier acceptance criteria were largely harmonized with Pharm. Eur. 3.2.9.
Furthermore, USP<381> stipulates that the physicochemical testing of coated products has to be performed on both the rubber substrate and the coated form.

The tables here below summarize the USP <381> and Pharm. Eur. 3.2.9. chemical testing on the FM257/2 substrate rubber and on OCP respectively.

Table : Pharm. Eur. 3.2.9 / USP <381> data, chemical part – FM257/2 substrate

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

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

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

Characteristic		Amount tested	Units	Limit	Typical Value	
Appearance of solution	Turbidity	Sol. S	NTU	Type I: 6.0 *(*)* Type II: 18.0 *(*)*		0.1
	Colour	Sol. S		See test procedure		pass
Acidity or alkalinity		Sol. S (20 ml)	ml 0.01M HCl ml 0.01M NaOH	0.8 0.3	Blank 0.05	0.05
					EP	0.05
					USP	0.00
Absorbance		Sol. S	A_{max}220-360 nm	Type I: 0.2 Type II: 4.0		0.01
Reducing substances		Sol. S (20 ml)	ml 0.002M $KMnO_4$	Type I: 3.0 Type II: 7.0		0.19
Extractable heavy metals		Sol. S	ppm Pb^{2+}	2	EP	<2
					USP	<2
Extractable zinc		Sol. S	ppm Zn^{2+}	5.0		<0.01
Ammonium		Sol. S	ppm NH_4^+	2		<2
Residue on evaporation (only for EP)		Sol. S (50 ml)	mg	Type I: 2.0 Type II: 4.0		0.1
Volatile sulphides		20 cm²	mg S^{2-}	0.02		<0.02

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

For OCP products Datwyler guarantees a shelf life period of 2 years after the packing date.
Compliance of FM257 (substrate for OCP) and of OCP itself with the chemical requirements of Pharm.Eur. 3.2.9 and USP <381> after 2 years shelf life is demonstrated in the tables below.

Table : Pharm. Eur. 3.2.9 / USP <381> data, chemical part – FM257/2 substrate

Characteristic		Amount tested	Units	Limit	Typical Value	
Appearance of solution	Turbidity	Sol. S	NTU	Type I: 6.0 *(*)* Type II: 18.0 *(*)*		0.3
	Colour	Sol. S		See test procedure		pass
Acidity or alkalinity		Sol. S (20 ml)	ml 0.01M HCl ml 0.01M NaOH	0.8 0.3	Blank 0.06	0.06
					EP	0.06
					USP	0.00
Absorbance		Sol. S	A_{max}220-360 nm	Type I: 0.2 Type II: 4.0		0.00
Reducing substances		Sol. S (20 ml)	ml 0.002M $KMnO_4$	Type I: 3.0 Type II: 7.0		0.23
Extractable heavy metals		Sol. S	ppm Pb^{2+}	2	EP	<2
					USP	<2
Extractable zinc		Sol. S	ppm Zn^{2+}	5.0		<0.01
Ammonium		Sol. S	ppm NH_4^+	2		<2
Residue on evaporation (only for EP)		Sol. S (50 ml)	mg	Type I: 2.0 Type II: 4.0		0.0
Volatile sulphides		20 cm²	mg S^{2-}	0.02		<0.02

** By definition corresponding with reference suspensions II and III respectively.*
(Data recorded for batch 30036882 after 2 years shelf life)

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

Characteristic		Amount tested	Units	Limit	Typical Value	
Appearance of solution	Turbidity	Sol. S	NTU	Type I: 6.0 *(*)* Type II: 18.0 *(*)*		0.1
	Colour	Sol. S		See test procedure		pass
Acidity or alkalinity		Sol. S (20 ml)	ml 0.01M HCl ml 0.01M NaOH	0.8 0.3	Blank 0.09	0.10
					EP	0.10
					USP	0.01
Absorbance		Sol. S	A_{max}220-360 nm	Type I: 0.2 Type II: 4.0		0.01
Reducing substances		Sol. S (20 ml)	ml 0.002M $KMnO_4$	Type I: 3.0 Type II: 7.0		0.23
Extractable heavy metals		Sol. S	ppm Pb^{2+}	2	EP	<2
					USP	<2
Extractable zinc		Sol. S	ppm Zn^{2+}	5.0		<0.01
Ammonium		Sol. S	ppm NH_4^+	2		<2
Residue on evaporation (only for EP)		Sol. S (50 ml)	mg	Type I: 2.0 Type II: 4.0		0.0
Volatile sulphides		20 cm²	mg S^{2-}	0.02		<0.02

** By definition corresponding with reference suspensions II and III respectively.*
(Data recorded for batch 30051238 after 2 years shelf life)

Figure : Typical IR-spectrum (4000-625cm^{-1}) of a pyrolysate (acc. Pharm. Eur. 3.2.9.) - FM257/2 substrate

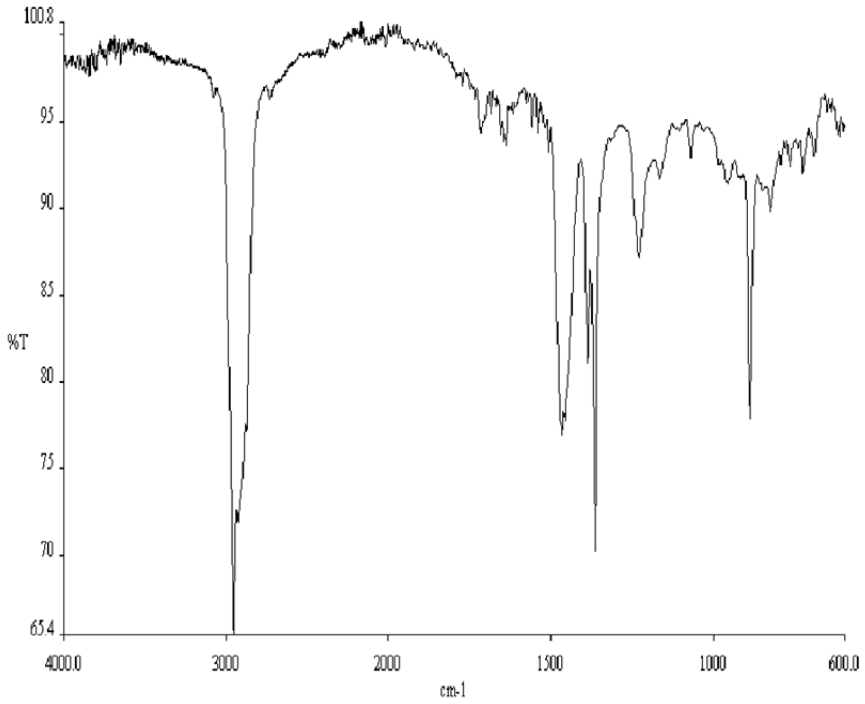


Figure : Typical IR-spectrum (4000-625cm^{-1}) of a pyrolysate (acc. to the Pharm. Eur. 3.2.9.) - OCP

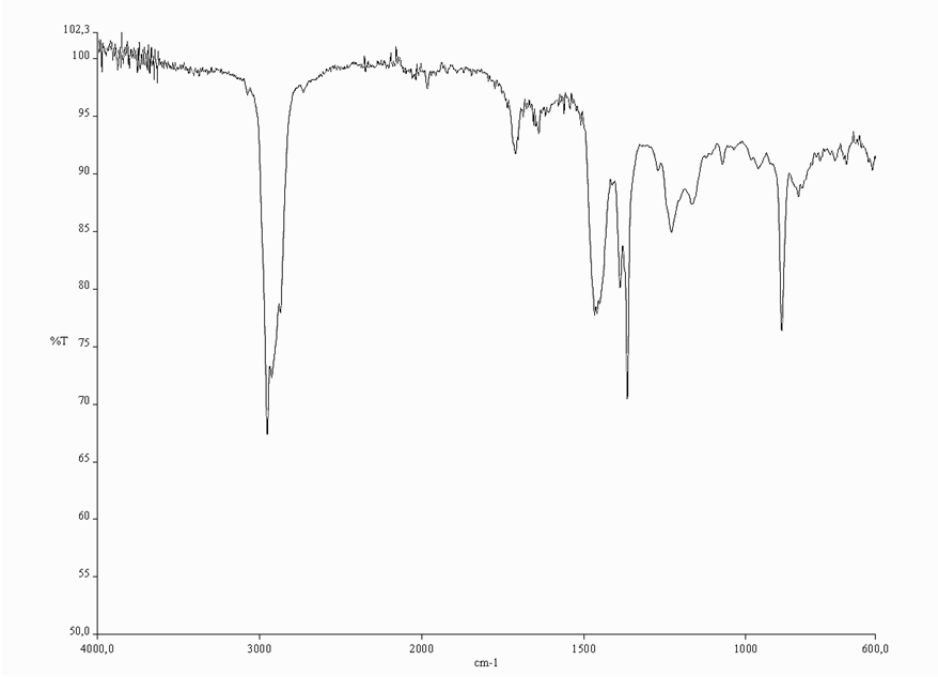


Figure : Typical UV-spectrum of an aqueous extract (acc. Pharm. Eur. 3.2.9./USP <381>) - FM257/2 substrate

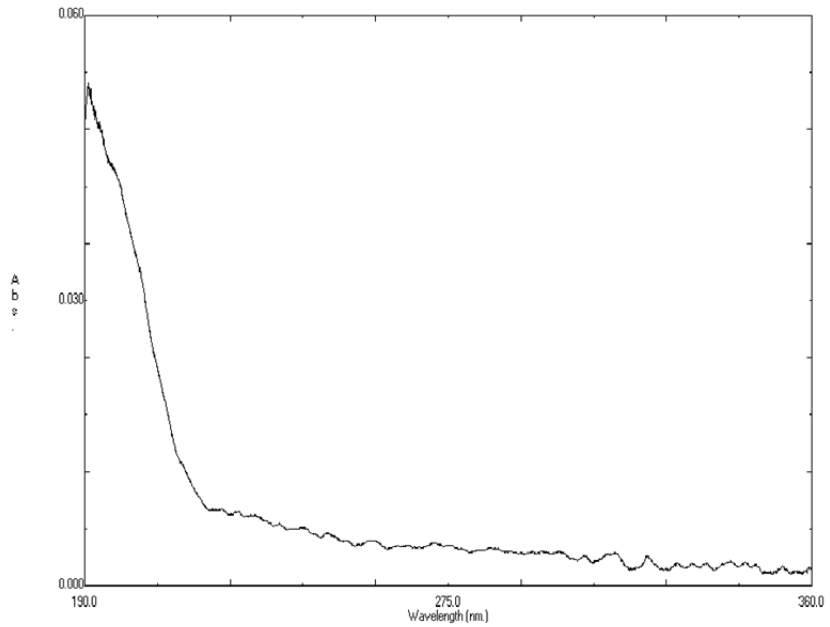
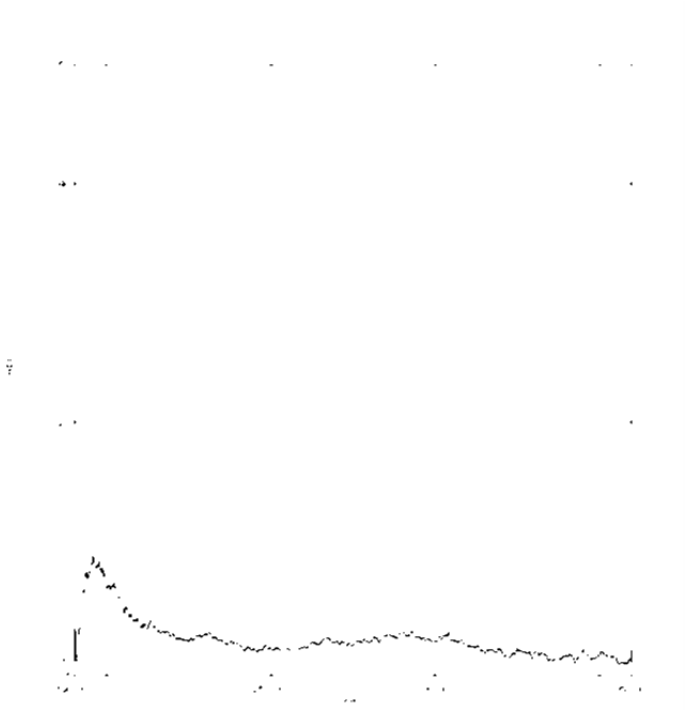


Figure : Typical UV-spectrum of an aqueous extract (acc. to the Pharm. Eur. 3.2.9./USP<381>) – OCP



Note : the two figures above have unequal y-axes.

5.1.2. Japanese Pharmacopeia 7.03

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

Due to the peculiar definition of the sample preparation (by rubber mass and not by rubber surface), results are closure design dependent (surface/volume ratio dependency). Results in the table are given for a 0.5ml plunger with a volume of 0.10cm³, a weight of 0.14g and a total surface of 1.88cm² (Ref. V9315). Bigger plunger designs such as the 1 ml long and 1-3ml plunger will show better results for the fact that the surface/volume ratio will be smaller (less rubber surface in contact with the extraction medium).

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

Table : JP 7.03 – OCP

CRITERIUM	AMOUNT TESTED	UNITS	LIMITS	RESULTS
Appearance (430-650 nm)	10 mm cuvet	%T at 430 nm %T at 650 nm	99.0% T 99.0% T	99.7 99.8
Foam test	5 ml	-	foam disap. < 3 min.	pass
pH	20 ml	pH units	difference with blank: max. 1.0 (*)	-0.4
Reducing substances	100 ml	ml 0.002 M $KMnO_4$	2.0	0.3
Evaporation residue	100 ml	mg	2.0	0
UV absorb. (220-350 nm)	10 mm cuvet	absorbance	0.2	0.02
Zinc	10 ml	ppm Zn^{2+}	1 ppm	0.01

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

5.2. ISO 8871-1

The requirements of ISO 8871-1, "Elastomeric parts for parenterals and for devices for pharmaceutical use – Part 1: Extractables in aqueous autoclavates", are identical to those set down in Pharm. Eur. 3.2.9.

Results for Pharm. Eur. 3.2.9. are given under paragraph 5.1.1.

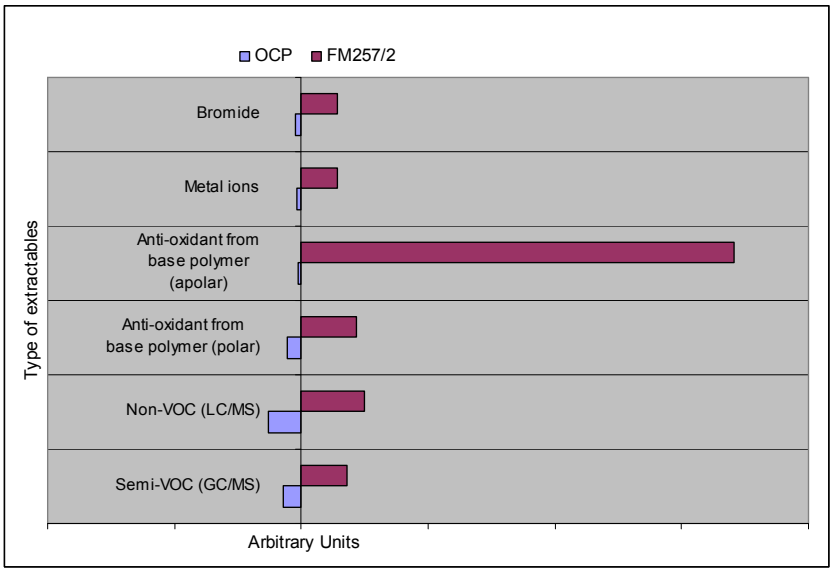
5.3. Extractable information

A detailed extractables report on OCP involving solvents of various polarities is available on request. Because of their confidential nature, the results of this extractables study are not given in full detail in this report. They will be available only after conclusion of specific agreements. Please contact your Datwyler sales representative.

The figure at the end of this sectionFigure compares a series of 'group' extractables for OCP and for the FM257/2 rubber substrate. For demonstration purposes, an indefinite but comprehensible view is given on the barrier effect of the coating towards the possible extractables and leachables of the rubber substrate.

Bromides and metal ions were measured in a pH=3 aqueous extract. The outcome for the relevant anti-oxidant is given for an apolar (n-hexane) and a polar (isopropanol) extraction medium.
The Non-VOC (Volatile Organic Compounds) and the Semi-VOC are the sum of all compounds found respectively for the GC/MS (Gas Chromatography/Mass Spectroscopy) and the LC/MS (Liquid Chromatography/Mass Spectroscopy) analyses on a pH=11 aqueous extract.
Results are expressed in arbitrary units to be able to evaluate the barrier effect in a relative way.

Figure : Demonstration of the barrier effect of the fluoropolymer coating



The barrier effect as visualized in the above figure thus decreases the likelihood of interactions of rubber leachables with a drug product.

6. Functional Properties

Functional testing as described in the USP<381> and Pharm.Eur. 3.2.9 (and ISO8871-5) is focused on products were the intended use involves piercing with a needle. For plungers, more relevant properties to be tested are the gliding behavior on the one hand and Plunger Barrel Seal Integrity (PBSI) on the other hand.

6.1. Design discussion

Two plunger types will be studied throughout this chapter:

- the 1ml long plunger as defined in the ISO11040-5 standard:
  - V9283 product design for uncoated;
  - V9403 for the OCP version;
- the 1-3ml plunger as defined in the ISO11040-5 standard:
  - V9258 product design for uncoated;
  - V9416 for the OCP version.

(drawings can be found under the attachments at the end of this document)

The main design differences between the uncoated and coated designs are the diameters and the radii of the rills of the plunger and the trimming edge. During the development of the OCP design, these modifications were chosen to aim for an optimal gliding behavior.

The figure below shows the effect of these minor changes (contact with glass) for the 1ml long design, once assembled in a glass barrel.

Figure : Assembled 1ml long plungers: V9283 FM257/2 (left) – V9403 OCP (right)

6.2. Gliding behavior

Generally speaking, 2 factors are important when discussing gliding behavior:

1. activation or break-loose force: force needed to bring the plunger in motion;
2. gliding force: force needed to keep the plunger moving after the activation.

Additionally, consistency or smoothness of the gliding curve over its path length is important in case of auto-injectors.
Gliding curves are recorded by using a Zwick/Roell BZ2.5/TH1S equipment with load-cell 1kN to move the plunger in the barrel with a speed of 100 mm/min till 70% of the liquid is removed and by recording the corresponding force curves.

6.2.1. Gliding behavior 1 ml long OCP

In this section the gliding behavior of 1 ml long OCP (V9403) is compared with the gliding behavior of uncoated siliconized 1 ml long plungers according to the ISO 11040-5 design (V9283). The effect of the mode of bulk sterilization and the effect of long term syringe storage temperature is studied as well.
SAF2 siliconization was applied to the uncoated plungers, since this is the Datwyler standard for such plungers. SAF siliconization uses a highly viscous (30,000cSt) hydrophobic silicone oil (polydimethylsiloxane). The target range for SAF2 is 15-35 µg silicone oil per cm² of rubber surface area.

In order to investigate the impact of the bulk sterilization mode of OCP plungers on gliding behavior, all of the following plunger types were included in the study :

1. Non-sterilized
2. Steam sterilized 30 mins/121°C, followed by overnight drying in a lab oven at 70°C
   Steam sterilization for 30 minutes at 121 °C, followed by drying, is the most frequently encountered industrial practice for steam sterilization of elastomeric parts.
3. Gamma sterilized with a 25 kGy dose
   Gamma sterilization of OCP parts at a maximum dose of 25 kGy is a commonly used industrial practice.

6.2.1.1. Syringe filling and storage

1 ml long glass syringes with tip cap manufactured in an industrial process were filled to nominal volume with water. Plungers were assembled in the barrels on lab scale making use of an appropriate insertion tube. The plunger was positioned at 2 +/- 1 mm above the liquid phase.

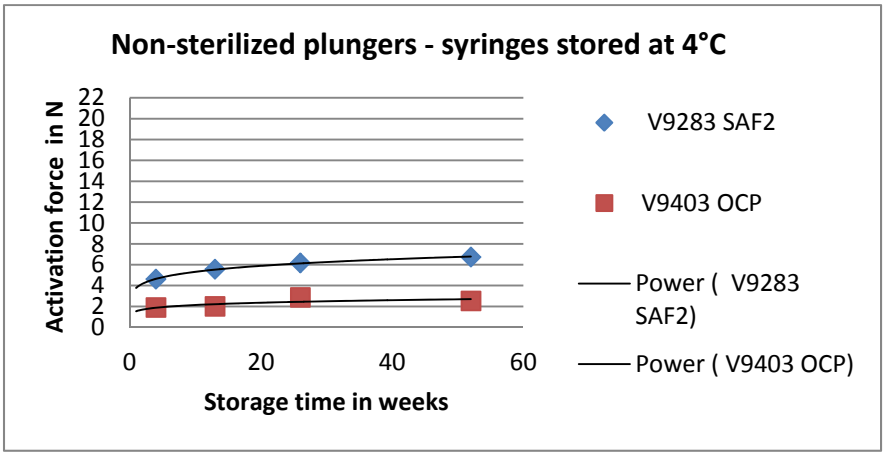
The filled syringes were stored at different conditions :

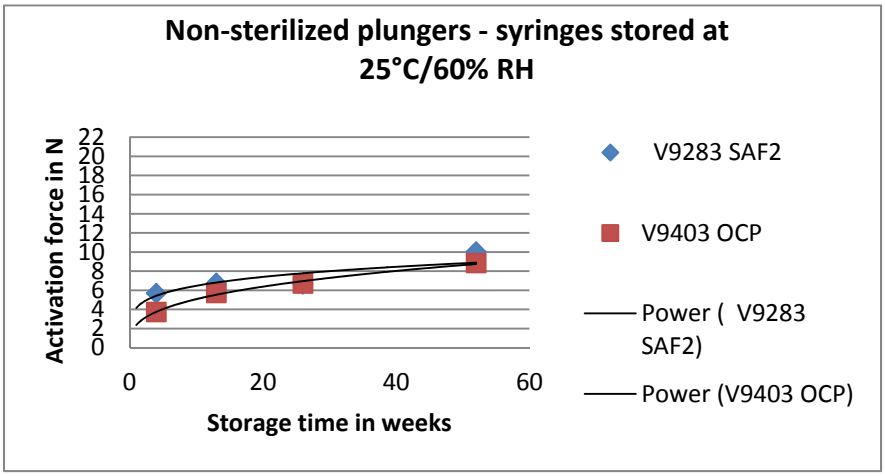
1. Storage at 4° C +/- 2 °C (refrigerator) up to 1 year
2. Storage at 25 °C / 60 % RH [2] (climate chamber) up to 1 year
3. Storage at 40 ° C / 75 % RH (climate chamber) up to 3 months

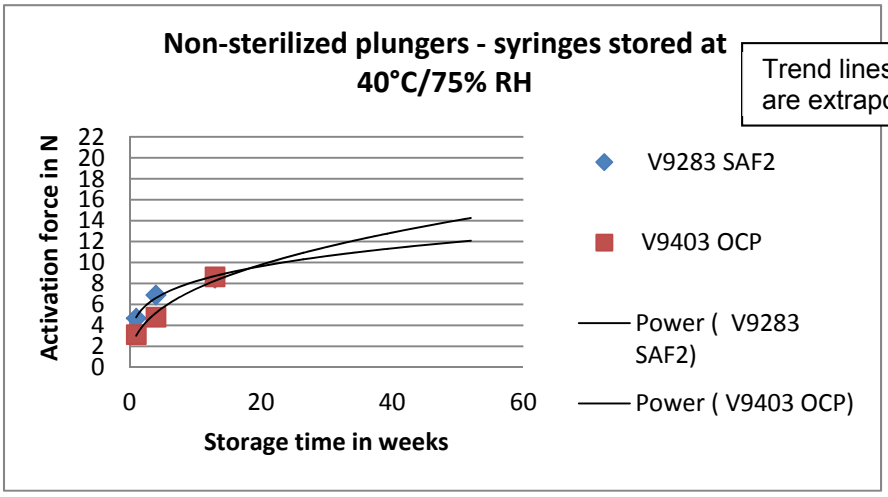
[2] RH = Relative Humidity

At each time point in the study activation and gliding forces were determined on a sample of 10 syringes for each storage condition.

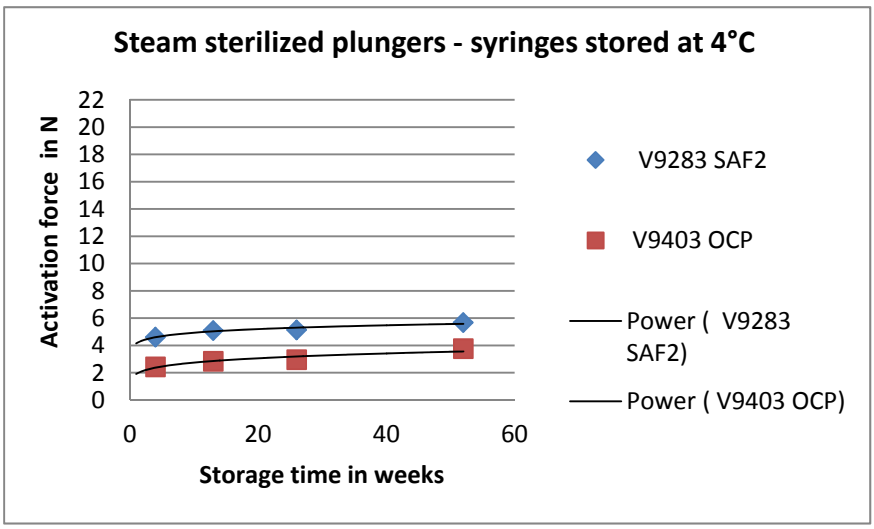
6.2.1.2. Activation force

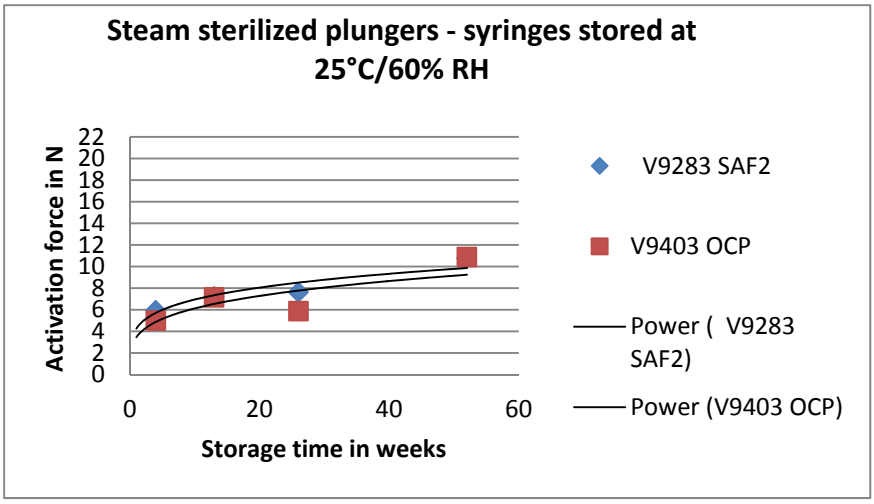


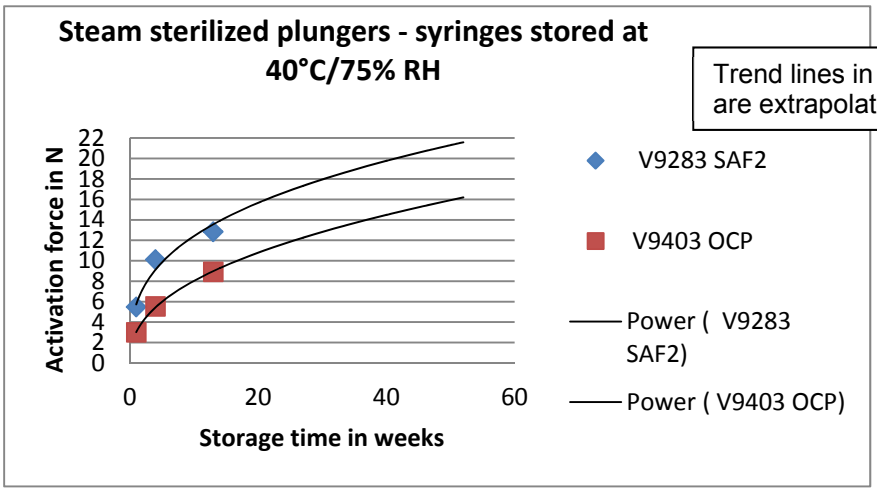




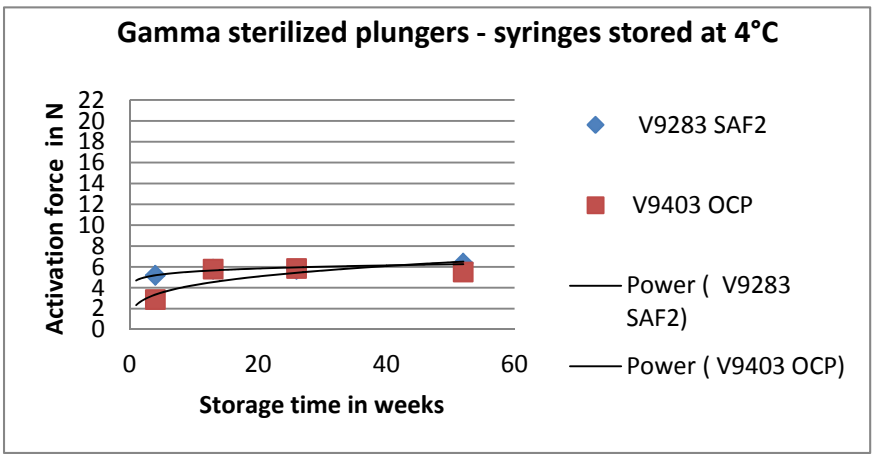
Trend lines in graph 40 °C/75 % RH are extrapolated

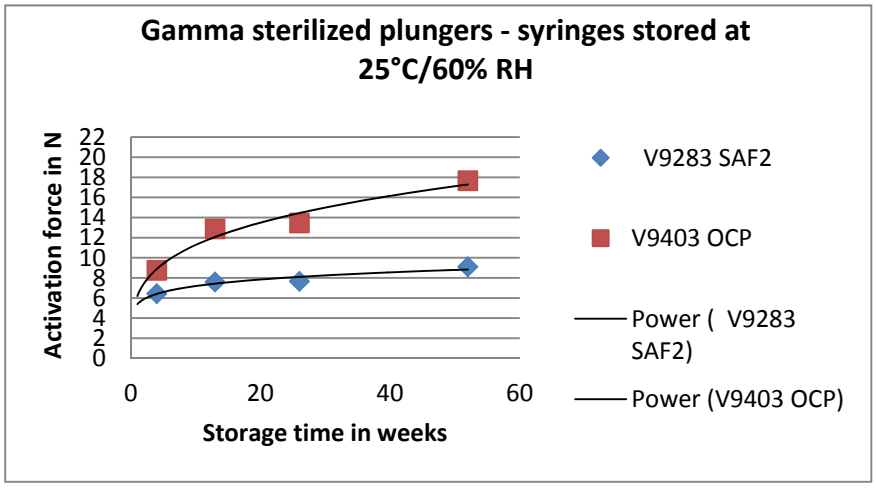


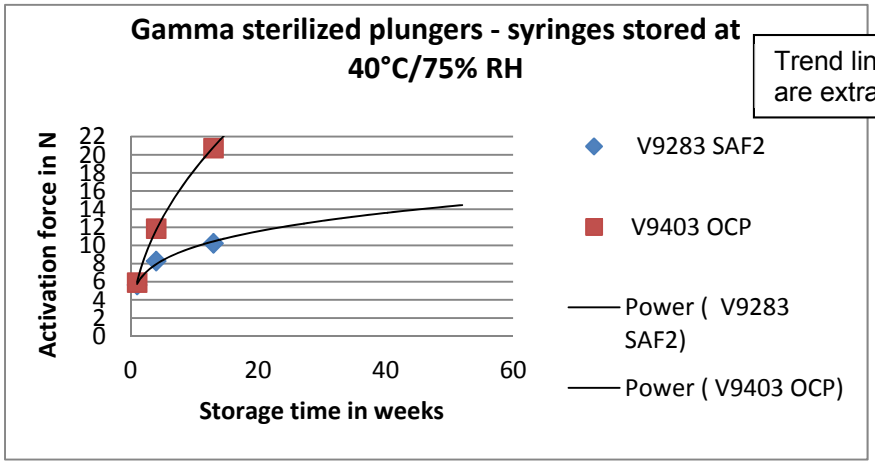




Trend lines in graph 40 °C/75 % RH are extrapolated



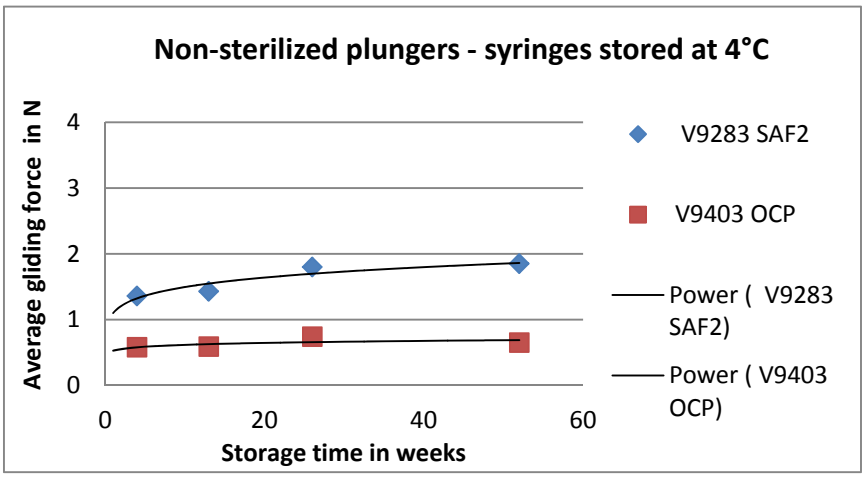


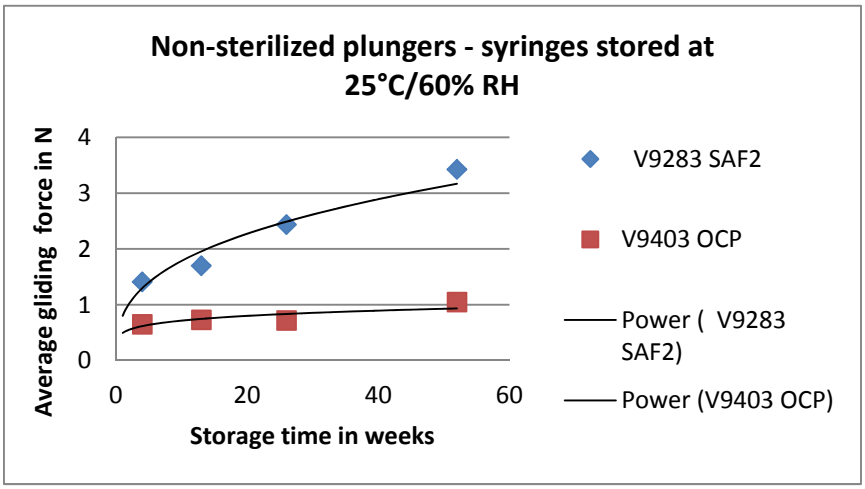


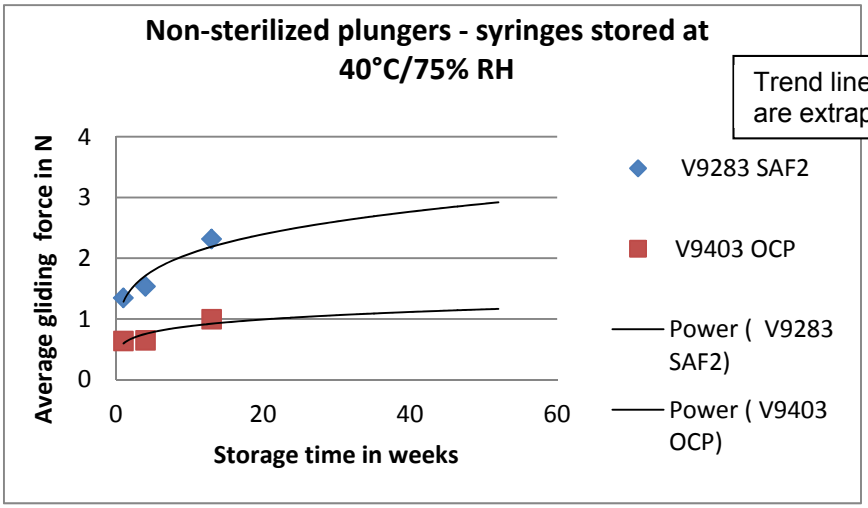
Trend lines in graph 40 °C/75 % RH are extrapolated

Unlike steam sterilization, gamma sterilization at 25 kGy causes an increase in activation force for syringes with 1 ml long OCP plungers when these syringes are stored at room temperature and higher. At 4 °C no such increase in comparison with uncoated plungers is being observed.

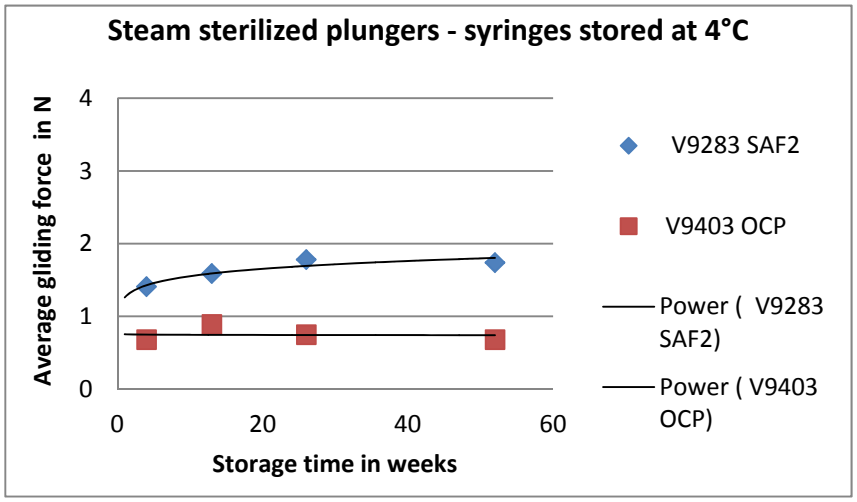
6.2.1.3 Gliding force

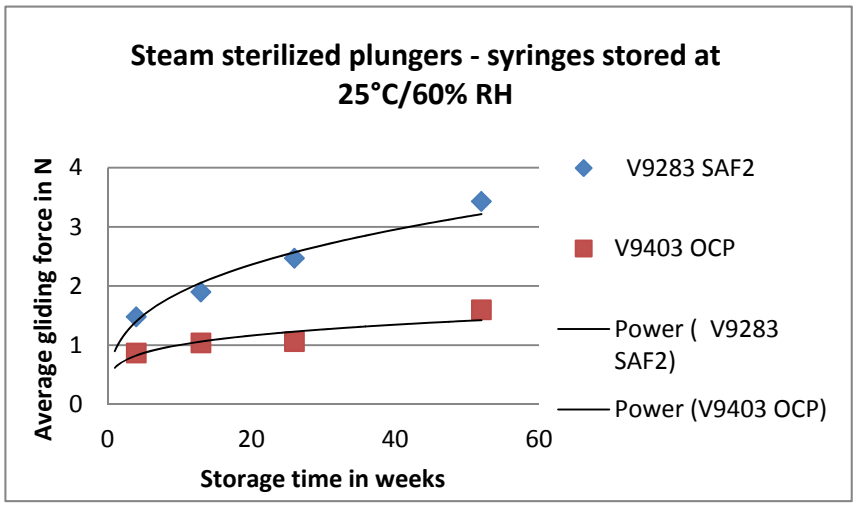


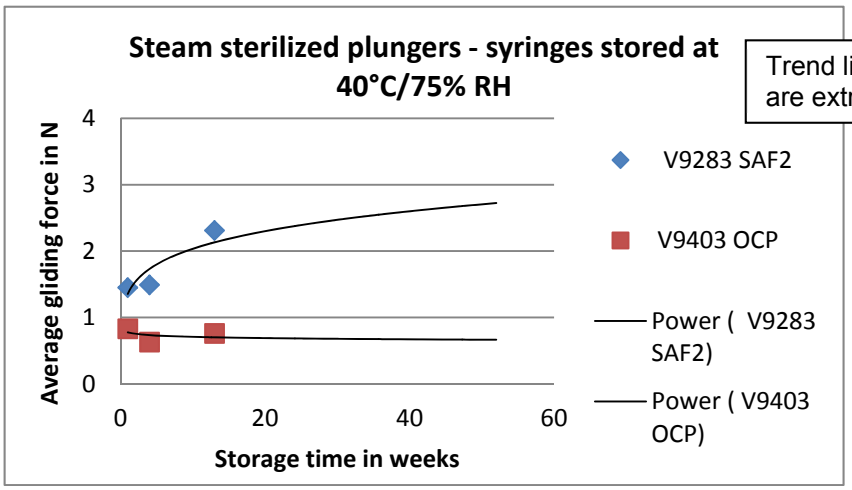




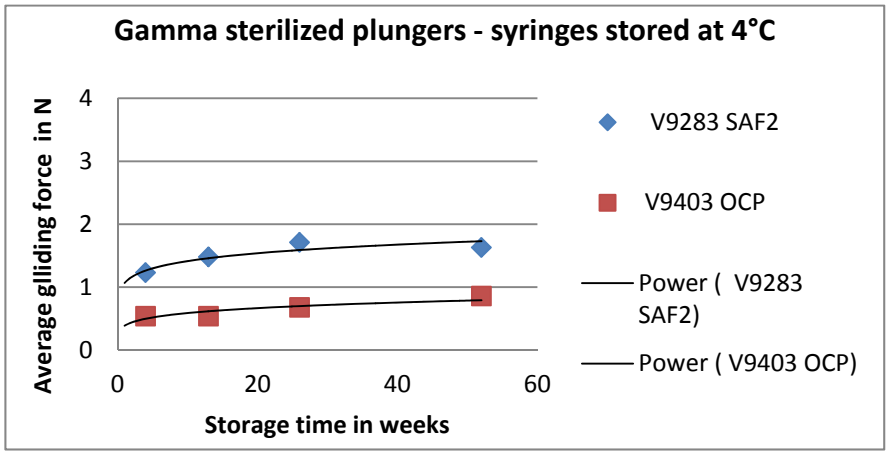
Trend lines in graph 40 °C/75 % RH are extrapolated

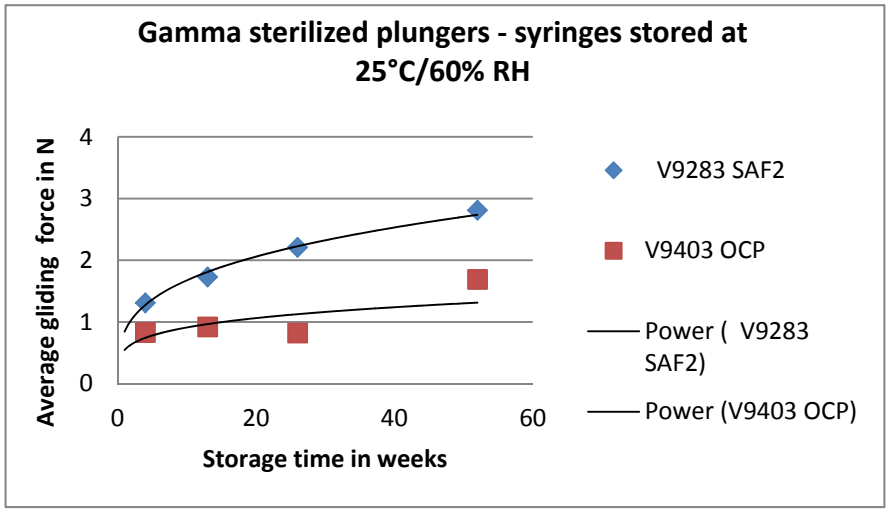


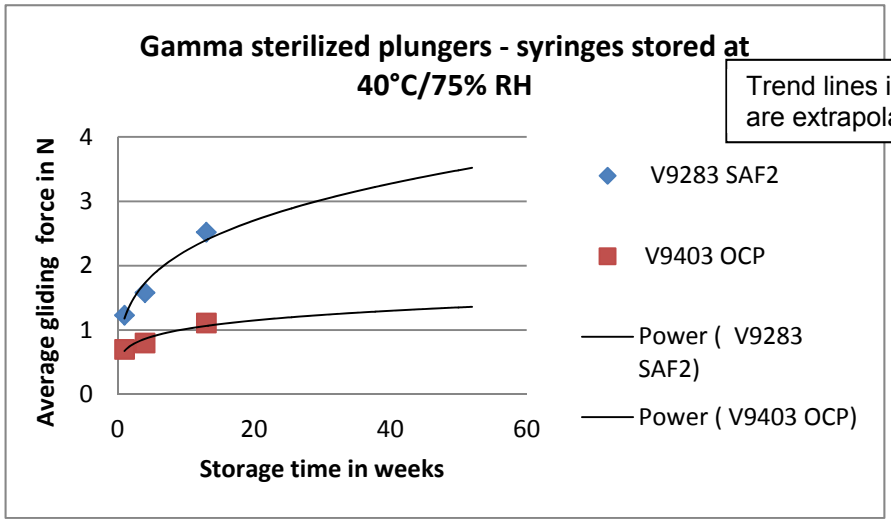




Trend lines in graph 40 °C/75 % RH are extrapolated







Trend lines in graph 40 °C/75 % RH are extrapolated

There is only a very weak effect of the sterilization mode of the plungers and of the storage time of the syringe on gliding forces in syringes with 1 ml long OCP plungers.
In this study gliding forces for syringes with OCP plungers were always lower than gliding forces for syringes with uncoated siliconized plungers.

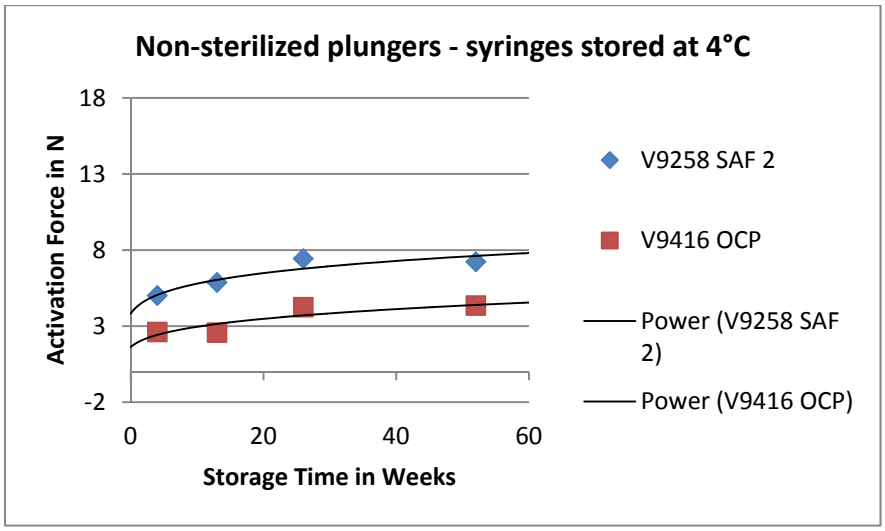
6.2.2. Gliding behavior 1 – 3 ml long OCP

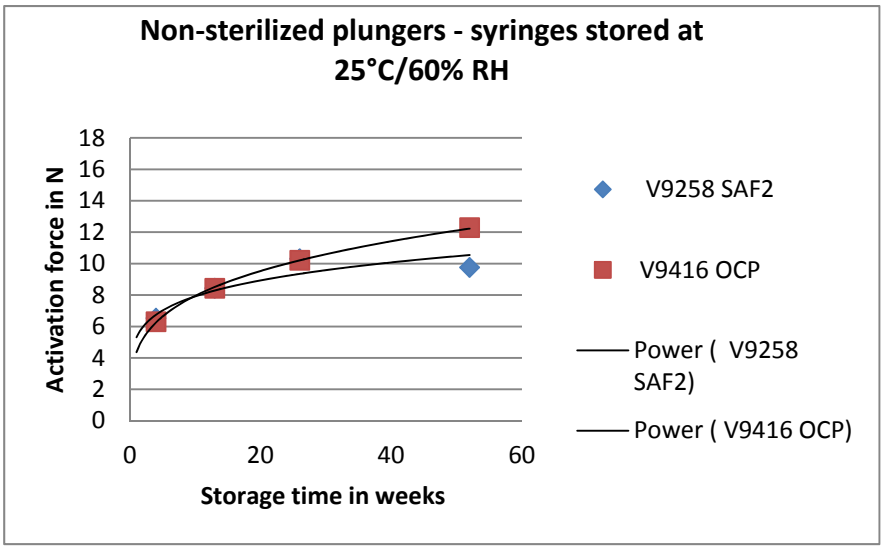
In this section the gliding behavior of 1-3 ml OCP (V9416) is compared with the gliding behavior of uncoated siliconized 1-3 ml long plungers according to the ISO 11040-5 design (V9258). Again, to the latter plungers a standard siliconization degree SAF2 was applied. The effect of the mode of bulk sterilization and the effect of long term syringe storage temperature is studied as well.

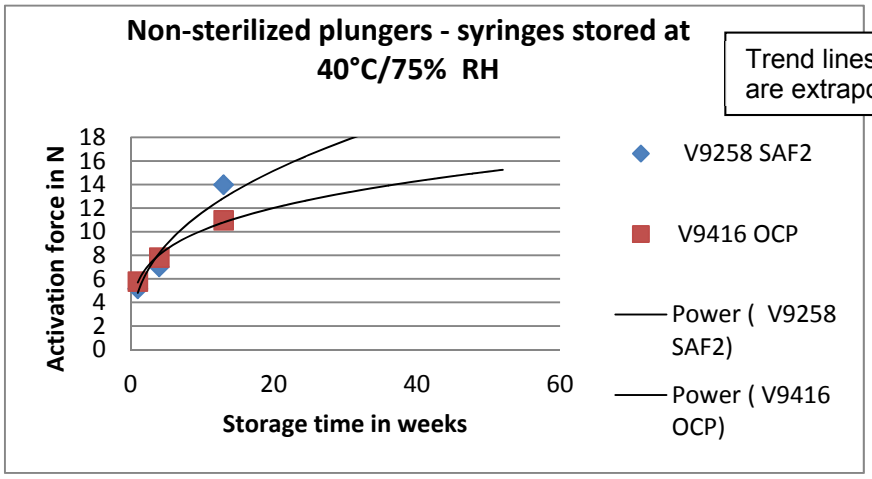
The same bulk sterilization conditions as in the previous section on 1 ml long plungers, as well as the same filled syringe storage conditions were applied.
Syringes used in the investigation were industrially manufactured 1-3 ml staked needle syringes.

6.2.2.1. Activation force

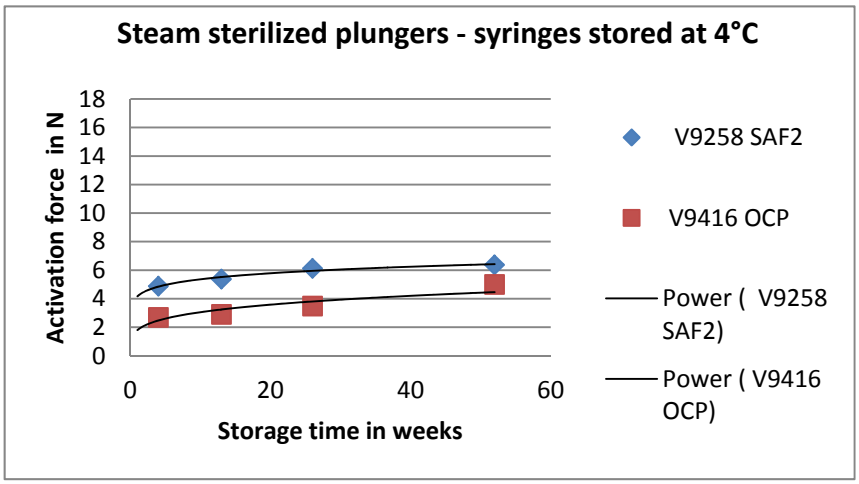
Activation forces in all of the graphs in this section are the average of 10 samples measured.

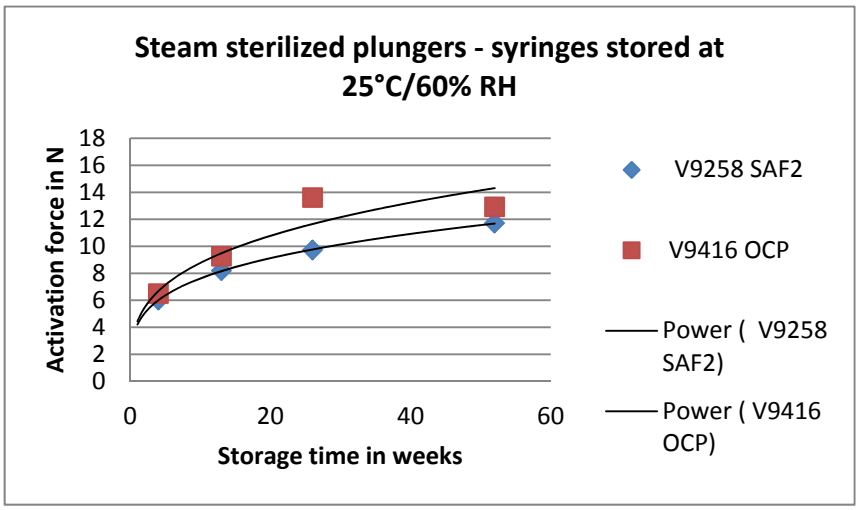


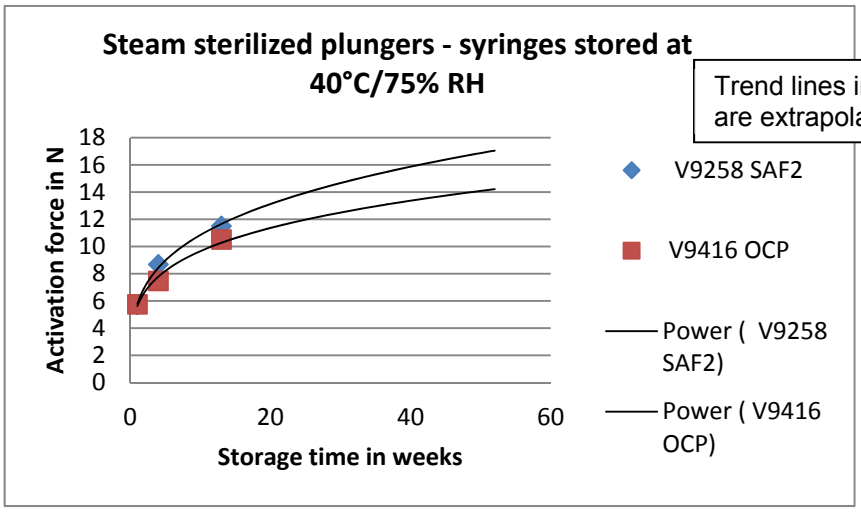




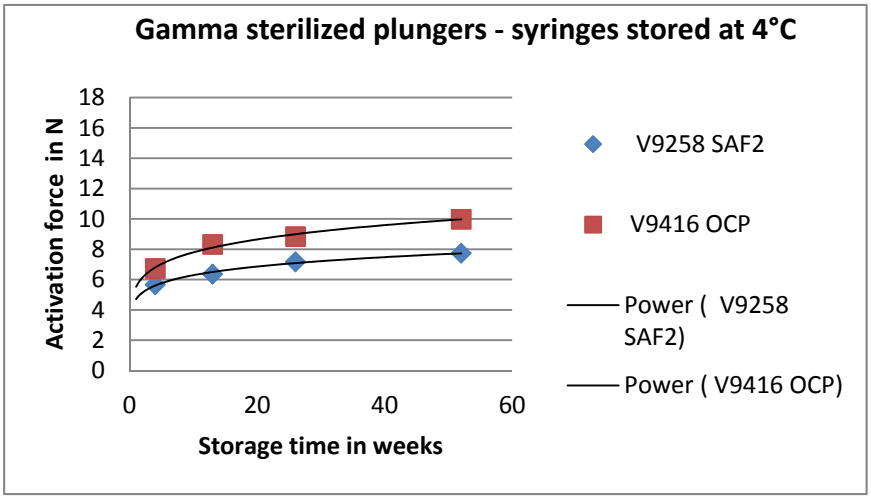
Trend lines in graph 40 °C/75 % RH are extrapolated

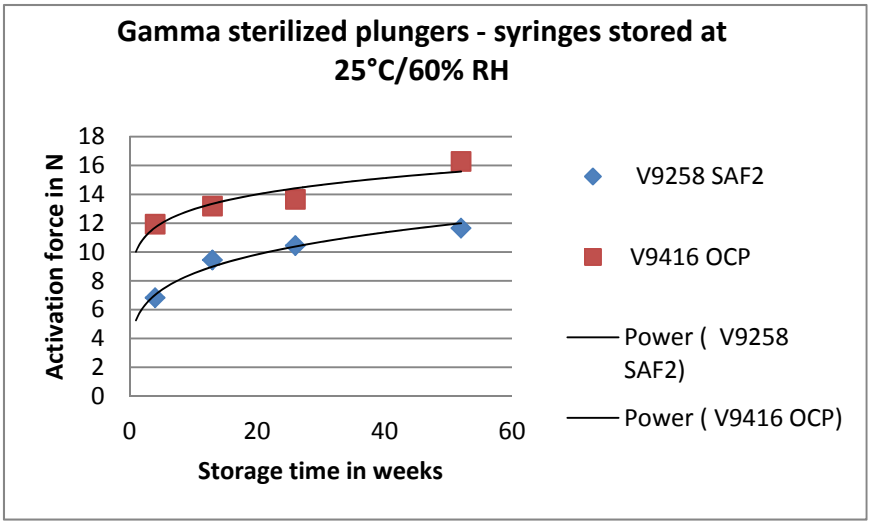


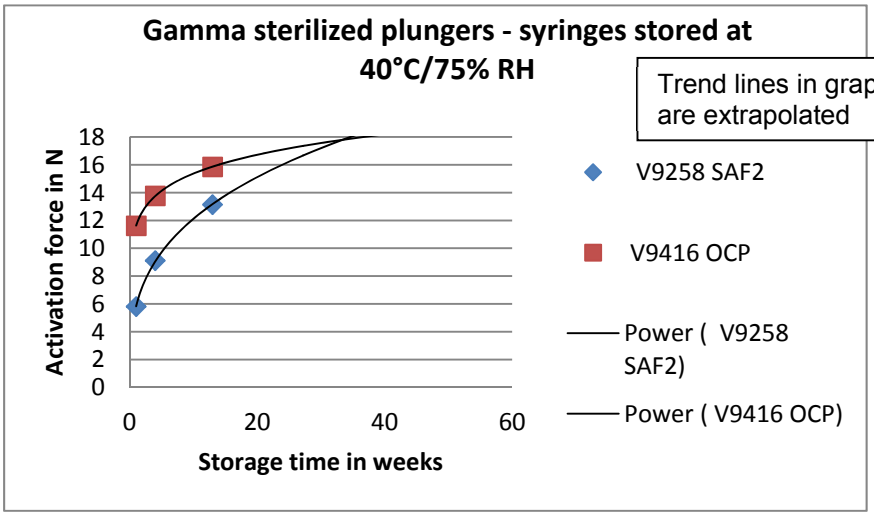




Trend lines in graph 40 °C/75 % RH are extrapolated





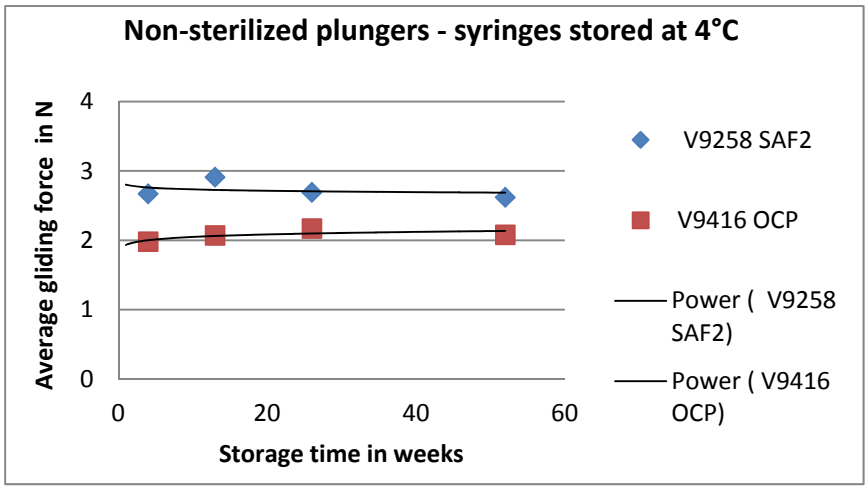


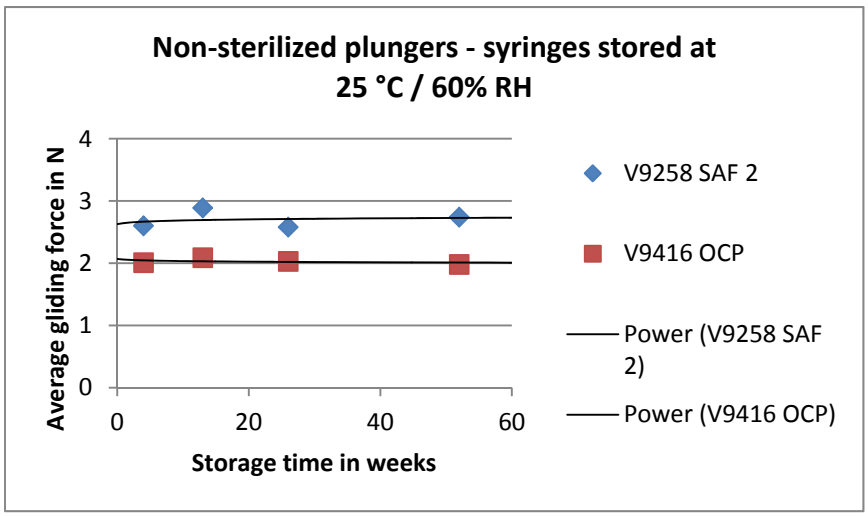
Trend lines in graph 40 °C/75 % RH are extrapolated

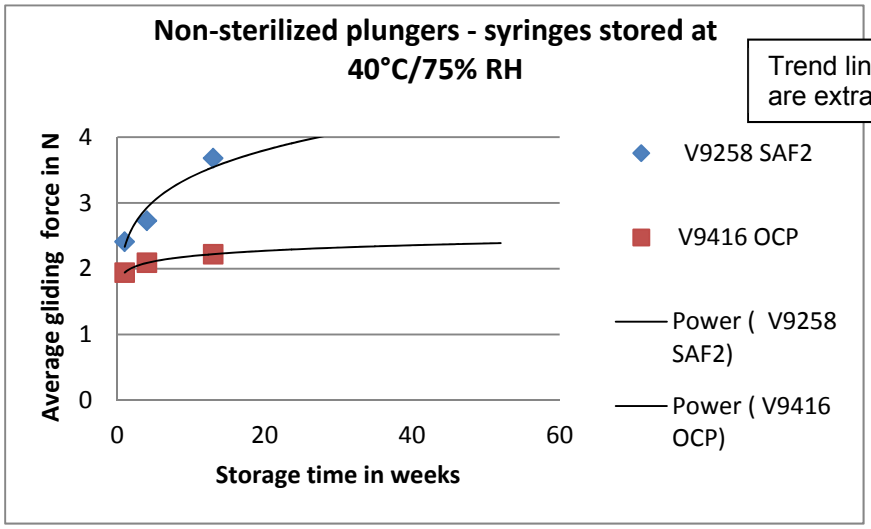
Unlike steam sterilization, gamma sterilization at 25 kGy causes an increase in activation force for syringes with 1-3 ml OCP plungers when these syringes are stored at room temperature and higher. At 4 °C the increase in comparison with uncoated plungers is more moderate.

6.2.2.2. Gliding force

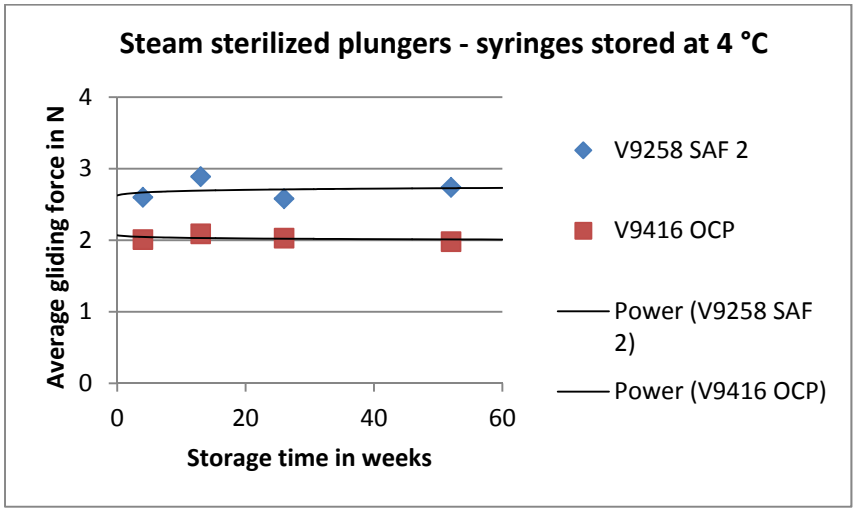
Gliding forces in all of the graphs in this section are the average of 10 samples measured.

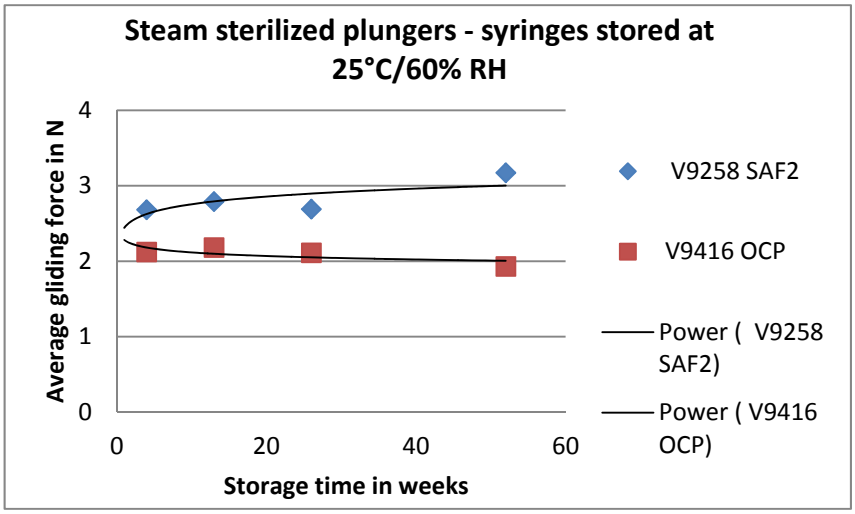


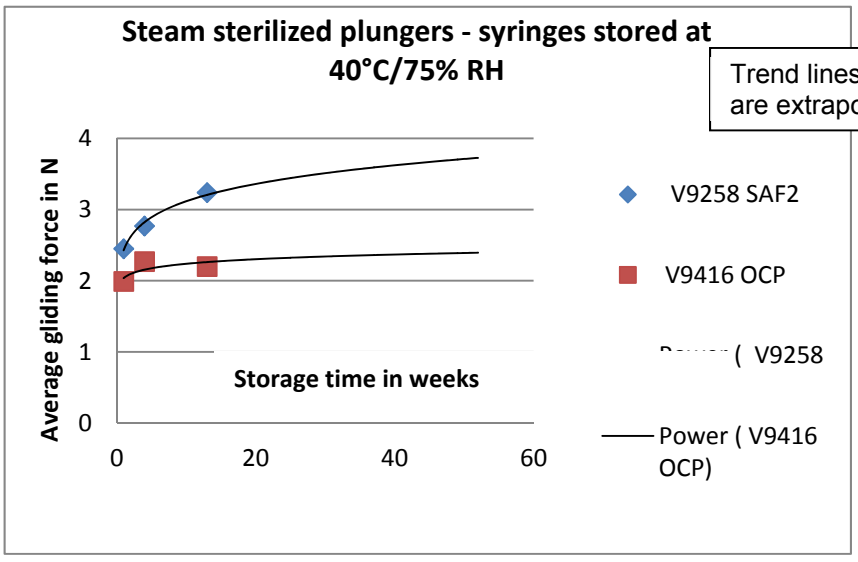




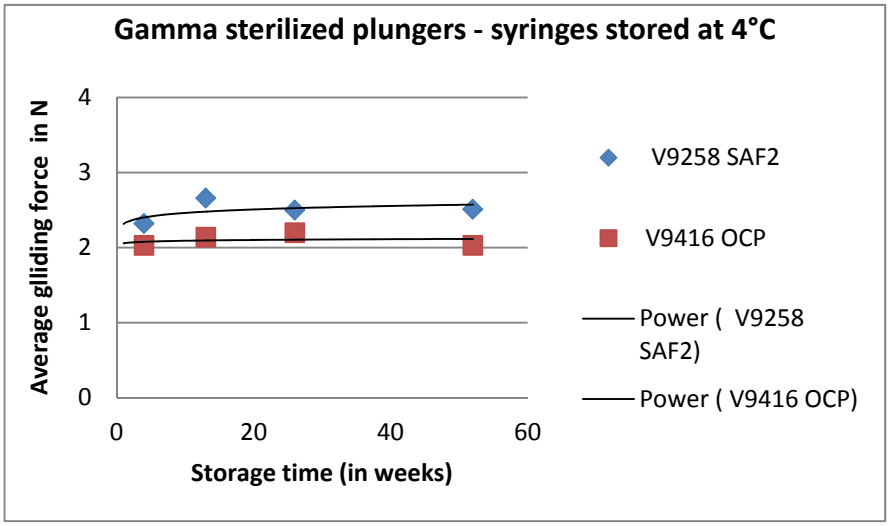
Trend lines in graph 40 °C/75 % RH are extrapolated

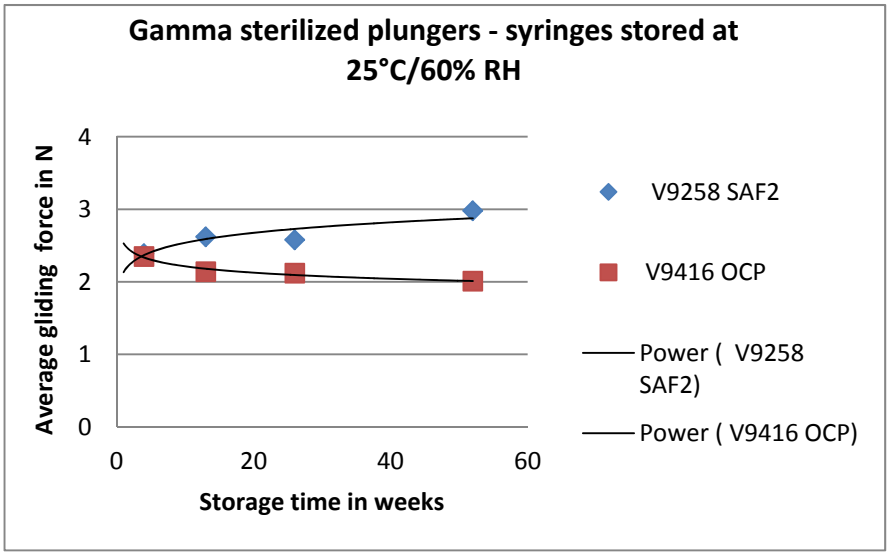


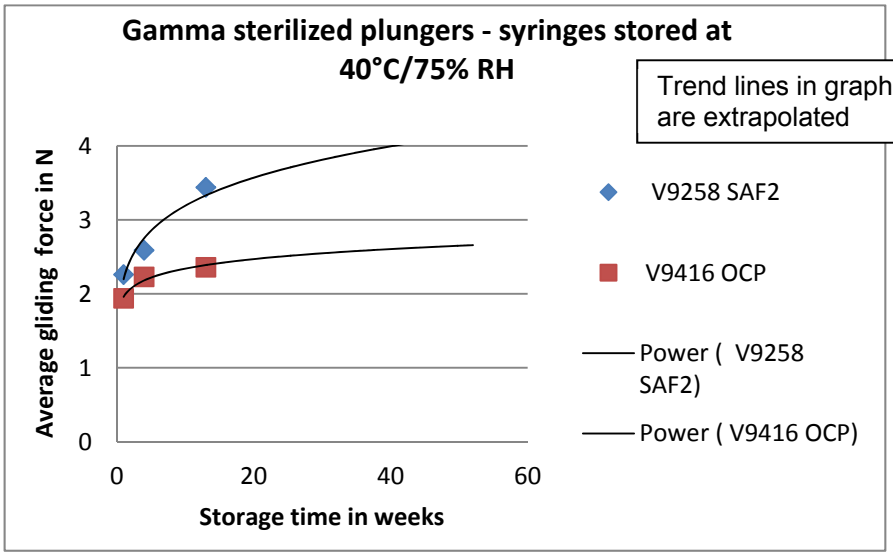




Trend lines in graph 40 °C/75 % RH are extrapolated







There is only a very weak effect of the sterilization mode of the plungers and of syringe storage time on gliding forces in syringes with 1-3 ml OCP plungers.
In this study gliding forces for syringes with OCP plungers were always lower than gliding forces for syringes with uncoated siliconized plungers

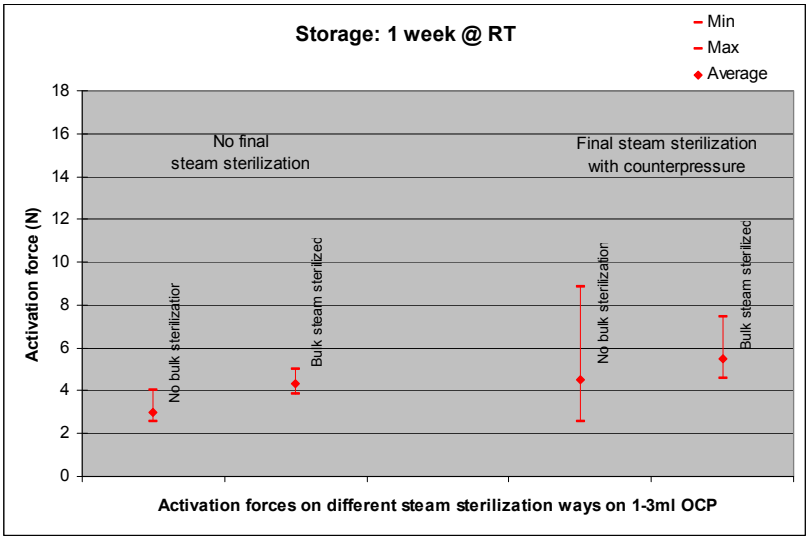
6.2.3. Terminal steam sterilization of assembled plungers

For less sensitive products like diluents, an alternative to aseptic filling is a final steam sterilization of the filled syringe. For such applications typically uncoated siliconized plungers are selected, since they are considered to be sufficient for the intended application.

For applications where coated plungers are more likely to be used, such as for instance for biotech products, a terminal steam sterilization of the filled syringe is unlikely, because of the thermal sensitivity of the drug. OCP is also not recommended for use in combination with such final steam sterilization in case lowest activation forces are required. Activation forces and specifically the variation in those activation forces increase as a result of such treatment. A similar increase in gliding forces and in their variation as a result of final steam sterilization has not been observed.

The effect on activation force of steam sterilization on bulk and assembled products can be seen in the figure below.

Figure : Activation forces after different steam sterilization ways for the 1-3ml OCP



6.2.4. Influence of barrel type

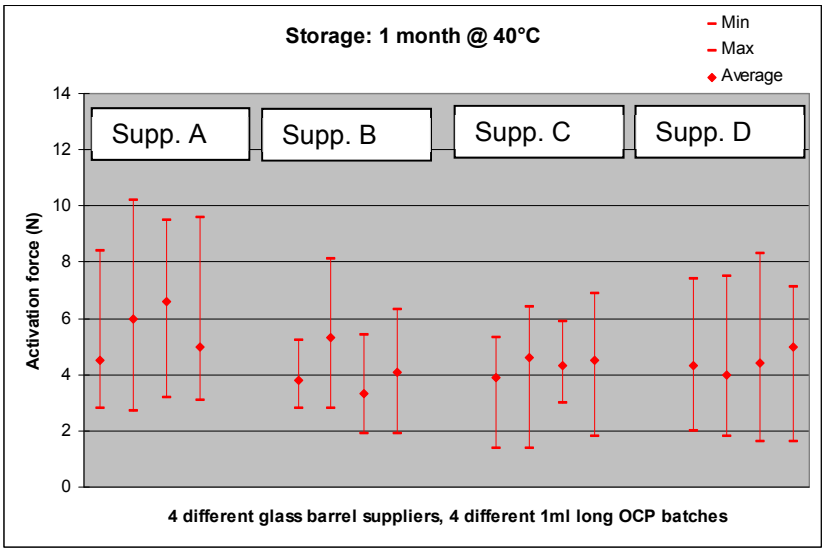
To understand the influence of different glass syringe brands, empty glass barrels were obtained from 4 different suppliers worldwide.

Activation forces, gliding curves and barrel inner diameters were investigated for 4 different 1ml long OCP batches.

Table : Inner diameter measurement on glass barrels from 4 different suppliers

Inner diameter glass barrel (in mm)	Supplier A (n=10)	Supplier B (n=10)	Supplier C (n=10)	Supplier D (n=10)
Min.	6.32	6.32	6.31	6.34
Average	**6.34**	**6.37**	**6.35**	**6.38**
Max.	6.37	6.40	6.38	6.42

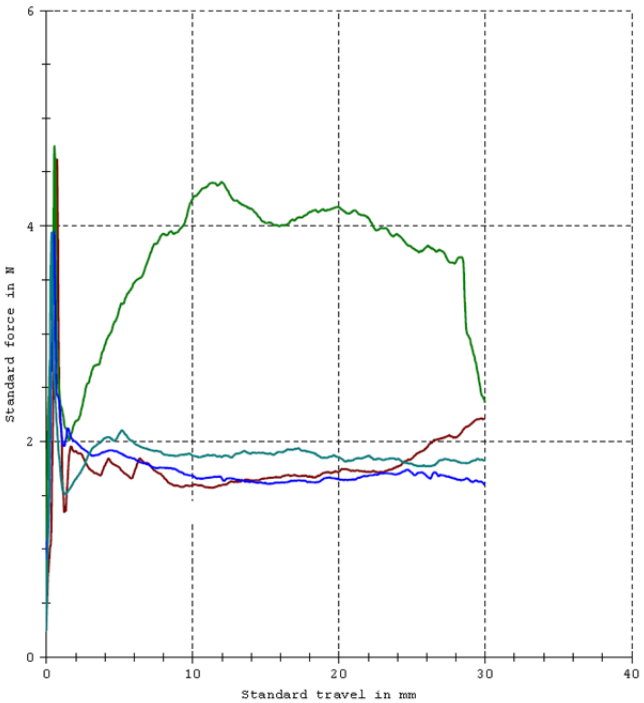
Figure : Activation forces for the different glass barrel suppliers



The origin of the glass barrel has a rather low influence on the activation force measured. Forces for barrels from supplier A are somewhat higher. This may be related to the smaller inner diameter measured for these barrels.

Testing on 1-3ml OCP plungers was not performed. A similar low influence on the activation forces can be expected.

Figure : Gliding curves of 4 different 1ml long glass barrels



The gliding force for supplier D (upper graph; dark green) is on average 2 times higher than for the others. This may be linked to insufficient or different siliconization of the inner glass barrel.

6.3. Plunger Barrel Seal Integrity (PBSI)

6.3.1. Methods

6.3.1.1. Sample preparation

Barrels are filled with a methylene blue dye solution. The plunger is positioned in the barrel by means of a positioning tube. The filled barrel is autoclaved at 121°C during 30 minutes in the lab autoclave. After autoclavation, the syringes are further stored at room temperature or at 40°C.
At t=0, the plunger is visually inspected for leaks past the first seal.

6.3.1.2. Method 1: Compression acc. to ISO 7886-1 Annex D

The plunger of an assembled syringe is moved to expel air from the barrel. The syringe nozzle is then sealed. The syringe is placed on a tensile bench. An axial force is applied to the syringe and a pressure of 300 kPa is generated by the relative action of the piston and the barrel. The axial force is maintained for 30s.

After the test, the tested syringes are visually inspected for leaks past the first seal of the plunger. The test is successful when no dye fluid has passed the first seal (= seal closest to the fluid in the barrel) of the plunger.

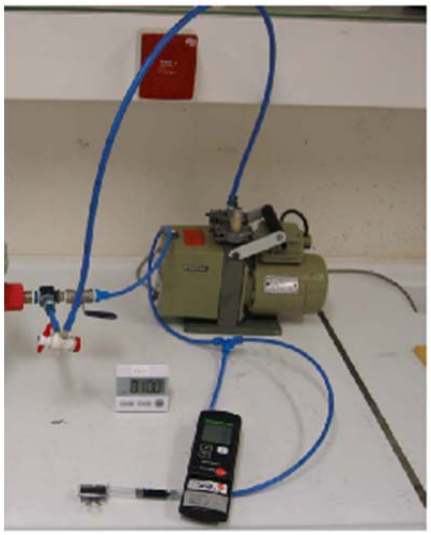
Figure : ISO 7886-1 Annex D compression test set up

6.3.1.3. Method 2: Aspiration according to ISO 7886-1 Annex B

This test equipment is set up so that it can produce a vacuum inside the syringe. A clamp blocks the syringe rod so that it cannot move. The vacuum inside the syringe will cause a tendency to suck in ambient air into the syringe when the plunger has bad sealing properties. This will be made visible by a loss of vacuum and bubble forming inside the barrel.
The vacuum pump is activated until a manometer reading of 88 kPa (880mbar) below ambient atmospheric pressure is reached. The syringe and manometer assembly is isolated by means of a vacuum-tight valve for

60 s. The beginning and end pressure is noted down. The syringe is examined for leakage of air past the plunger during this period.
After 60s the assembly is aerated. No significant drop in vacuum is allowed (maximum 20mbar).

Figure : ISO 7886-1 Annex B aspiration test set up



6.3.1.4. Method 3: Container closure integrity (dye ingress study)

In this case, the syringes are filled with plain water but are submerged in a methylene blue solution. The whole is placed under an atmosphere at 300mbar below ambient atmospheric pressure for 16 hours.
After 16 hours, the syringes are put back at ambient atmospheric pressure and left to stand for 30 minutes.
After 30 minutes, the syringes are rinsed with water and inspected for leakage past the seals.
No leakage should be observed.

6.3.2. PBSI Results

6.3.2.1. PBSI results for the 1ml long OCP design

The plunger barrel seal integrity tests performed after one month storage at 40°C show that all tested products meet the criteria of the 3 tests: no leakage could be detected in any of the tested OCP samples.

Table : PBSI results for 1ml long OCP

V9403 OCP	PBSI after 1 month @ 40°C # of leaks		
	Method 1 (n=10)	Method 2 (n=10)	Method 3 (n=20)
CH803001	0/10	0/10	0/20
CH803002	0/10	0/10	0/20
CH803003	0/10	0/10	0/20
CH743001	0/10	0/10	0/20

Variants of Method 1 were applied to products from another batch of V9403 OCP (batch 30245195).

The variation consisted of the following :

1. barrels were filled with a solution containing 0.1 % (m/v) methylene blue + 0.1 % polysorbate (Tween 80) + 5 % Bovine Serum Albumin (BSA) in WFI

2. barrels were filled with a solution containing 0.1 % (m/v) methylene blue + 1 % polysorbate (Tween 80) in WFI

3. barrels were filled with a solution containing 0.1 % (m/v) methylene blue (control)

Polysorbate is often used as an excipient in protein formulations where it acts as a surfactant. Proteins themselves, such as BSA, equally may have a tensio-active character.
The goal of this study thus was to investigate the influence of surfactants on the PBSI behavior of V9403, 1 ml long OCP.

75 barrels of each type were filled. Each time 25 barrels were stored

- At 2-8 °C / 1 week
- At 25 °C / 75 % RH (relative humidity) / 1 week
- At 40 °C / 75 % RH / 1 week

After storage the barrels were subject to the pressure conditions of Method 1. No leakage was found in any of the tested barrels.

Table : PBSI results for 1 ml long OCP (with polysorbate/BSA dye solution)

OCP batch 30245195	Stored 1 week		
Filled with aq. soln.	2 – 8 °C	25 °C / 75 % RH	40 °C / 75 % RH
MB + PS + BSA	0 / 75	0 / 75	0 / 75
MB + PS	0 / 75	0 / 75	0 / 75
MB	0 / 75	0 / 75	0 / 75

MB = methylene blue ; PS = polysorbate ; BSA = Bovine Serum Albumin

6.3.2.2. PBSI results for the 1-3ml OCP design

The plunger barrel seal integrity tests performed after one week storage at 40°C show that all tested products meet the criteria of the 2 test methods used: no leakage could be detected in any of the tested OCP samples.

Table : PBSI results for 1-3ml OCP

V9416 OCP	PBSI after 1 week @ 40°C # of leaks	
	Method 1 (n=25)	Method 3 (n=25)
30191085	0/25	0/25
30194008	0/25	0/25
30194009	0/24*	0/24*

** One syringe showed leakage prior to testing, most probably caused by a fiber between the plunger and the barrel.*

Note: no testing according to Method 2 was performed for 1-3 ml.

6.3.3. Effect of bulk sterilization mode of OCP plungers on PBSI

- Steam sterilization:
  Plungers were bulk steam sterilized at 121°C during 30 minutes, and then dried overnight at 70°C.

- Gamma sterilization:
  Plungers were bulk gamma irradiated (Cobalt-60) with an irradiation dose of 25 kGy.

The barrels were filled with water and the plungers positioned by means of a positioning tube. Similar to other test work in this chapter, these products received an additional final steam sterilization step in assembled form. The filled barrels were autoclaved at 121°C during 30 minutes in the lab autoclave.
After steam sterilization, the barrels were further stored at 40°C.

Table : PBSI results using bulk sterilized products, 1 week at 40°C

1ml long plunger OCP	PBSI after 1 week @ 40°C # of leaks		
	Method 1 (n=5)	Method 2 (n=5)	Method 3 (n=20)
Steam	0/5	0/5	0/20
Gamma	0/5	0/5	0/20
EtO	0/5	0/5	0/20

Table : PBSI results using bulk sterilized products, 1 month at 40°C

1ml long plunger OCP	PBSI after 1 month @ 40°C # of leaks		
	Method 1 (n=5)	Method 2 (n=5)	Method 3 (n=20)
Steam	0/5	0/5	0/20
Gamma	0/5	0/5	0/20
EtO	0/5	0/5	0/20

Bulk sterilization does not show any influence on the plunger barrel seal integrity.

6.4. Minimum and maximum interference situations

Designs for both the rubber plunger and the glass barrel are defined in ISO 11040-4 and ISO 11040-5, including dimensional tolerances. Specifically the diameter may have an effect on the functionality of the system.

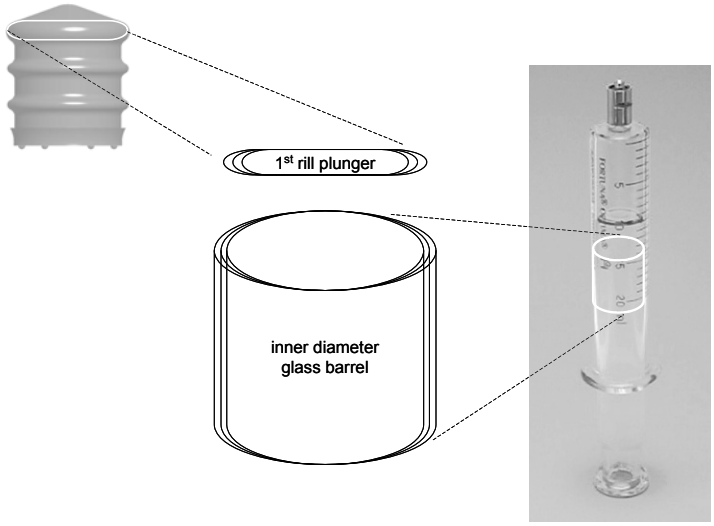
1ml long:
The 1ml long plunger uncoated (V9403 – see attachments) has for the first rill a dimension of 6.70±0.10mm. Bearing in mind the coating thickness of 20µm, this dimension in coated version is 6.74±0.10mm.

A glass syringe barrel for 1ml long for the inner diameter typically has 6.35±0.10mm (cfr. ISO11040-4).

1-3ml:
The 1ml long plunger uncoated (V9416 – see attachments) has for the first rill a dimension of 9.20±0.10mm. Bearing in mind the coating thickness of 20µm, this dimension in coated version is 9.24±0.10mm.

A glass syringe barrel for 1-3ml for the inner diameter typically has 8.65±0.20mm (cfr. ISO11040-4). However, in practice and confirmed by industry specialists, a tolerance as found on the market of ±0.10mm is more realistic. Therefore, testing is done considering an inner glass barrel diameter of 8.65±0.10mm.

Figure : Diameter tolerances for both rubber plunger and glass barrel



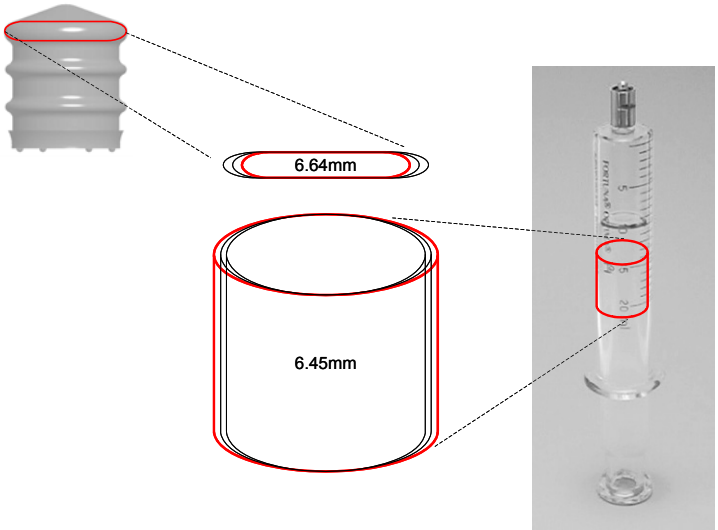
2 extreme situations are theoretically possible:

- Minimum interference situation (plunger stopper at minimum with a glass barrel at maximum tolerance) where PBSI may be endangered;
- Maximum interference situation (plunger stopper at maximum with a glass barrel at the minimum tolerance) where the activation and gliding force may be endangered.

6.4.1. Minimum interference situation

6.4.1.1. PBSI at minimum interference for 1ml long

Figure : Minimum interference situation between rubber plunger and glass barrel (picture example is for 1ml long)



In this situation there is an overlap or interference of 0.19mm between rubber and glass. To obtain the 0.19mm interference, a special mould P8550C (see attachment) that generated rubber parts at the desired diameter was made. These parts were used in combination with nominal glass barrels.

All plungers and barrel diameters were individually measured and 50 combinations were made with interference 0.19mm (0.18 and 0.17mm still accepted).

All 50 combinations were assembled and tested according to Method 1 and Method 3, already described under paragraph 6.3.1.

All tested samples at minimum interference show no leakage in the seal integrity test and the compression leak test.
Minimum plunger-barrel interference indicates that there are no problems with plunger-barrel seal integrity.

Table : PBSI results for the minimum interference situation, 1ml long

	P8550C OCP 1st rill diameter: measured: 6.50-6.51-6.52-6.63-6.54-6.55-6.56mm	Method 1 # with leaks	Method 3 # with leaks
Glass barrel inner diameter: measured: 6.31-6.32-6.33-6.34-6.35-6.36-6.37mm	Matrix of 50 combinations made with interference between 0.17-0.19mm	0/50	0/50

6.4.1.2. PBSI at minimum interference for 1-3ml

A similar reasoning as for the 1ml long (see 6.4.1.1) can be made for the 1-3ml where in a worst-case scenario the minimum interference or overlap is 0.39mm (plunger: 9.14mm – barrel: 8.75mm).

A special design, P8562F (see attachment), was made with a diameter resulting in an interference of 0.39mm when using glass barrels with nominal diameter.

Only Method 1 was chosen for the test work, however in this case Method 1 was completed by the same test including each time a manipulation of the push rod (moving the push rod sideways) and by the same test including a manipulation with a smaller non-standard push rod.

All tested samples at minimum interference and at minimum interference with manipulation of the pushrod show no leakage in the compression leak test.
Minimum plunger-barrel interference indicates that there are no problems with plunger-barrel seal integrity.

Table : PBSI results for the minimum interference situation, 1-3ml

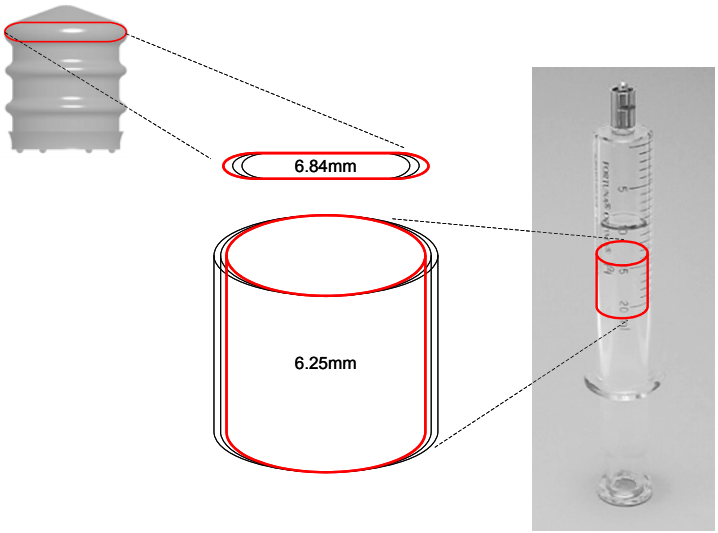
	PBSI after 24h @ 40°C # with leaks		
	Method 1	**Method 1+ manipulation with push rod**	**Method 1 + manipulation with non-standard smaller push rod**
P8562F OCP	0/99*	0/99*	0/99*

* *Note: only 99 from the 100 syringes were taken into account. One syringe showed leakage caused by a fiber between the plunger and the barrel. This is attributed to filling under lab conditions.*

6.4.2. Maximum interference situation

6.4.2.1. Gliding behavior at maximum interference for 1ml long

Figure : Maximum interference situation between rubber plunger and glass barrel (picture example is for 1ml long)



An overlap or interference of 0.59mm is present and this might affect the gliding behavior of assembled syringes.
To mimic this specific overlap, a dedicated mould (P8550A – see attachments) was used to manufacture OCP products that in combination with glass barrels at nominal diameter gave combinations with interference of 0.59mm (0.60 and 0.61mm still accepted).

50 filled (water) syringes with maximal plunger-barrel interference were steam sterilized at 121°C for 30 minutes. After steam sterilization, syringes were stored at 40°C and the activation force was measured after 1-week storage (25 measurements) and after 1-month storage (25 measurements).

Table : Activation force results at maximum interference situation

	P8550A OCP 1st rill diameter: measured: 6.92-6.93-6.94-6.95-6.96mm	Activation force 1 week@ 40°C	Activation force 1 month@ 40°C
Glass barrel inner diameter: measured: 6.33-6.34-6.35-6.36-6.37mm	Matrix of 50 combinations made with interference between 0.59-0.61mm	n=25samples Min.= 3.5N Avg.= 4.9N Max. = 5.7N	n=25samples Min.= 2.4N Avg.= 6.1N Max. = 7.8N

On average, the activation force of 1ml long OCP that are at the maximum interference level is higher when comparing with nominal measured values (see paragraph **Error! Reference source not found.**), but still within an acceptable range.

6.4.2.2. Gliding behavior at maximum interference for 1-3ml

Based on the satisfying results for the 1ml long design, maximum interference testing for the 1-3ml has not been generated.

6.5. Machineability on industrial scale

All test work described in this document is performed on barrels assembled manually by means of an insertion tube and on lab scale.
In the early stage of the OCP development, a small industrial scale run has been performed with success at one of Datwyler's customers.

On the market, two assembly ways are established:

1. by means of an insertion tube;
2. by means of vacuum placement.

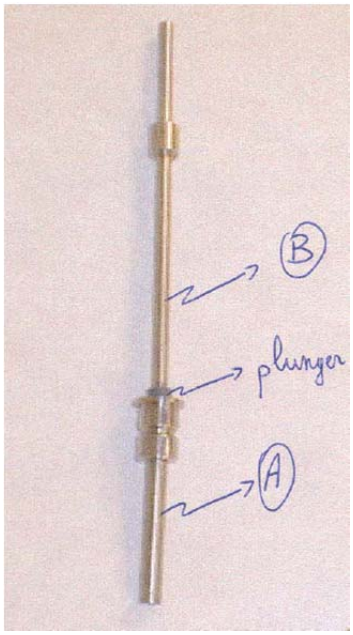
When plungers are assembled in vacuum, the problem of trapped air that pushes back the inserted plunger is avoided. Compression or deformation of the plunger with this method is kept minimal. On this basis vacuum assembly is the recommended method.

The assembly principle with an insertion tube is that the plunger is positioned on top of a positioning tube (A in the figure below) and that a push rod (B in the figure below) compresses the plunger and pushes it through the positioning tube in place. Using this method will compress the coated plunger to a certain extent. The percentage of compression is determined by the plunger diameter and the positioning tube diameter. The latter must be kept as big as possible in diameter to minimize the compression of the plunger.

Caution must be taken in assembling OCP plungers with insertion tubes. Insertion tubes that are used for uncoated siliconized plungers may not be suitable for OCP plungers of the same syringe size. Dimensional and surface treatment modifications of insertion tubes may be necessary to enable machineability.

In rare cases, small wrinkling may be seen on the coating surface. Such small wrinkling however will not adversely affect the barrier properties of the coating.

Figure : Example of a -dismantled- insertion tube with a plunger in the starting position.



B = pushing rod used for plunger insertion

A = insertion tube

Note

In case OCP plungers are sterilized by steam before aseptic filling , caution must be taken that they are sufficiently dried before further processing. With a product in the Omniflex family *other than OCP*, it has been observed on rare occasions that processing of large amounts of coated products, that were insufficiently dried after steam sterilization, lead to deposition on certain parts of the filling line of a material that is related to the coating. Residual moisture for the products in question was determined to be at 0.7 %.
After further drying of products of the same batch, no such objectionable conditions were met anymore.
Based on the similarity between the product in question and OCP, the same caution is indicated for OCP.

7. Biological Properties

7.1. USP <1031>

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

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

7.2. USP <87>

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

7.3. USP <88>

Though the USP<88> can be considered redundant, both the intracutaneous test and the systemic injection test have been performed on OCP samples. Copies of the corresponding reports are included in this section.

7.4. ISO 8871-4

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

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

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

Figure : Elution test (USP<87>) – OCP

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TEST RESULT REPORT

Project Number:	**TE 09894**	**Study Number:**	**09-B2281-N1**
Sponsor:	**Helvoet Pharma Belgium NV**	**Report Date:**	**07/12/2009**
Contact:	*Mrs. Nadia Nouri*		
Address:	Industrieterrein Kolmen 1519 3570 Alken, Belgium	Date Sample Arrival: Technical Initiation:	30/11/2009 01/12/2009
PO.Number:	PB0903864	Technical Completion:	04/12/2009

Study	**Elution Test - ISO**	Temp/Time	37°C/24 hours
Test Item	FM257/2 V9403 OCP 0 kGy t=0	Ratio	25cm²/20mL
Lot	929001	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. 07

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).

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

ir. Peter Cornelis
Study Director

Vanessa Ruymen
Quality Assurance

Figure : Intracutaneous test (USP<88>) (for information only) – OCP

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TEST RESULT CERTIFICATE

Sponsor	Helvoet Pharma	Technical Initiation	05/27/98
Address	Industrieterrein Kolmen 1 3570 Alken, Belgium	Technical Completion	05/30/98
Contact	Mrs. Anita Thijs	Report Date	06/04/98
P.O. Number	PB 9S01133	Project Number	98-2951

TEST ARTICLE	FM257/2 V9227 "Omniflex for Plungers"	Ratio	4 grams per 20 mL
LOT#	814011	Vehicles	0.9% USP Sodium Chloride for Injection (NaCl), Cottonseed Oil (CSO)
STUDY	Intracutaneous Test - 2 Extracts	Temp/Time	37°C for 24 hours

REFERENCE: USP 23, NF 18, 1995.

GENERAL PROCEDURE: The Intracutaneous Test is designed to evaluate local responses to the extracts of test articles, following intracutaneous injection into rabbits. 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 are rated on a numerical scale for the test article and control extracts. The injection sites on each animal were observed for signs of erythema and edema 24, 48, and 72 hours after injection of the test article. Observations were scored according to the Draize Scale for Scoring Skin Reactions. Observations conducted also included all clinical signs.
All average erythema and edema scores for the test and control sites at 24, 48 and 72 hours were tested separately and divided by 12 (2 animals x 3 scoring periods x 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 average for the test article is not significantly greater than that for the control.

RESULTS: The test sites injected with the test article extract did not exhibit any signs of erythema, edema or necrosis through the seventy-two hour observation point. These test sites were compared to the control sites with scores of 0 for all observation points. There was no difference in reaction to the test article compared to that observed for the control sites.

CONCLUSION: The test article meets the requirements of USP 23, NF 18, 1995 for the Intracutaneous Test using extracts prepared with 0.9% USP Sodium Chloride for Injection, and Cottonseed Oil.

AUTHORIZED PERSONNEL:

Laurence Lister, B.S
Study Director

Vinita Amin, A.S.
Quality Assurance

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(781) 275-3330

Figure : Systemic injection test (USP<88>) (for information only) - OCP

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TEST RESULT CERTIFICATE

Sponsor	Helvoet Pharma	Technical Initiation	05/27/98
Address	Industrieterrein Kolmen 3570 Alken, Belgium	Technical Completion	05/30/98
Contact	Mrs. Anita Thijs	Report Date	06/04/98
P.O. Number	PB9801133	Project Number	98-2950

TEST ARTICLE	FM257/2 V9227 "Omniflex for Plungers"	Ratio	4 grams per 20 mL
LOT#	814011	Vehicles	0.9% USP Sodium Chloride for Injection USP (NaCl), Cottonseed Oil (CSO)
STUDY	Systemic Injection Study (2 Extracts)	Temp/Time	37°C for 24 hours

REFERENCE: USP 23, NF18, 1995, Pp. 1699-1702

GENERAL PROCEDURE: The test article was extracted at a ratio of 4 grams per 20 mL extraction vehicle, (0.9% NaCl, and CSO), at 37°C for 24 hours. The test article extracts and corresponding blanks were injected systemically in mice. The injections were in the amounts and routes set forth by USP 23. Signs of biological reactivity were observed for up to 72 hours post treatment.

RESULTS: None of the animals injected with the test article extracts or the control article 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 USP 23, NF18, 1995 for the Systemic Injection Test.

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8. Moisture content

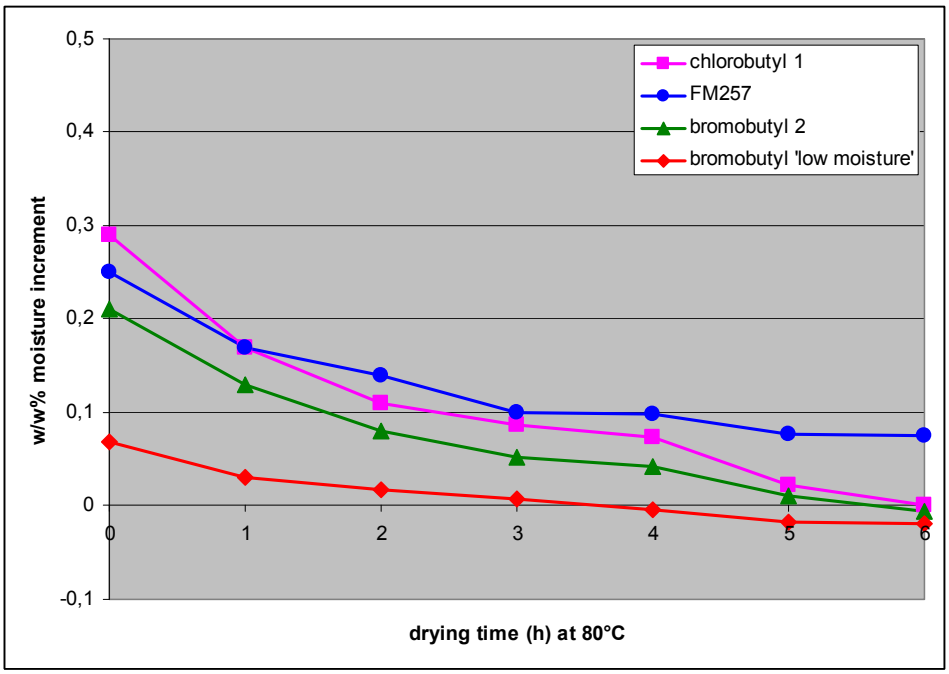
Results given are only indicative as the actual moisture content is dependent on numerous factors like stopper design, packaging way, climate, etc.

The effect of the coating on the moisture uptake/release of the FM257/2 substrate rubber can be considered negligible. Hence, results of FM257/2 are reported here below and they can be used for OCP as well.

Typical moisture content of rubber compound FM257/2 after the final treatment at Datwyler, i.e. after washing, drying and packaging, is around 0.3 w/w% (3 mg water/g rubber)

Additional moisture will be absorbed during a steam sterilization step, going from ~0.3 w/w% for a standard cycle of 30min at 121°C up to ~1 w/w% after 120min at 121°C. The graph below shows the uptake of some standard compounds after steam sterilization and the moisture release upon drying at 80°C.

Figure : Moisture uptake after autoclaving 30min at 121°C and moisture release after drying at 80°C - FM257 substrate



9. OCP formats

Omniflex Coated Plungers are available in the following formats:

1. **Bulk**
   The plungers are washed with a validated washing program (FLCO). After washing and drying they are packed in multiple protective polyethylene bags (non-sterilizable).

2. **Ready-for-Sterilization ('RfS')**
   OCP plungers are FLCO washed and dried. Then they are packed in steam-sterilizable bags (RfS bags) and protective non-sterilizable polyethylene overwrapping. Steam sterilization of the plungers in the RfS bags after removal of the protective overwrapping is performed before syringe filling.

3. **Ready-To-Use ('RTU')**
   OCP plungers are FLCO washed and dried. Then they are packed in multiple multilayer bags that are compatible with gamma irradiation ('RTU bags'). The products are gamma sterilized at a contractor, using a validated irradiation process.
   OCP plungers are equally available in irradiation compatible Rapid Transfer Port bags from Getinge La Calhène.

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

10. Available designs

This edition of the OCP technical documentation is focused on the 1ml long and the 1-3ml plunger design, described in the ISO11040-5. The corresponding Datwyler designs are V9403 respectively V9416 and can be found under the drawing attachments.

Next editions may come with additional designs like the standard 0.5ml plunger.

More specific designs and customer owned designs may be manufactured as OCP. Feasibility and subsequent validation studies must be performed case by case. In that case, please contact your Datwyler sales representative.

11. References

1. *ISO 37 "Rubber, vulcanised or thermoplastic - Determination of tensile stress-strain properties"*
2. *ISO 815 "Rubber vulcanised or thermoplastic - Determination of compression set at ambient, elevated or low temperatures"*
3. *ISO 2230 "Rubber Products – Guideline for storage"*
4. *ISO 2781 "Rubber, vulcanised or thermoplastic – Determination of density"*
5. *ISO 7619 "Rubber, vulcanised or thermoplastic – Determination of indentation hardness Part 1 : Durometer method (Shore hardness)"*
6. *ISO 8871-1 "Elastomeric Parts for Parenterals and for devices for Pharmaceutical Use"*
7. *ISO 11040-4 "Prefilled syringes - Part 4 : Glass barrels for injectables"*
8. *ISO 11040-5 "Prefilled syringes - Part 5 : Plungers for injectables"*
9. *ASTM D3985 - 05 Standard Test Method for Oxygen Gas Transmission Rate Through Plastic Film and Sheeting Using a Coulometric Sensor*
10. *ASTM F1249 - 06 Standard Test Method for Water Vapor Transmission Rate Through Plastic Film and Sheeting Using a Modulated Infrared Sensor*
11. *Pharm.Eur. 5.2.8. "Minimising the risk of transmitting TSE via medicinal products"*
12. *Pharm.Eur. 3.2.9. "Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders."*
13. *USP <381> "Elastomeric Closures for Injection"*
14. *USP <87> "Biological Reactivity Tests, in Vitro"*
15. *USP <88> "Biological Reactivity Tests, in Vivo"*
16. *Pharm. Jap. 7.03 "Test for Rubber Closures for Aqueous Infusions"*
17. *European Directive 94/62/EC on Packaging and Packaging Waste*
18. *Coalition of North Eastern Governors (CONEG) Heavy Metals Legislation*
19. *Compound data sheet FM257/2, dated 02 January 2002*
20. *Datwyler R&D report R0262*
21. *Datwyler R&D report R0169*
22. *Datwyler R&D report R0173*
23. *Datwyler R&D report R0164*
24. *Datwyler R&D report R0156*
25. *Datwyler R&D report R0152*
26. *Datwyler R&D report R0140*
27. *Extractables reports OCP (TE09106) and FM257(TE09105)*
28. *Datwyler R&D report R0243*
29. *Datwyler report CS0181 Ed. 1*
30. *Datwyler report CS0112/8 Ed. 1*
31. *Datwyler R&D report R0336*
32. *Datwyler R&D report R0337*

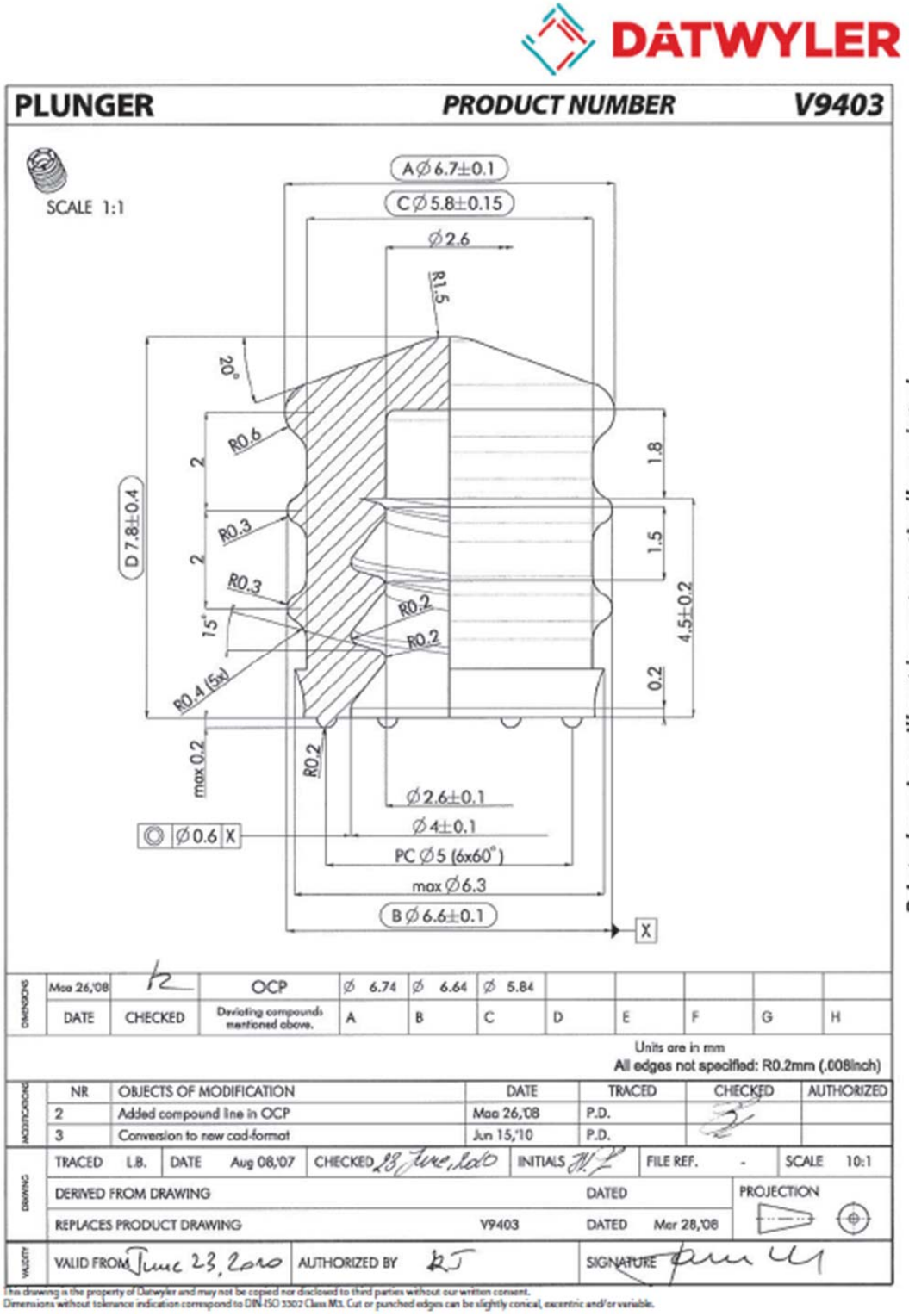
12. History

Edition (Issue Date)	***Change (chapter + change)***	***Comment (Rationale)***
1 (January 2010)	Complete revision of March 2003 version	First document
2 (May 2010)	p.14 Comment added on JP7.03 Data for 1-3ml design added throughout chapter 7 1-3ml drawings added to chapter 11 Chapter 10 adapted accordingly	Further elucidation of the JP extraction method. Release 1-3ml OCP Release 1-3ml OCP Release 1-3ml OCP
3 (February 3, 2012)	• Replaced 'Helvoet Pharma' by 'Datwyler' throughout document • Removed numbering of	• Name change of company • New format

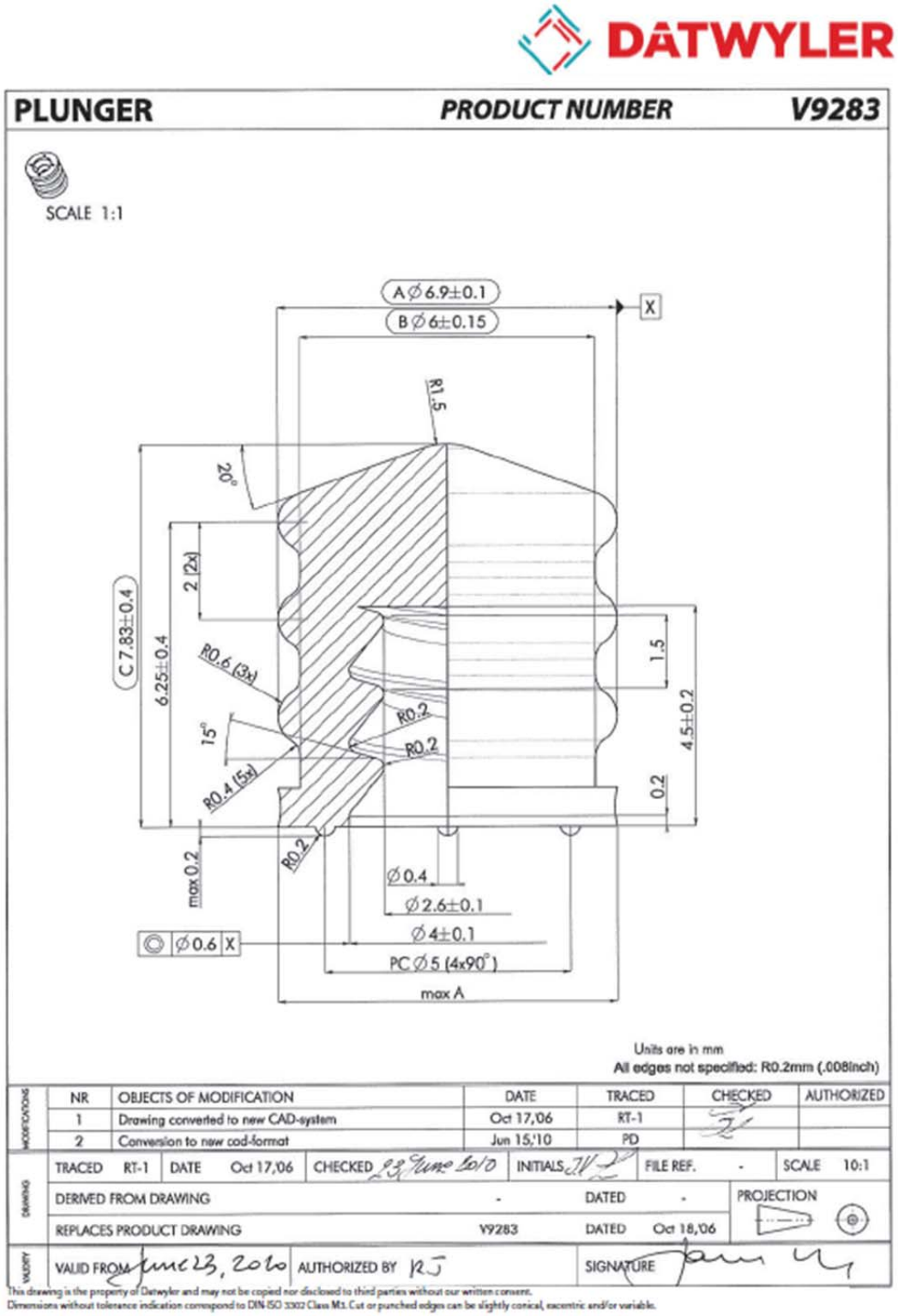
	tables and figures throughout document	
	• Rephrased cautionary statements under sections # 1, 2.1 and 2.6	• Update to current company standard
	• Deleted sentence on RfS and RTU from section #1 'Description' and replaced it by new section #9 'OCP formats'. (Sections higher than #9 therefore are renumbered).	• More extensive description of available OCP formats
	• Added USP <381> as reference to UV spectra sub 5.1.1	• Change in USP <381> in May 2009
	• Added chemical USP/Pharm. Eur data at 2 years shelf life under 6.1.1	• Data having become available
	• Changed % Transmission limits from '99' into '99.0' sub 5.1.2	• Correction versus previous edition
	• Complete rework of 6.2 'Gliding behavior'	• New more systematic data having become available
	• Added sentence on gliding forces to second paragraph of 6.2.3	• Addition
	• Added extra labels in figure sub 6.2.4	• Clarification
	• Added PBSI test results with surfactant containing solution sub 6.3.2.1	• Data having become available
	• Omitted results for ethylene oxide sterilized parts sub 6.3.3	• In line with section 6.2
	• Omitted results for 'gliding behavior' sub 6.3.3	• These data now make part of section 6.2
	• Changed last sentence of third paragraph of section 6.5 and added extra paragraph on insertion tube assembly	• Vacuum assembly being recommended over insertion tube assembly
	• Added note sub 6.5 on drying of steam sterilized OCP before processing	• Observation for other coated product in Omniflex family
	• Replaced USP <87> data in section 7 with more recent data	• Data in latest format
	• Completed section 'References' with additional references	• Reference to additional data

13. Attachments : Product drawings

1ml long OCP design (V9403)



1 ml long ISO 11040-5 design (V9283), design for uncoated plungers



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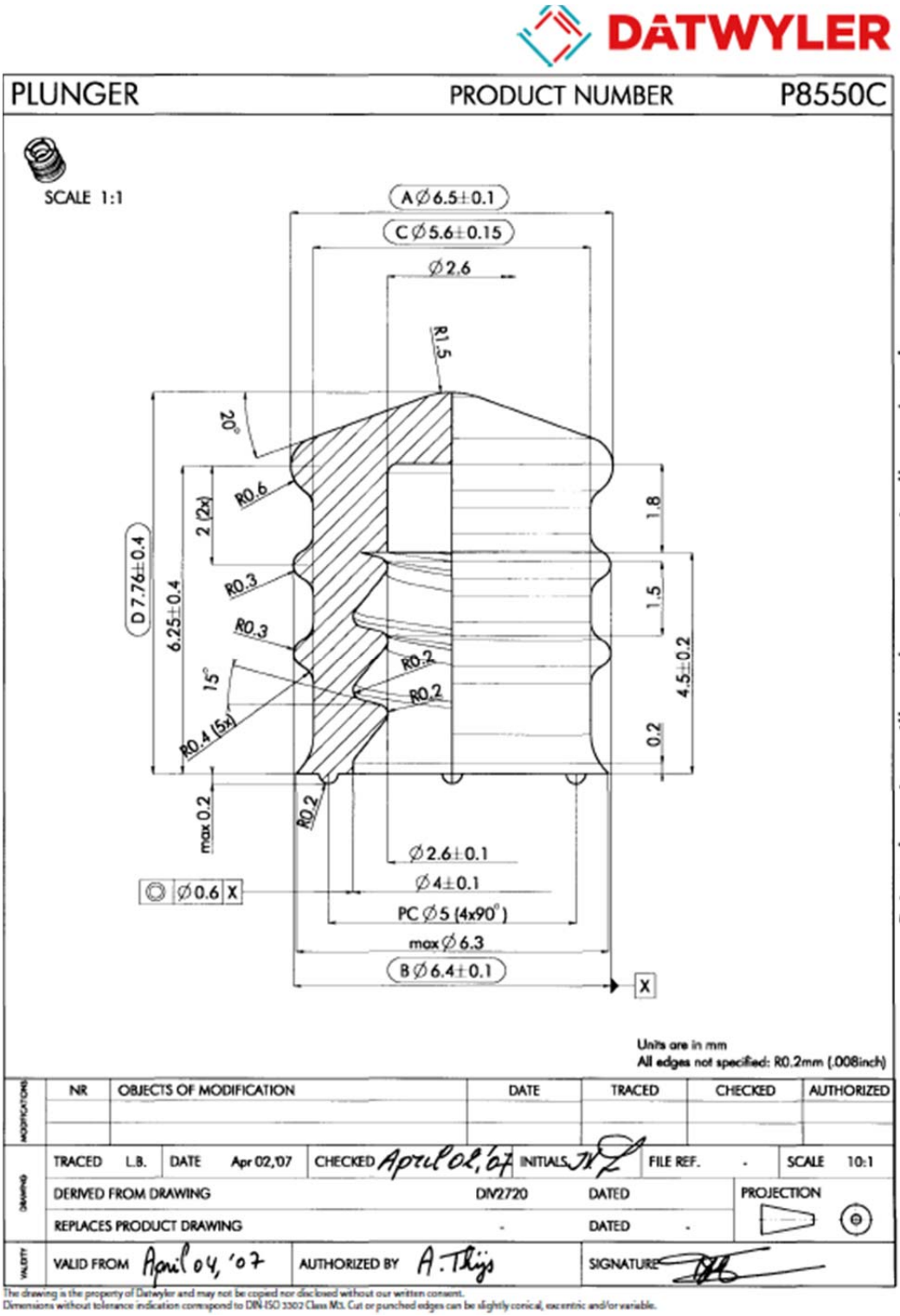
1ml long OCP adapted design (P8550C), decreased diameters



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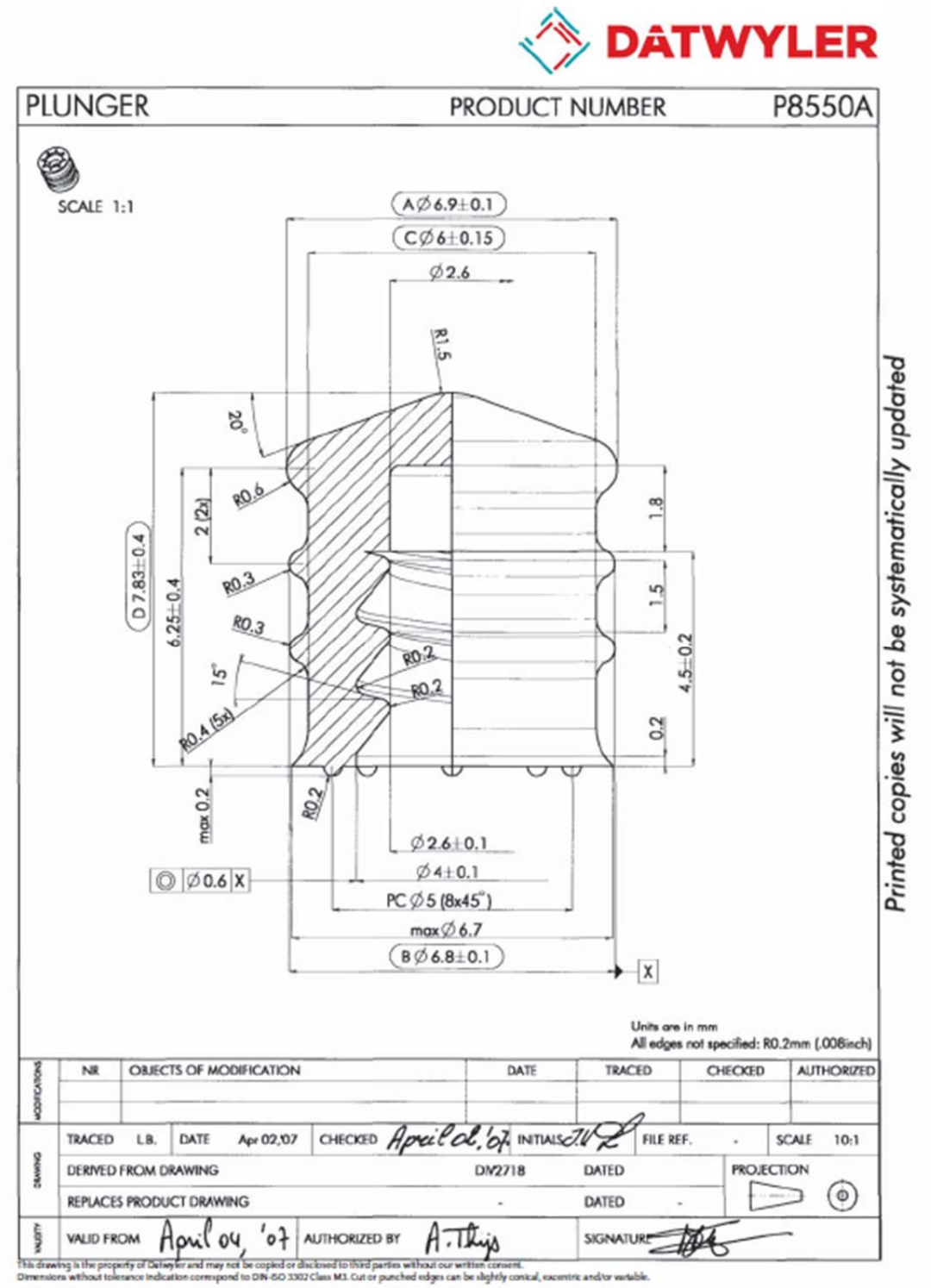
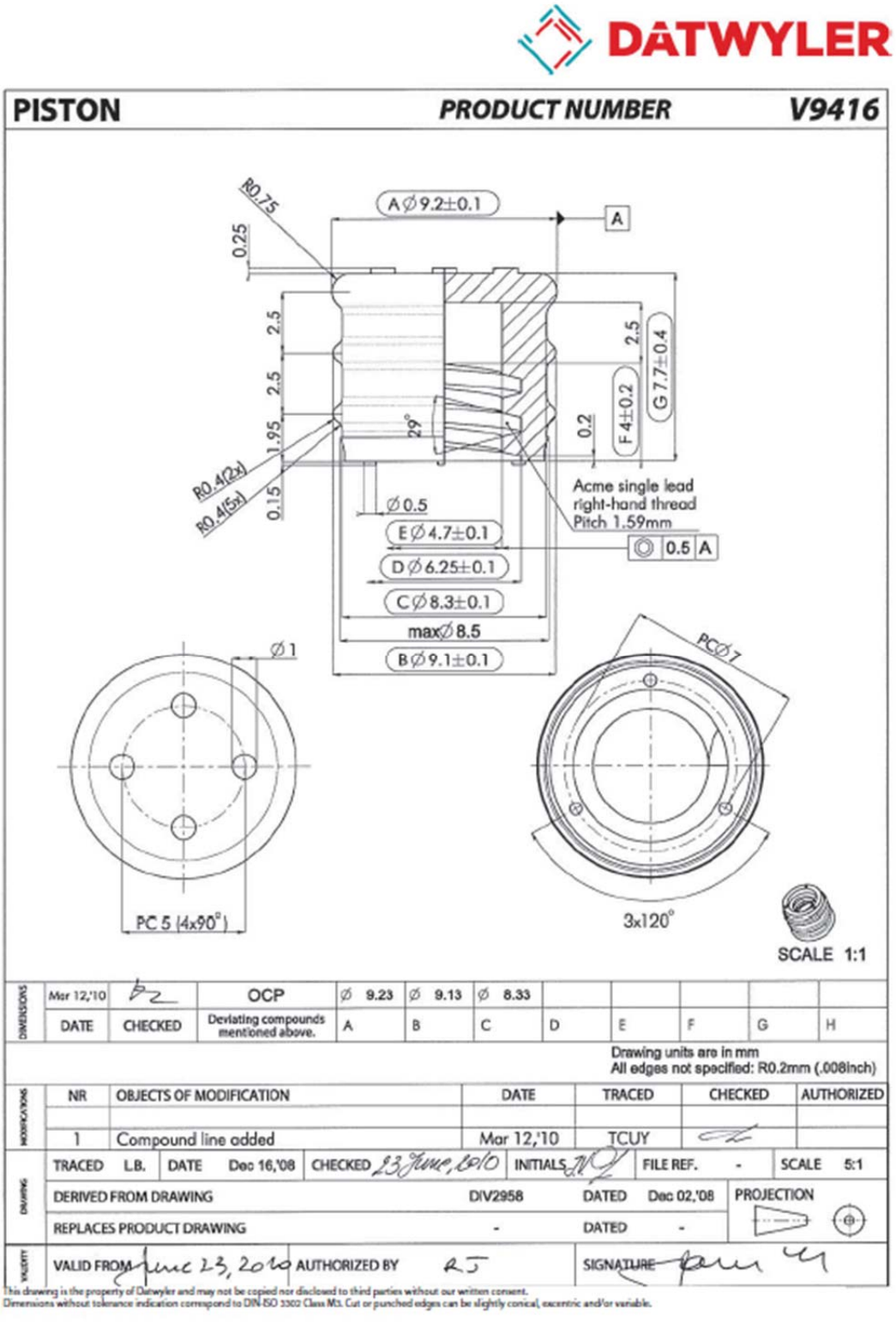
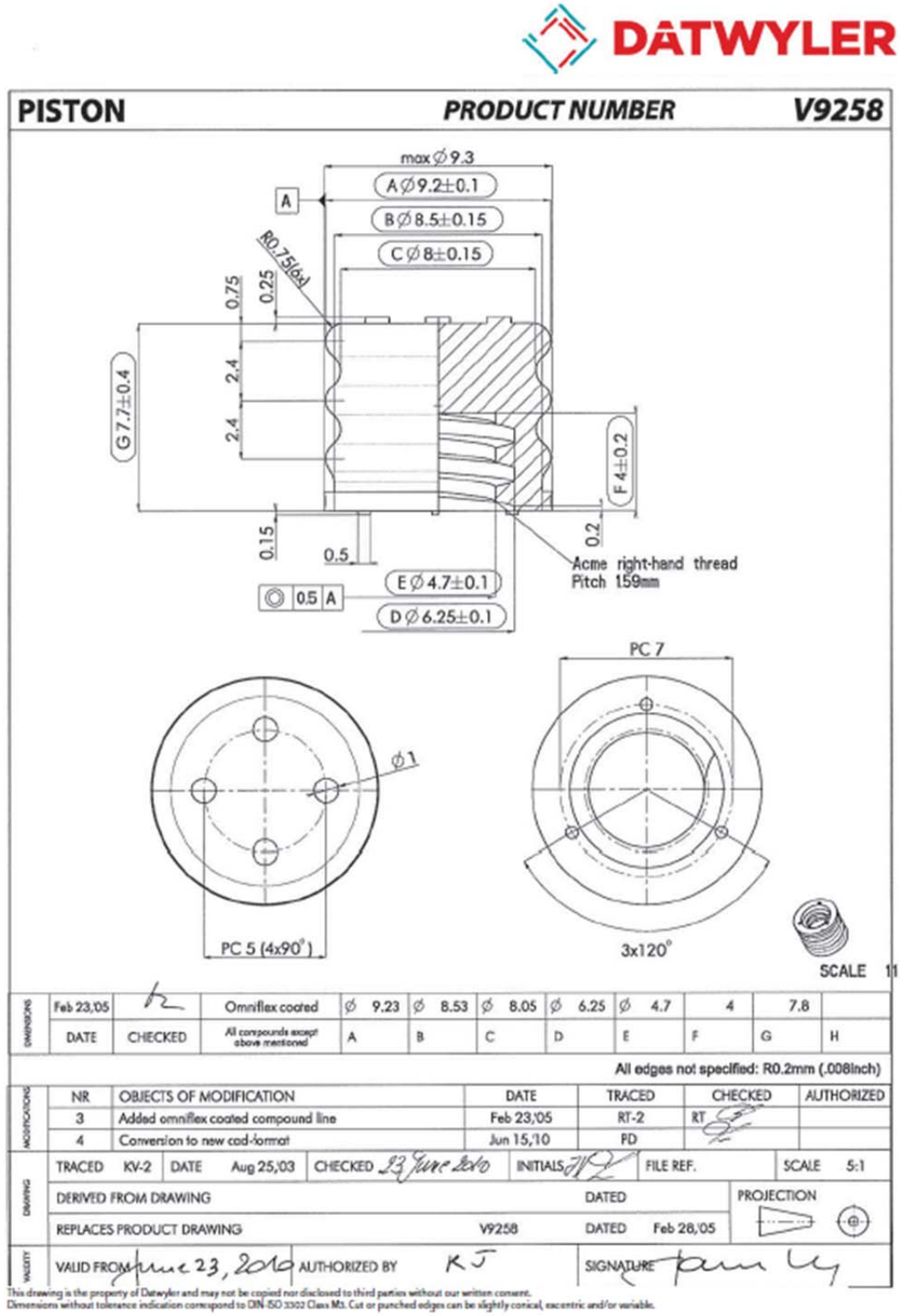
1ml long OCP adapted design (P8550A), increased diameters



1-3ml OCP design (V9416)



1-3ml ISO11040-5 design (V9258), design for uncoated plungers



1-3ml OCP adapted design (P8562F), decreased diameters