
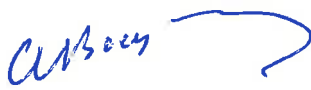




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**YBPR OF FRAGMIN 7500 IU 0.3ML DS
CANADA**


ISSUED BY: Ward Boeykens	Site Compliance Administrator, PGM-Puurs, Belgium	 15 NOV 2011
APPROVED BY: Bram Baert	Site Compliance Administrator, PGM-Puurs, Belgium	 15 NOV 2011

On-going stability study numbers: ST07299LF, ST07264ZF,
ST09040ZF, ST09111LF
and ST10197LF

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Study information

Study	Lot	Condition (°C/%RH)	Fill (ml)	Container	Lot Quantity	Start Date	Mfg Date	Mfg Place	Reason
ST07264ZF	74313-51	30/65	0.3	0.5 ml DS	174375	26/09/2007	jun/07	Vetter	Follow-up
ST07299LF	74279-51	25/60	0.3	0.5 ml DS	65875	24/10/2007	mrt/07	Vetter	Follow-up
ST09040ZF	74538-51	30/65	0.3	0.5 ml DS	143228	30/03/2009	jan/09	Vetter	Follow-up
ST09111LF	74611-51	25/60	0.3	0.5 ml DS	107393	16/07/2009	Jun/09	Vetter	Follow-up
ST10197LF	74751-51	25/60	0.3	0.5 ml DS	136833	14/07/2010	May/10	Vetter	Follow-up

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Schedule

		ABSORBANCE AT 405 NM	ANTI FACTOR XA ACTIVITY	ANTI-FACTOR IIA ACTIVITY	CLARITY	DESCRIPTION	EJECTABLE AMOUNT	EJECTABLE VOLUME	ENDOTOXINS	FREE SULPHATE	HEPARIN FRAGMENTS MOLECULAR WEIGHT LESS THAN 3000	HEPARIN FRAGMENTS MOLECULAR WEIGHT MORE THAN 8000	MOLECULAR WEIGHT NUMBER AVERAGE	MOLECULAR WEIGHT PEAK MOLECULAR WEIGHT	MOLECULAR WEIGHT AVERAGE	OSMOLALITY	pH	RATIO ANTI-FACTOR XA/IIA	STERILITY	VISUAL INSPECTION
ST07264ZF	00 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	12 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	24 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	36 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ST07299LF	00 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	12 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	24 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	36 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ST09040ZF	00 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	12 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	24 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	36 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ST09111LF	00 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	12 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	24 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	36 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ST10197LF	00 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	12 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	24 MONTHS	X	X	X	X	X				X	X	X	X	X	X	X	X	X		X
	36 MONTHS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Current procedures and limits

Test	Test method	Limits
Description	Visual	A clear, colorless or straw coloured solution
pH	Ph. Eur.	5.0 to 7.5
Visual inspection	Ph. Eur.	Clear and practically free from particles
Clarity	T627	Not more than reference I
Anti-factor Xa activity	H236	22500 to 27500 IU/ml
Anti-factor IIa activity	S643	7700 to 11900 IU/ml
Ratio Anti-factor Xa/IIa	H236 / S643	1.9 to 3.2
Molecular weight Number Average	M602	4500 to 5300
Molecular weight Weight Average	M602	5600 to 6400
Molecular Weight Peak Molecular Weight	M602	4300 to 5500
Heparin Fragments Molecular Weight Less Than 3000	M602	5.0 to 13.0 %
Heparin Fragments Molecular Weight More Than 8000	M602	15.0 to 25.0 %
Free Sulphate	I615	Not more than 500 mcg/ml
Absorbance at 405 nm	UV/VIS	Not more than 0.40
Ejectable volume	Ph. Eur	0.30 to 0.33 ml/syringe
Ejectable amount	Multiply anti-factor Xa with ejectable volume	6700 to 9100 IU (anti-factor Xa)/single dose syringe
Sterility	Ph. Eur.	Meets test
Endotoxins	Ph. Eur.	Not more than 2.5 EU/1000 IU
Osmolality	O206	250 to 750 mosm/kg

Registered shelf life is 36 months.

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Note: Test results of studies that are still in progress are reported as To Be Determined (TBD).

Qualitative tests

DESCRIPTION


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
12 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
24 MONTHS	MEETS TEST	MEETS TEST	TBD
36 MONTHS	MEETS TEST	TBD	TBD

30DEGC / 65% RH

	ST07264ZF	ST09040ZF
00 MONTHS	MEETS TEST	MEETS TEST
12 MONTHS	MEETS TEST	MEETS TEST
24 MONTHS	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	TBD

All results within limits up to testing period: no problems reported.

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VISUAL INSPECTION

25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
12 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
24 MONTHS	MEETS TEST	MEETS TEST	TBD
36 MONTHS	NOT MEETS TEST	TBD	TBD

30DEGC / 65% RH

	ST07264ZF	ST09040ZF
00 MONTHS	MEETS TEST	MEETS TEST
12 MONTHS	MEETS TEST	MEETS TEST
24 MONTHS	NOT MEETS TEST	MEETS TEST
36 MONTHS	NOT MEETS TEST	TBD

Out Of Specification (OOS) results for visual inspection were observed for study ST07299LF at 36 months and for study ST07264ZF at 24 months and at 36 months. The particles have been identified (visually) as being Silicon oil. A full investigation has been performed and the conclusion is that there is no safety or efficacy concern associated with the presence of Silicon oil particles in Fragmin Solution. All other results are within limits up to testing period: no problems reported.

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CLARITY

25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
12 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
24 MONTHS	NOT MEETS TEST	MEETS TEST	TBD
36 MONTHS	MEETS TEST	TBD	TBD


30DEGC / 65% RH

	ST07264ZF	ST09040ZF
00 MONTHS	MEETS TEST	MEETS TEST
12 MONTHS	MEETS TEST	MEETS TEST
24 MONTHS	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	TBD

An Out Of Specification (OOS) result for Clarity was observed for study ST07299LF at 24 months. The failed clarity test is due to the presence of silicon droplets which can influence the measurement due to the dispersion of the droplets. An in depth investigation has been performed and the presence of silicone oil was confirmed microscopically and by Infrared. The presence of Silicone oil originates from the siliconization step of the barrels and stoppers at Vetter. It has no extraneous origin as is specified in the USP in the definition of Particulate Matter, but is rather inherent to the manufacturing process.

A toxicity statement is available that shows that the quantity of silicon that was found in the samples does not pose a risk to the patients. The conclusion is that there is no safety or efficacy concern associated with the presence of Silicon oil particles in Fragmin Solution.

All other results within limits up to testing period: no problems reported.

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STERILITY


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	TBD	TBD

30DEGC / 65% RH

	ST07264ZF	ST09040ZF
00 MONTHS	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	TBD

All results within limits up to testing period: no problems reported.

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ENDOTOXINS


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	TBD	TBD

30DEGC / 65% RH

	ST07264ZF	ST09040ZF
00 MONTHS	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	TBD

All results within limits up to testing period: no problems reported.

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Quantitative Tests (trends)

	ANTI-FACTOR IIA ACTIVITY
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25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	9350	9950	9400
12 MONTHS	9300	9450	9500
24 MONTHS	9150	9500	TBD
36 MONTHS	9250	TBD	TBD

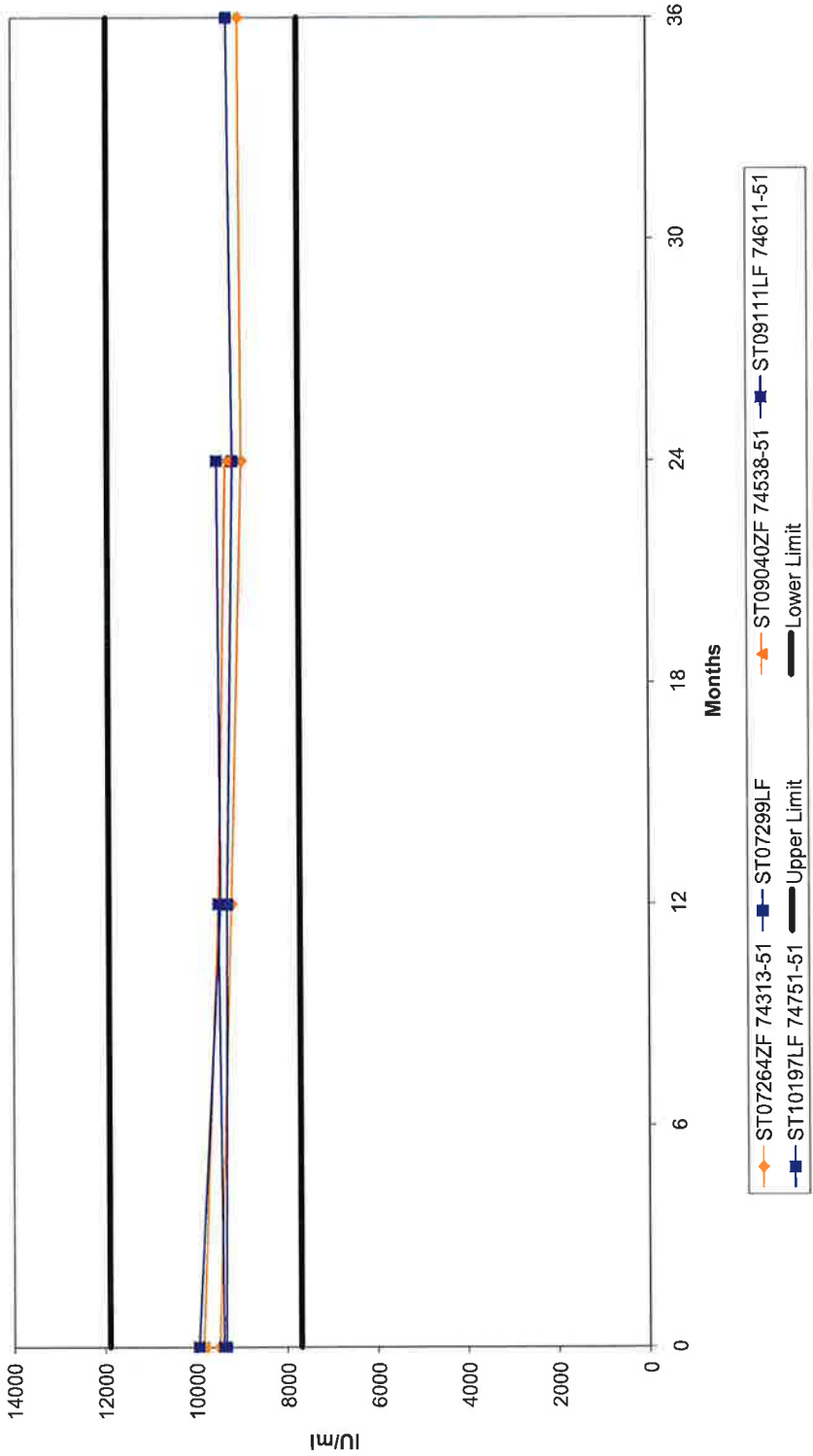
30DEGC / 65% RH

	ST07264ZF	ST09040ZF
00 MONTHS	9500	9850
12 MONTHS	9200	9500
24 MONTHS	8950	9300
36 MONTHS	9000	TBD

All results within limits up to testing period: no problems reported.

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ANTI-FACTOR IIA ACTIVITY



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ANTI-FACTOR XA ACTIVITY

25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	24000	24600	24300
12 MONTHS	23700	24500	24500
24 MONTHS	23900	24200	TBD
36 MONTHS	23900	TBD	TBD

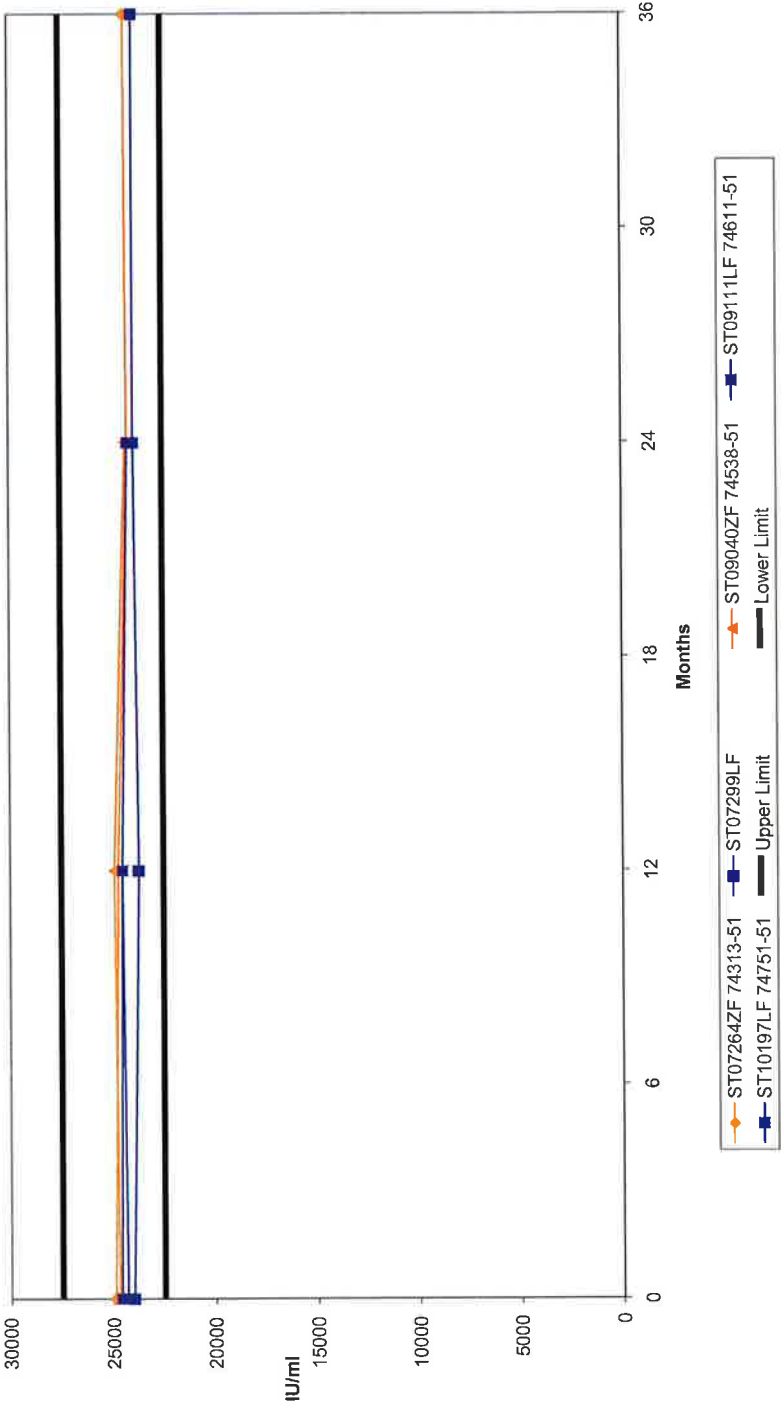
30DEGC / 65% RH


	ST07264ZF	ST09040ZF
00 MONTHS	24900	24700
12 MONTHS	24700	24900
24 MONTHS	24200	24300
36 MONTHS	24300	TBD

All results within limits up to testing period: no problems reported.

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ANTI-FACTOR XA ACTIVITY



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RATIO ANTI-FACTOR XA/IIA


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	2.6	2.5	2.6
12 MONTHS	2.5	2.6	2.6
24 MONTHS	2.6	2.5	TBD
36 MONTHS	2.6	TBD	TBD

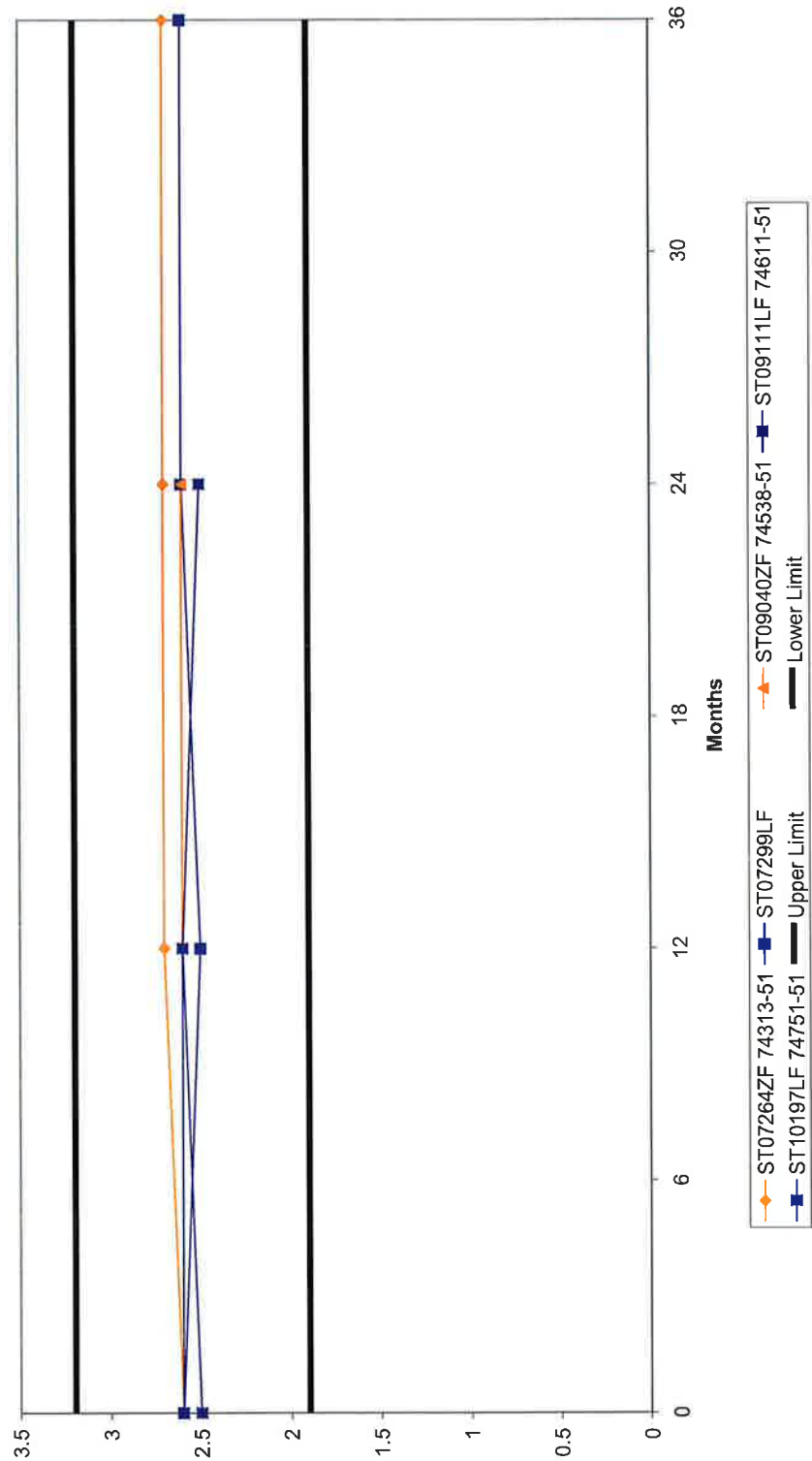
30DEGC / 65% RH


	ST07264ZF	ST09040ZF
00 MONTHS	2.6	2.5
12 MONTHS	2.7	2.6
24 MONTHS	2.7	2.6
36 MONTHS	2.7	TBD

All results within limits up to testing period: no problems reported.

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RATIO ANTI-FACTOR XA/IIA



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MOLECULAR WEIGHT NUMBER AVERAGE


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	4811	4827	4788
12 MONTHS	4752	4754	4705
24 MONTHS	4753	4688	TBD
36 MONTHS	4702	TBD	TBD

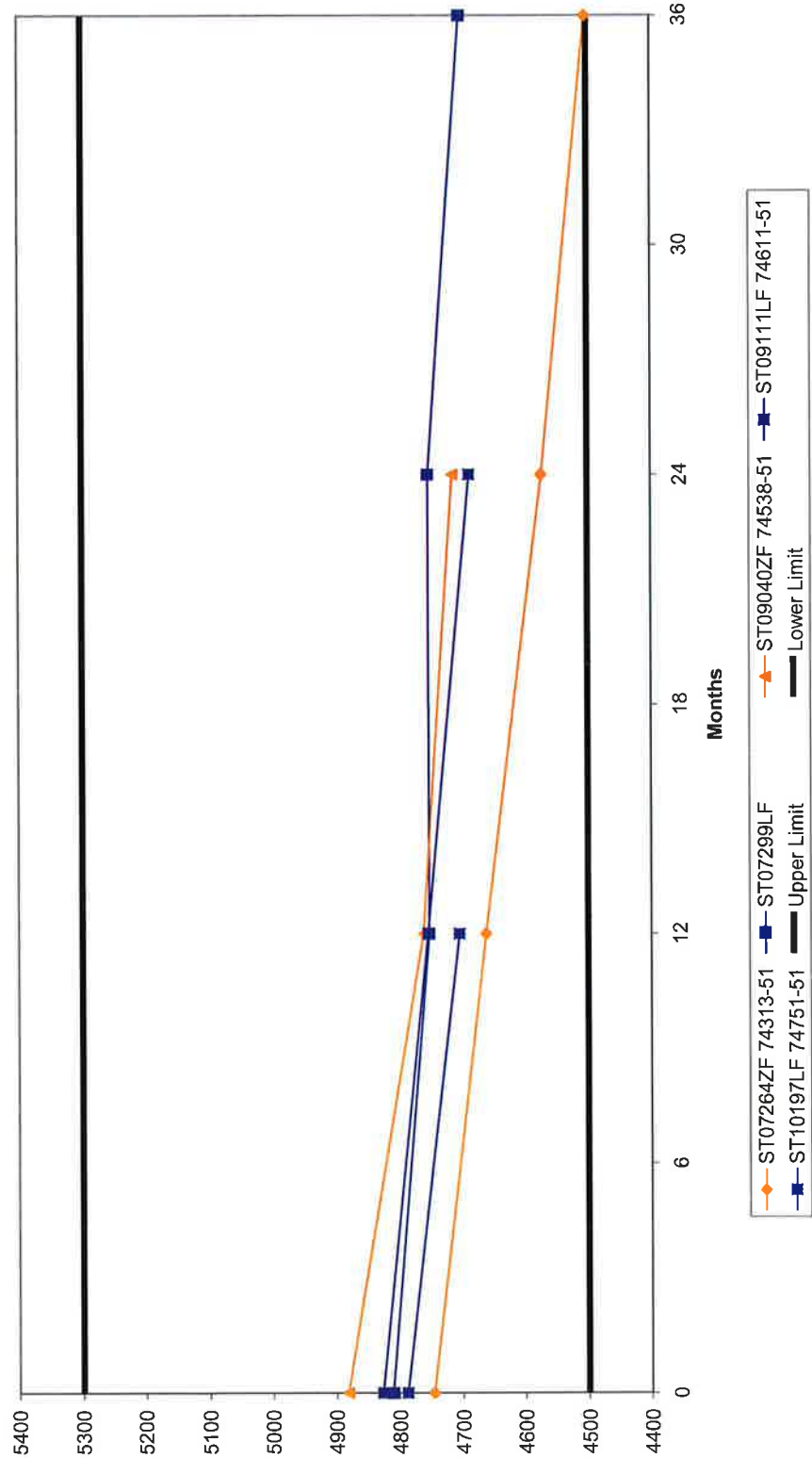
30DEGC / 65% RH

	ST07264ZF	ST09040ZF
00 MONTHS	4746	4882
12 MONTHS	4662	4761
24 MONTHS	4573	4714
36 MONTHS	4503	TBD

All results within limits up to testing period: no problems reported.

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MOLECULAR WEIGHT NUMBER AVERAGE



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MOLECULAR WEIGHT WEIGHT AVERAGE

25DEGC / 60% RH


	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	6048	6042	5990
12 MONTHS	5958	5975	5929
24 MONTHS	5928	5922	TBD
36 MONTHS	5881	TBD	TBD

30DEGC / 65% RH

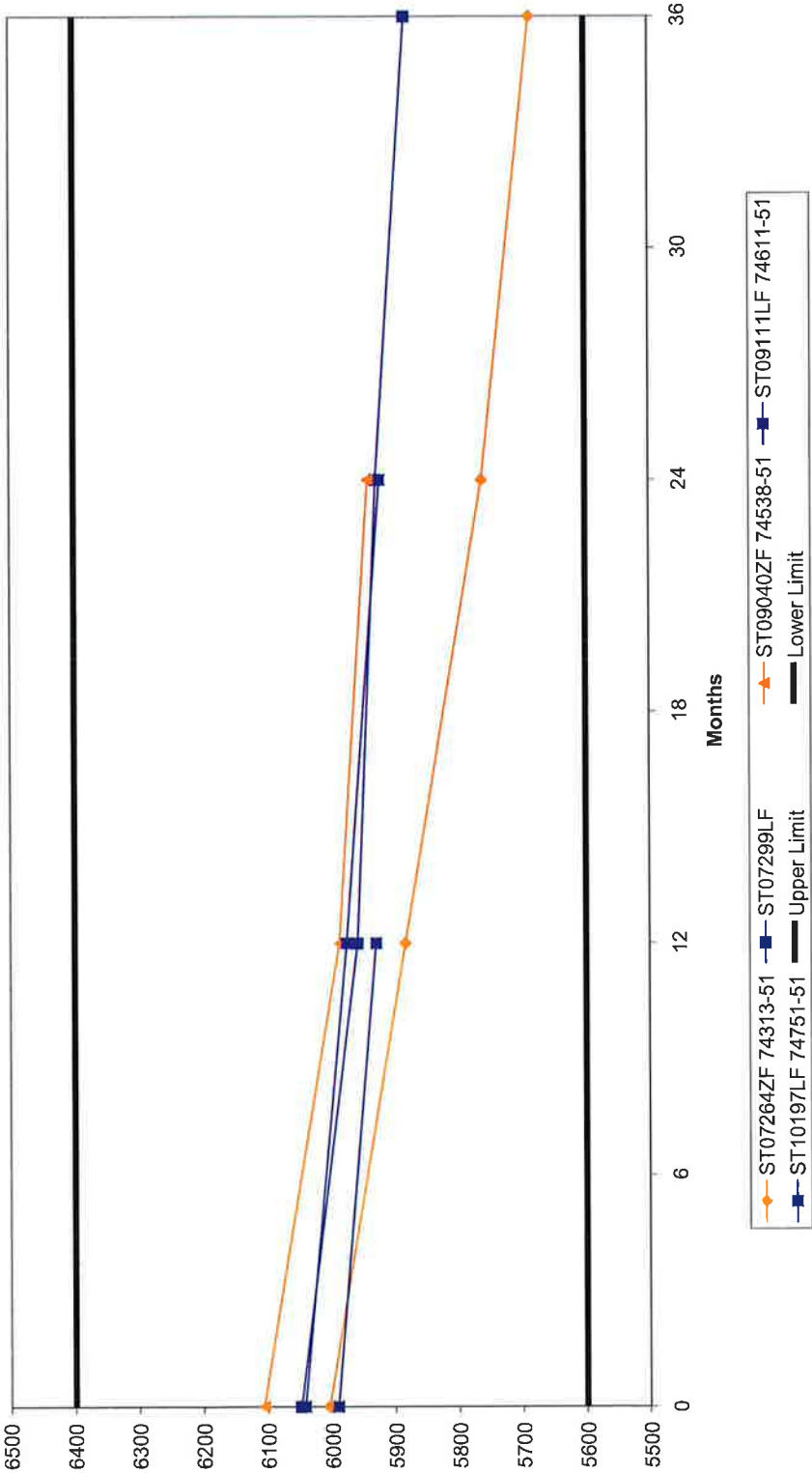
	ST07264ZF	ST09040ZF
00 MONTHS	6004	6106
12 MONTHS	5883	5986
24 MONTHS	5762	5940
36 MONTHS	5686	TBD

All results within limits up to testing period: no problems reported.

Molecular Weight

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MOLECULAR WEIGHT WEIGHT AVERAGE



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MOLECULAR WEIGHT PEAK MOLECULAR WEIGHT

25DEGC / 60% RH


	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	4587	4598	4600
12 MONTHS	4464	4542	4444
24 MONTHS	4442	4429	TBD
36 MONTHS	4406	TBD	TBD

30DEGC / 65% RH

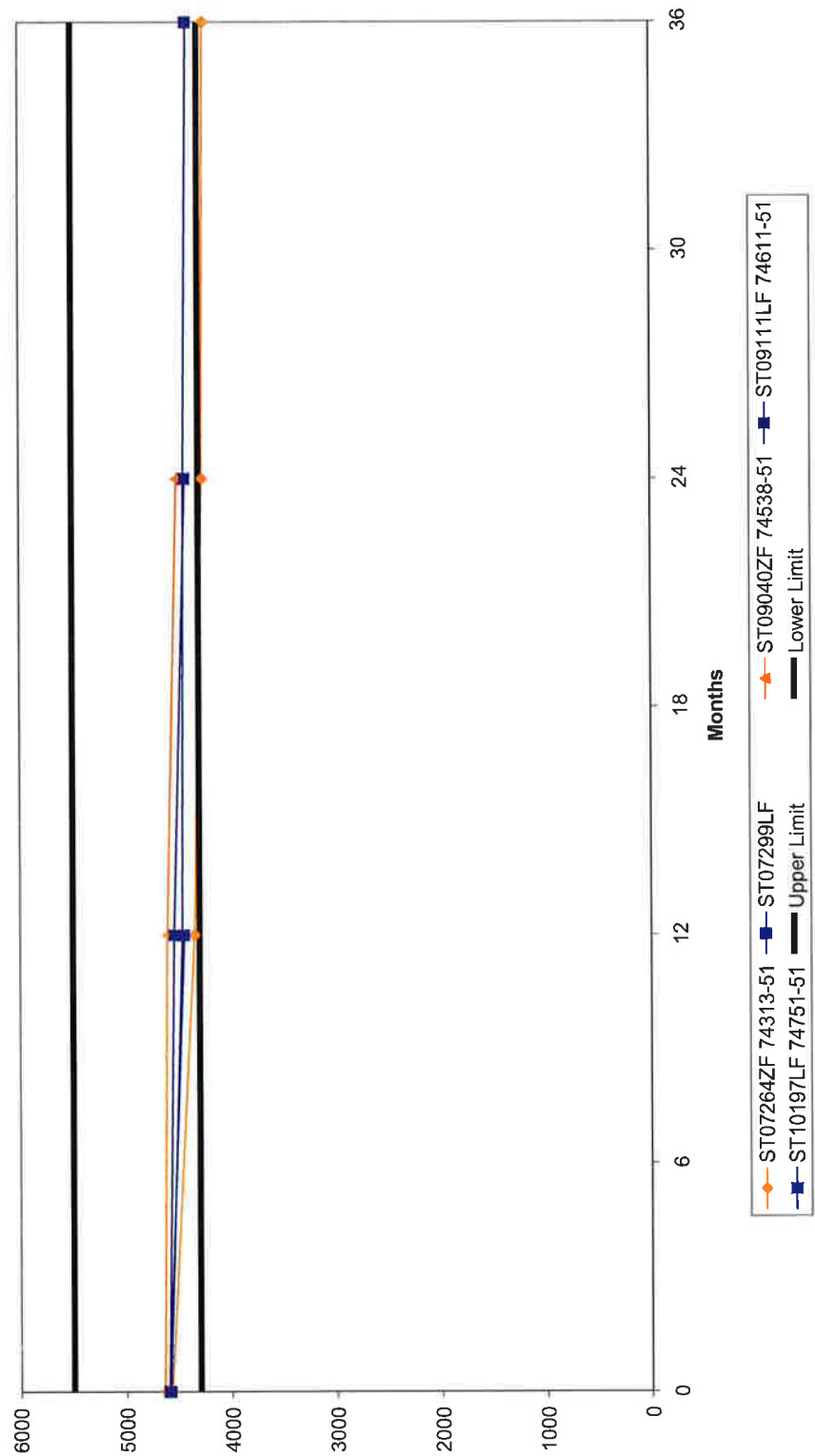
	ST07264ZF	ST09040ZF
00 MONTHS	4569	4640
12 MONTHS	4342	4604
24 MONTHS	4266	4506
36 MONTHS	4244	TBD


Out of Specification results for Peak Molecular Weight were observed for study ST07264ZF at 24 and 36 months. Results were confirmed during retesting as outlined in the YBPR 2010 report.

Molecular weight distribution is defined by the number molecular weight, average molecular weight, and the peak molecular weight. Only the average molecular weight is a required parameter in the current Ph. Eur. Dalteparin Sodium monograph. Since the data for the number molecular weight and average molecular weight are within specification, the low value for peak molecular weight is not considered a safety or efficacy issue. All other results are within specifications up to testing period, no problems reported.

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MOLECULAR WEIGHT PEAK MOLECULAR WEIGHT



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HEPARIN FRAGMENTS MOLECULAR WEIGHT LESS THAN 3000

25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	10.5	9.9	10.3
12 MONTHS	10.4	10.7	11.3
24 MONTHS	10.3	11.4	TBD
36 MONTHS	10.6	TBD	TBD

30DEGC / 65% RH

	ST07264ZF	ST09040ZF
00 MONTHS	11.6	9.3
12 MONTHS	11.8	10.4
24 MONTHS	12.6	10.8
36 MONTHS	13.3	TBD

An Out Of Specification result was reported for study ST07264ZF at the 36 months time point. A further investigation indicated that an increase of Heparin Fragments MW < 3000 observed on the drug product is correlated to the same test performed on the API material at release and when the stability studies were initiated (time zero)

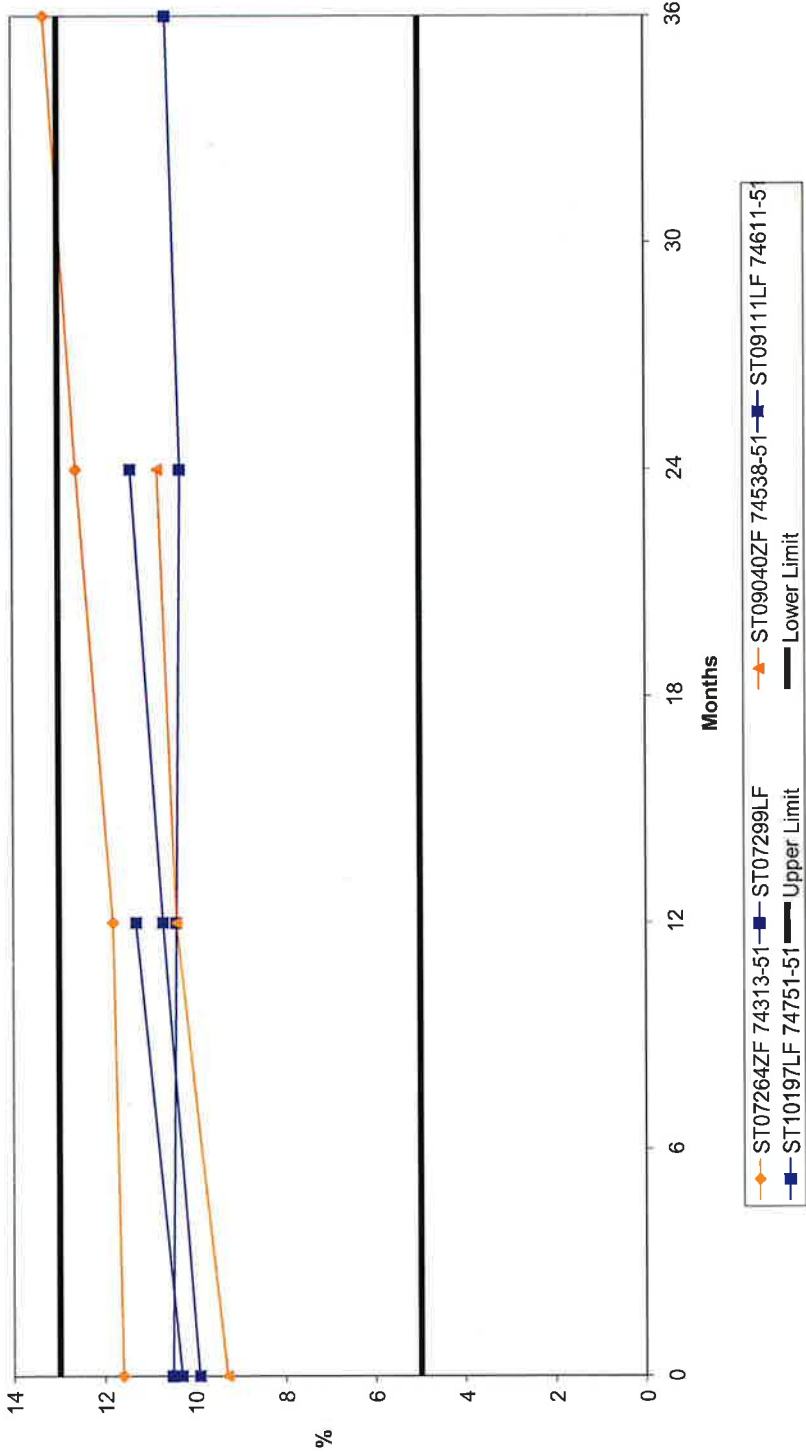
As a result of the investigation, the limits of Heparin Fragment MW < 3000 test on the API material were tightened to ensure results within specification on the finished product.


Furthermore, since Anti-Factor XA Activity and Anti-Factor IIA activity remain within specifications, it is considered that the high value of Heparin Fragment MW < 3000 is not a safety or efficacy issue.

All other results are within limits up to testing period: no problems reported.

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HEPARIN FRAGMENTS MOLECULAR WEIGHT LESS THAN 3000



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HEPARIN FRAGMENTS MOLECULAR WEIGHT MORE THAN 8000

25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	20.5	20.0	19.5
12 MONTHS	19.2	19.4	18.7
24 MONTHS	18.7	18.7	TBD
36 MONTHS	18.3	TBD	TBD

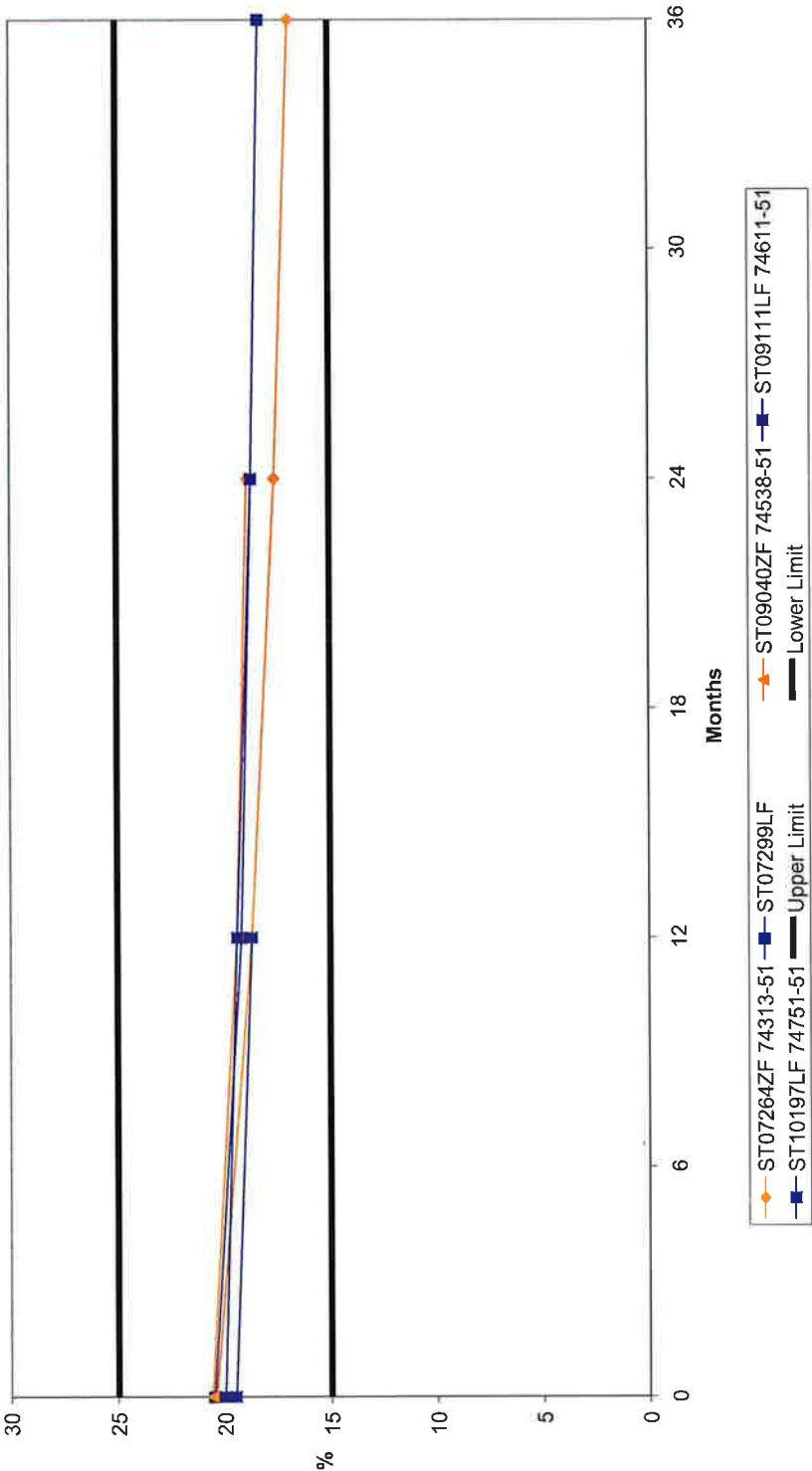
30DEGC / 65% RH


	ST07264ZF	ST09040ZF
00 MONTHS	20.4	20.6
12 MONTHS	18.7	19.4
24 MONTHS	17.6	18.9
36 MONTHS	16.9	TBD

All results within limits up to testing period: no problems reported.

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HEPARIN FRAGMENTS MOLECULAR WEIGHT MORE THAN 8000



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25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	6.1	6.4	6.2
12 MONTHS	5.8	5.7	5.8
24 MONTHS	5.6	5.7	TBD
36 MONTHS	5.5	TBD	TBD

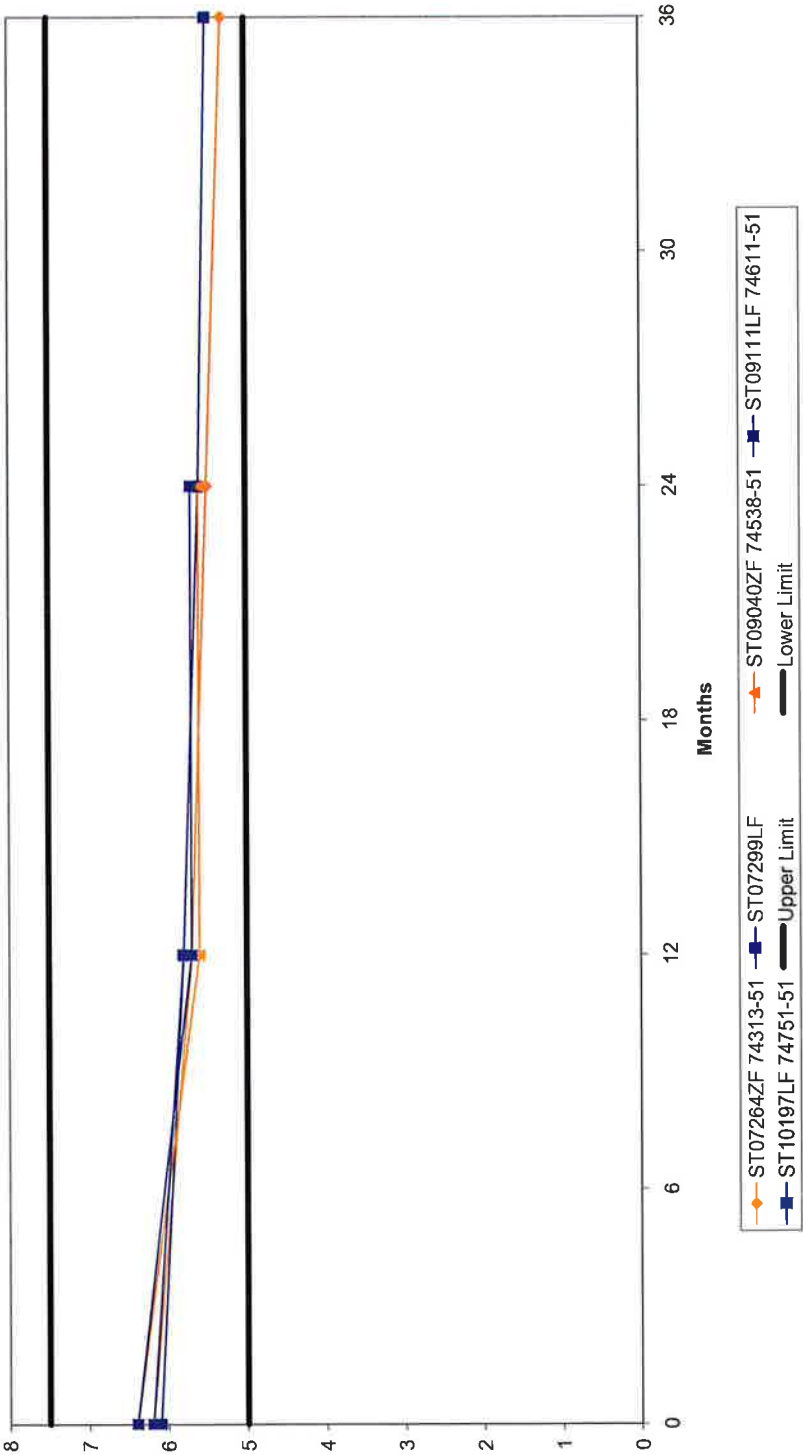
30DEGC / 65% RH


	ST07264ZF	ST09040ZF
00 MONTHS	6.2	6.4
12 MONTHS	5.7	5.6
24 MONTHS	5.5	5.6
36 MONTHS	5.3	TBD

All results within limits up to testing period: no problems reported.

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FREE SULPHATE


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	92	57	69
12 MONTHS	125	115	131
24 MONTHS	155	168	TBD
36 MONTHS	232	TBD	TBD

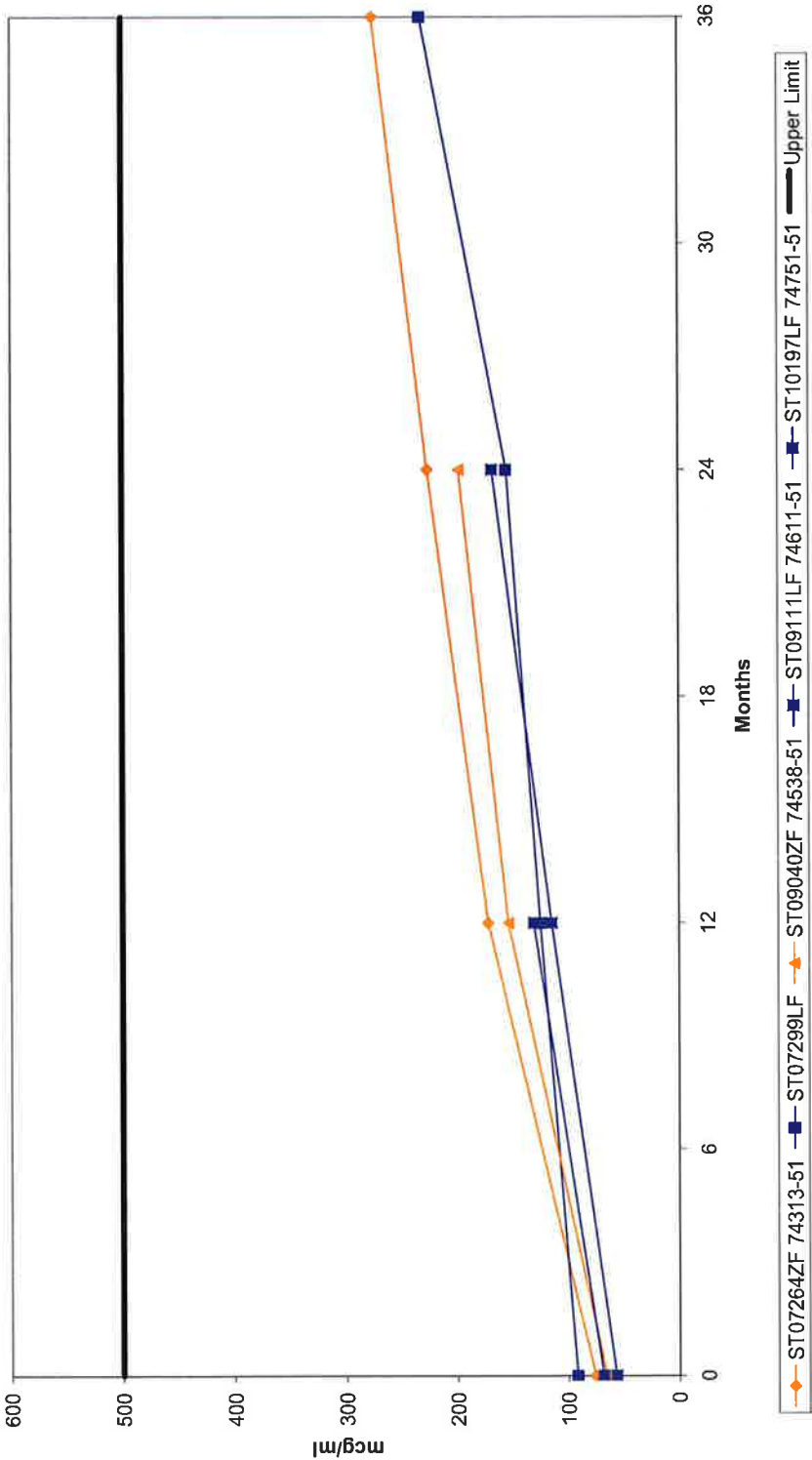
30DEGC / 65% RH


	ST07264ZF	ST09040ZF
00 MONTHS	76	66
12 MONTHS	172	154
24 MONTHS	226	198
36 MONTHS	275	TBD

All results within limits up to testing period: no problems reported.

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FREE SULPHATE



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OSMOLALITY


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	466	453	512
12 MONTHS	464	463	511
24 MONTHS	464	462	TBD
36 MONTHS	474	TBD	TBD

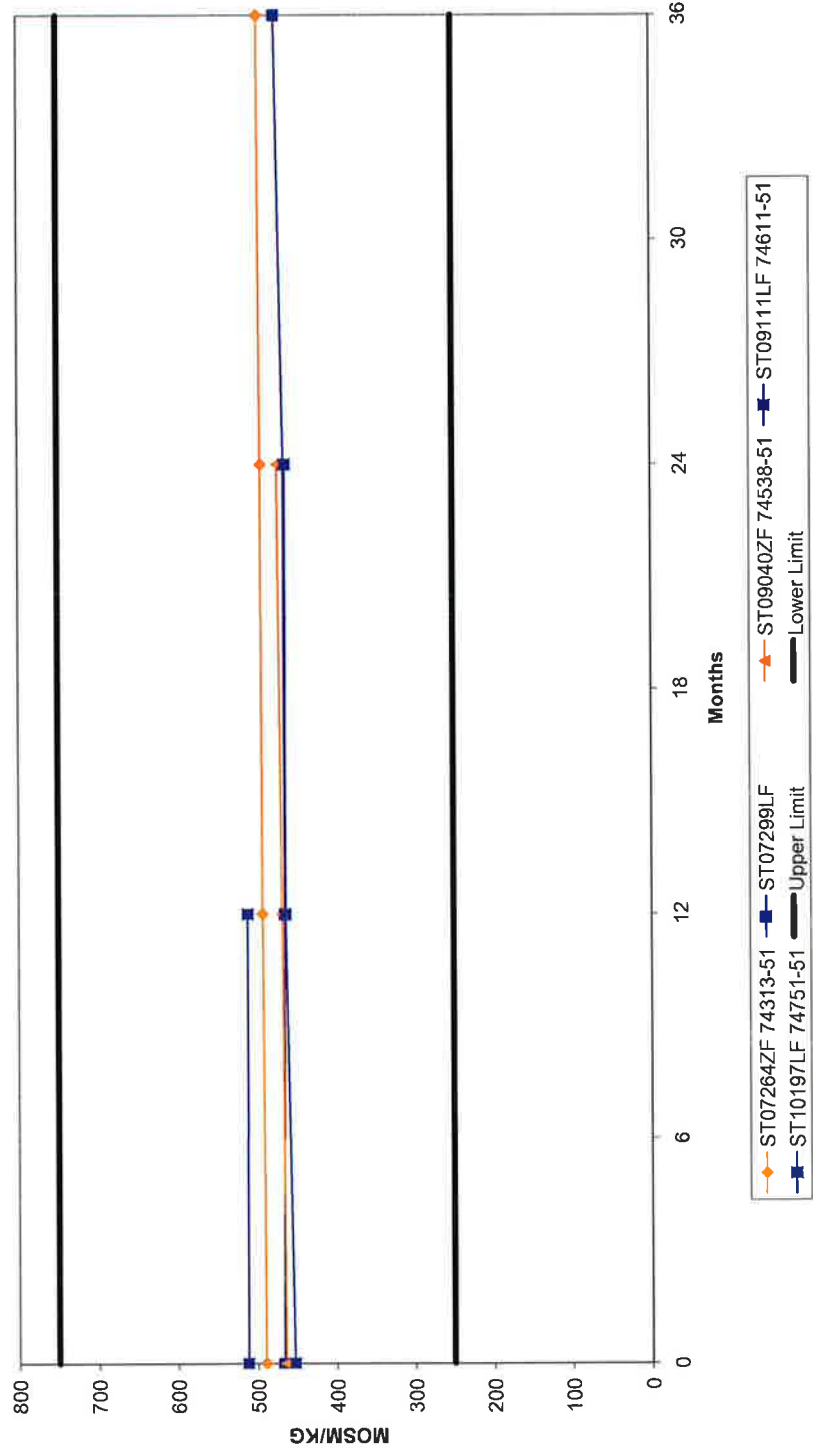
30DEGC / 65% RH


	ST07264ZF	ST09040ZF
00 MONTHS	489	464
12 MONTHS	492	467
24 MONTHS	493	472
36 MONTHS	496	TBD

All results within limits up to testing period: no problems reported.

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OSMOLALITY



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ABSORBANCE AT 405 NM


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	0.06	0.02	0.02
12 MONTHS	0.15	0.05	0.06
24 MONTHS	0.25	0.09	TBD
36 MONTHS	0.19	TBD	TBD

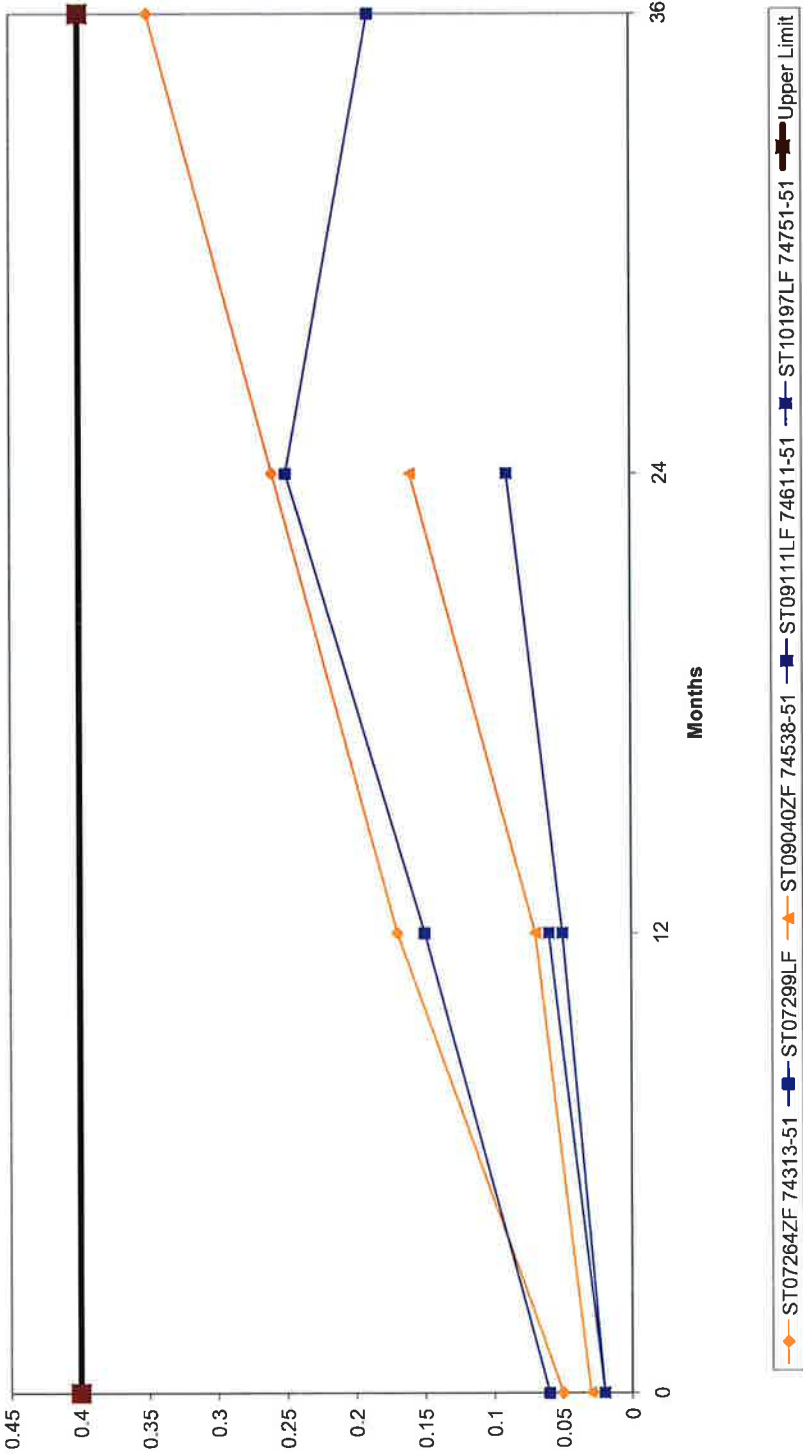
30DEGC / 65% RH


	ST07264ZF	ST09040ZF
00 MONTHS	0.05	0.03
12 MONTHS	0.17	0.07
24 MONTHS	0.26	0.16
36 MONTHS	0.35	TBD

All results within limits up to testing period: no problems reported.

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ABSORBANCE AT 405 NM



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EJECTABLE VOLUME


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	0.31	0.32	0.31
36 MONTHS	0.31	TBD	TBD

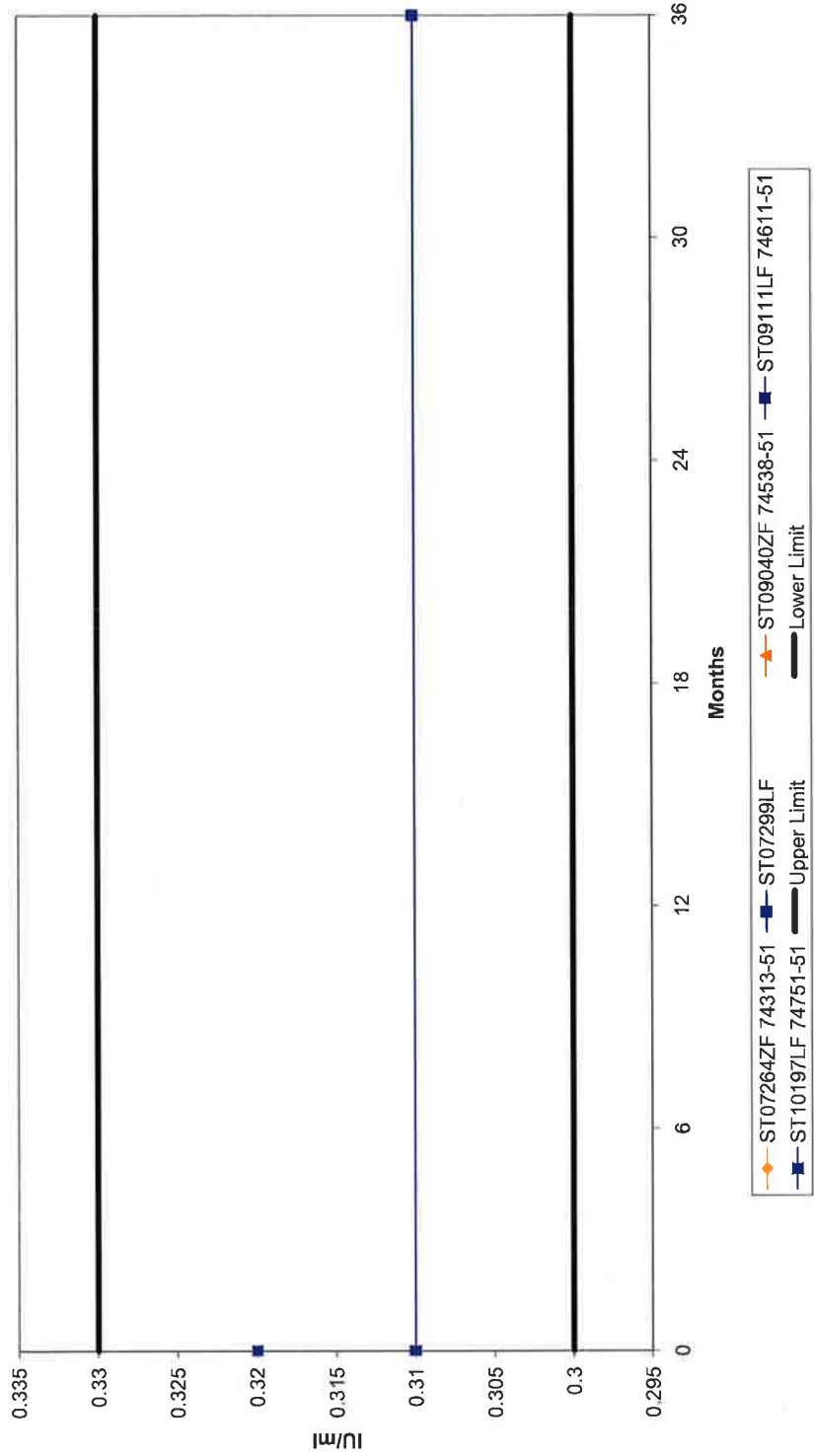
30DEGC / 65% RH


	ST07264ZF	ST09040ZF
00 MONTHS	0.31	0.31
36 MONTHS	0.31	TBD

All results within limits up to testing period: no problems reported.

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EJECTABLE VOLUME



Specification: P9733001002CA	Pfizer Puurs, Belgium STABILITY	
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EJECTABLE AMOUNT


25DEGC / 60% RH

	ST07299LF	ST09111LF	ST10197LF
00 MONTHS	7440	7872	7533
36 MONTHS	7409	TBD	TBD

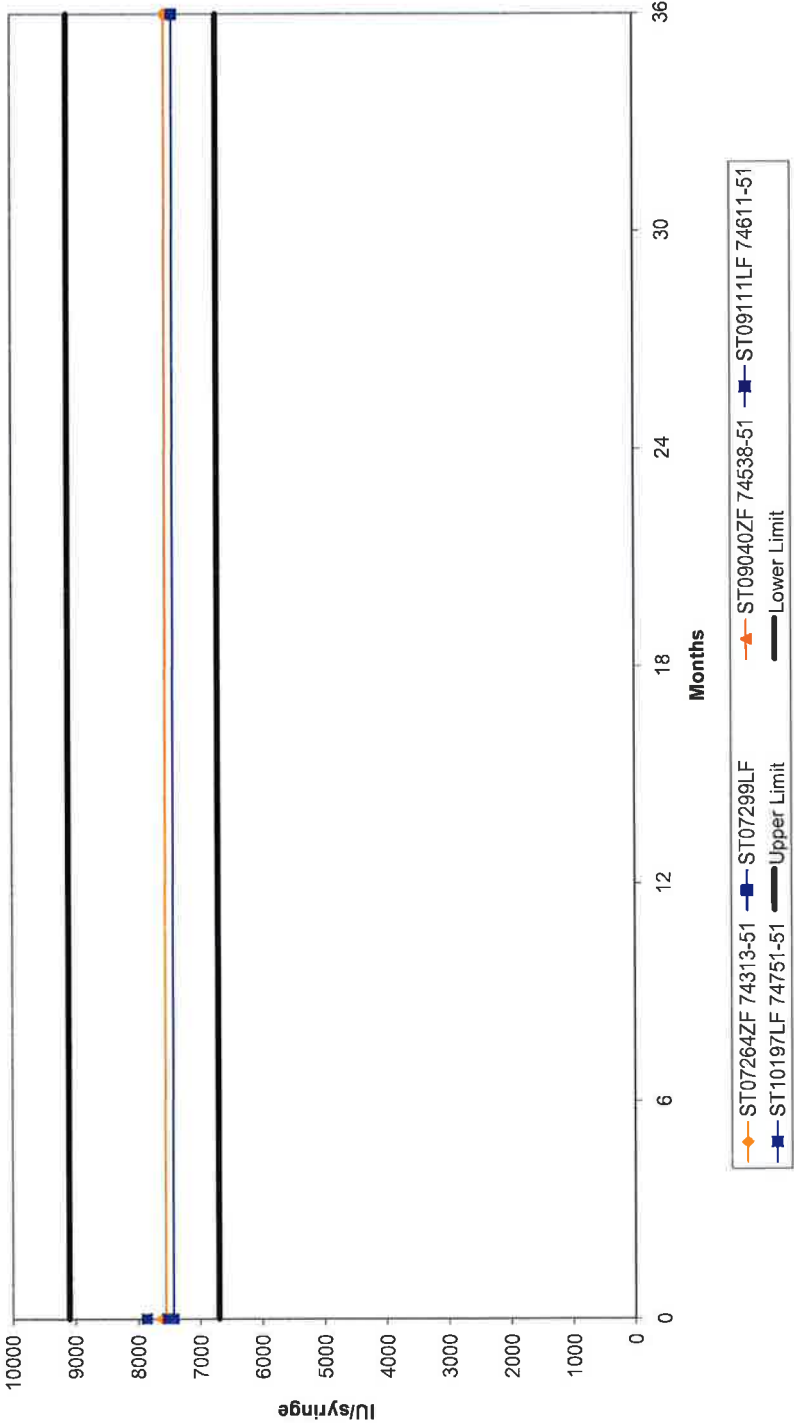
30DEGC / 65% RH

	ST07264ZF	ST09040ZF
00 MONTHS	7567	7657
36 MONTHS	7533	TBD

All results within limits up to testing period: no problems reported.

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EJECTABLE AMOUNT



End of report

