

Stability Report

Accelerated and long-term testing with registration batches BIWG 98 SE drug substance	Number SR 200-02-01
	Date 00.00. 0000
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Responsible Company Successful Pharma KG Biberach	

Responsible:

Analytical Sciences Department

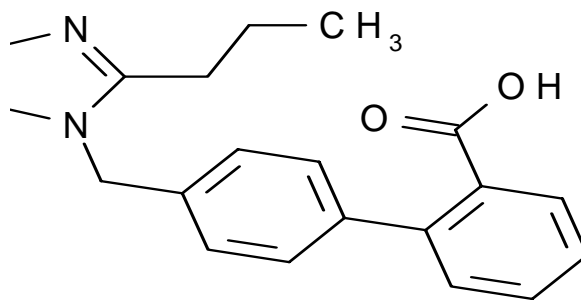
Drug Product Analysis
Laboratory AZ

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1. Summary

1.1 Structural formula



BIWG 98 SE

1.2 Stability results

The Stability Report comprises the primary stability data of the three registration batches of BIWG 98 SE drug substance.

The samples were stored up to 18 respectively 12 months at 25°C/60 % r.h. and up to 6 months at 40°C/75 % r.h..

No change in organoleptic, physico-chemical, chemical properties took place. Not sensitive to light. No interaction with the packaging material took place.

An overview is given in the following table.

Batch No.	Test attributes	Storage conditions		Storage time [months]	Analytical results
		[°C]	[% r.h.]		
S96013*	Appearance	25	60	0,3,6,9,12,(18) *	no change
		40	75	3,6	no change
S96014	Odour	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
S96015	Colour of solution	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
	Clarity of solution	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
	Melting behaviour	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
	Loss on drying	25	60	0,3,6,9,12,(18)	no change
		40	75	3,6	no change
	Degradation of BIWG 98 SE	25	60	0,3,6,9,12,(18)	no degradation
		40	75	3,6	no degradation
	Assay of BIWG 98 SE	25	60	0,3,6,9,12,(18)	no fall in assay
		40	75	3,6	no fall in assay

* batch No. S96013 18 months, S96014, S96015 12 months

The data of assay of BIWG 98 SE are also presented graphically

The primary Accelerated- and Long-Term Stability test results confirmed fully the data of the Stress Testing with the drug substance, documented in the Stability Report "Active Ingredient Stability Profile of BIWG 98 SE drug substance, No. SSRS 200-01-01 dated 00.00.0000".

Summarizing the primary and the supportive stability data, it can be concluded: The NME drug substance BIWG 98 SE is stable. It should be stored in a tight container.

**1.3 Proposed Re-test period and Container closure system
information**

A preliminary re-test period of 24 months is derived from the resulting data. The stability testing will be continued up to 60 months, with the intention of extending the re-test period up to 60 months, if the data adequately support that conclusion. After 60 months the samples are analysed for immediate use.

Example: After release re-test period: 60 months
 After 5 years analysis before immediate use

Preliminary Re-test period		
Container closure system	Climatic zone	Re-test period
Polyethylene bag in stainless steel container	II	24 months

Storage instructions:

According to the results no storage instructions are required, even if the shelf-life will be extended up to 60 months. Nevertheless storage instructions may be necessary due to the national requirements.

Countries	Storage instructions
EU	none
Japan	none
USA	Store at 25°C, excursion permitted to 15 - 30°C

1.4 Commitment: On-going Stability testing

The stability testing will be continued as On-going Stability Testing according to the ICH Guideline "Stability Testing".

Part 1

Continuation of the storage and investigation of the three registration batches up to 60 months.

Batches	Storage condition	Storage period Testing frequency [months]	Testing specifications
S96013 S96014 S96015	25°C/60 % r.h.	(18), 24, 36, 48, 60	TSS 90-A-01/02

Part 2

After marketing authorisation 3 production batches are put on stability.

Batches	Storage condition	Storage period Testing frequency [months]	Testing specifications
3 production batches	25°C/60 % r.h.	0, 6, 12, 18, 24, 36, 60	TSS 90-A-01/02 or equivalent

The available data will be submitted annually.

2. Introduction

In this report the primary stability testing is described with the 3 registration batches of the NCE drug substance BIWG 98 SE. The investigations were performed according to the ICH Guideline "Stability Testing of New Drug Substances and Drug Products".

3 Material and Methods

3.1 Batch information

3.1.1 Manufacture

The three registration batches have been manufactured in pilot plant scale by the same synthetic route and use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale.

Batch No.	S96013	S96014	S96015
Manufacturer	Successful Pharma KG Biberach		
Date of manufacture	Aug. 0000	Sept. 0000	Nov. 0000
Site of manufacture	Pilot Plant		
Scale of manufacture	Pilot Scale		
Batch size	100 kg	99 kg	101 kg
Start of Stability Testing	Sept. 0000	Oct. 0000	Dec. 0000

3.2 Container Closure System

A tight container is necessary according to the stress investigations with the drug substance. Therefore the samples were packed in 500 ml glass flasks with twist-off closure lined with polyethylene foil type Lupolene 3020 D.

The same polyethylene foil is used in the stainless steel containers of the chemical production. Therefore a possible interaction can be investigated. The tight stainless steel container was simulated by the glass flask with the twist-off closure.

3.3 Test attributes

In stability testing of BIWG 98 SE the attributes were investigated

- which are potentially susceptible to change during the course of storage and
- which are likely to influence quality, safety and/or efficacy.

The following test attributes have been selected according to the results of the stress investigations with the drug substance:

Appearance, odour, colour of solution, clarity of solution, melting behaviour, water content, degradation of BIWG 98 SE, assay of BIWG 98 SE, Assessment of container closure system.

3.4 Analytical procedures

The analytical procedures were stability indicating and completely validated according to the ICH Guidelines on validation.

Specificity was demonstrated by separating the drug substance from 3 degradation products caused by stress investigation.

Intermediate precision:	RSD 0.65 %, single analysis was possible since RSD 0.65 % < 1 %
Initial assay:	3-fold
Reporting threshold:	0.05 % according to the ICH Guideline "Impurities in New Drug Substances", each impurity > 0.05 % (reporting threshold) can be quantitated.

The test attributes, the analytical procedures and the release specifications are summarized in the:

"Stability Testing Specifications BIWG 98 SE drug substance No. TSS 900-A-01/02".

The validation procedures and the corresponding data are summarized in the:

"Validation Report BIWG 98 SE drug substance No. VRS 900-A-01/V01".

The analytical procedures were developed for the stability testing of BIWG 98 SE drug substance. The same analytical procedures were used for the investigation of the registration batches.

3.5 Test attributes and Acceptance criteria

Test attributes	Release acceptance criteria
Appearance	White to off-white substance
Odour	Almost imperceptible
Colour of the solution	Not more intensely coloured than reference solution Y 4
Clarity of the solution	Not more opalescent than reference suspension II
Melting behaviour	265 - 270°C (DSC at 3 K/min)
Loss on drying	Not more than 1 %
Degradation of BIWG 98 SE	Imp. I not more than 0.3 %, Imp. II not more than 0.3 %, any unspecified impurity (degradation) up to 0.1%, total impurities not more than 0.7 %
Assay of BIWG 98 SE	98.0 - 101.0 %
Assessment of container closure system	Appearance unchanged.

3.6 Stability test protocols

3.6.1 Accelerated and long-term testing according to the ICH Guideline Stability Testing of Drug Substances and Products

Batch No.	Container closure system	Storage conditions [°C/%r.h.]	Storage period Testing frequency [months]	Stability Testing Specifications
S96013	Polyethylene bag in twist-off glass flask	25°C/60%	0,3,6,9,12,18, (24, 36, 48, 60) ¹	TSS 90-A-01/02
		40°C/75%	3,6	
S96014	Polyethylene bag in twist-off glass flask	25°C/60%	0,3,6,9,12, (18, 24, 36, 48, 60) ¹	TSS 90-A-01/02
		40°C/75%	3,6	
S96015	Polyethylene bag in twist-off glass flask	25°C/60%	0,3,6,9,12, (18, 24, 36, 48, 60) ¹	TSS 90-A-01/02
		40°C/75%	3,6	

¹On-going Stability testing

3.6.2 Photostability testing according to the ICH Guideline Photostability Testing of New Drug Substances and Products

For confirmatory studies samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours (400-800 nm) and an integrated near ultraviolet energy of not less than 200 Wh/m² (320 - 400 nm). The Suntest CPS (Atlas Corp.) is used. It is equipped with a Xenon lamp 22 hours at irradiance level of 250 W/m² $\hat{=}$ 22.5 W/m² with filter fulfilled the requirements.

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with registration batches
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Batch No.	Container closure system	Light source	Storage time	Stability Testing Specifications
S96013	Open petri-dish	Xenon lamp	22 hours	TSS 90-A-01/02

4 Results and Evaluation

4.1 Graphic of test results

Batch No.: S96013

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time

Storage conditions

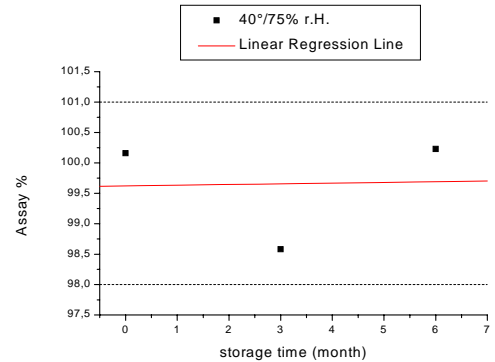
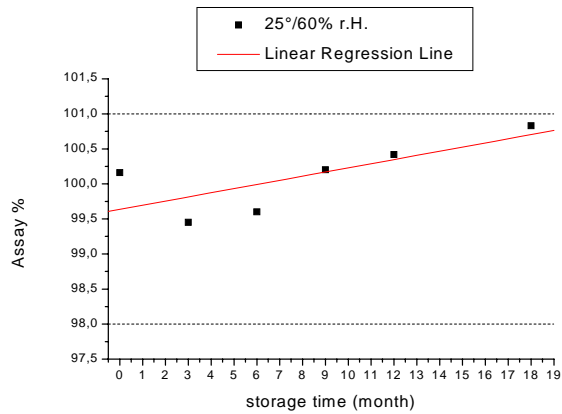
[months]

25°C/60%

40°C/75%

Assay of BIWG 98 SE

98.0 - 101.0 %



Batch No.: S96014

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time

Storage conditions

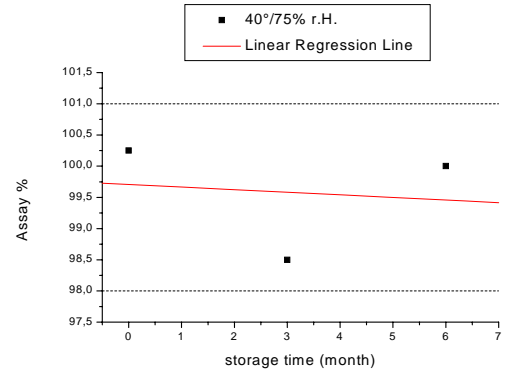
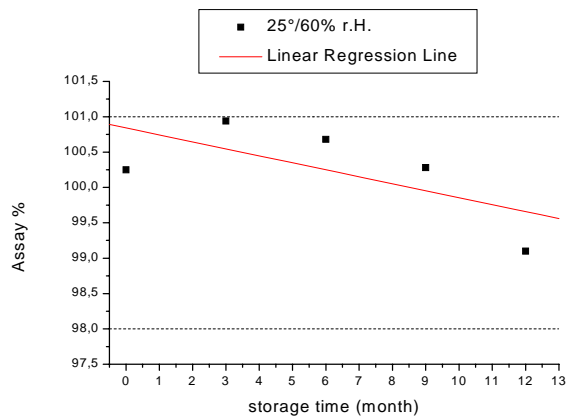
[months]

25°C/60%

40°C/75%

Assay of BIWG 98 SE

98.0 - 101.0 %



Batch No.: S96015

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time

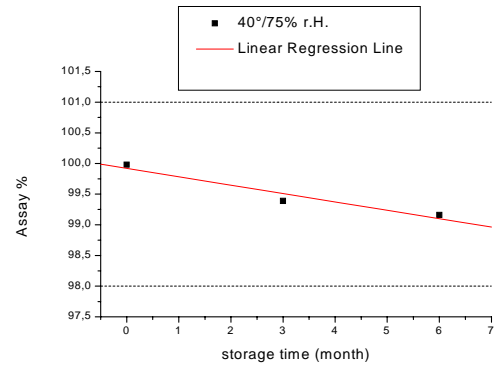
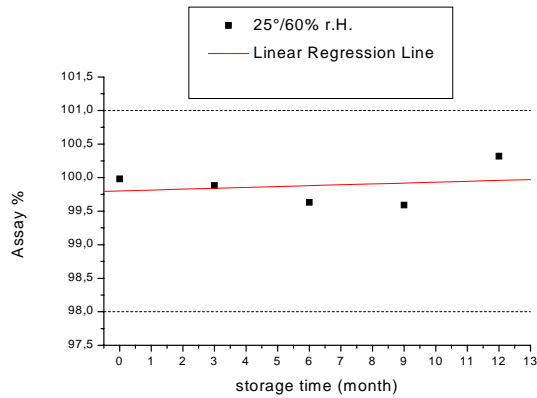
Storage conditions

[months] 25°C/60%

40°C/75%

Assay of BIWG 98 SE

98.0 - 101.0 %



4.2 Test results

Batch No.: S96013

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time

Storage conditions

[months] 25°C/60%

40°C/75%

Appearance

White to off-white substance

0		White to off-white substance	
3	unchanged		unchanged
6	unchanged		unchanged
9	unchanged		
12	unchanged		
18	unchanged		

Odour

Almost imperceptible

0		Almost imperceptible	
3	unchanged		unchanged
6	unchanged		unchanged
9	unchanged		
12	unchanged		
18	unchanged		

Colour of the solution

Not more intensely coloured than reference solution Y 4

0		Y 5 - Y 4	
3	Y 5 - Y 4		Y 5 - Y 4
6	Y 5 - Y 4		Y 5 - Y 4
9	Y 5 - Y 4		
12	Y 5 - Y 4		
18	Y 5 - Y 4		

Batch No.: S96013

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time

Storage conditions

[months] 25°C/60%

40°C/75%

Clarity of the solution

Not more opalescent than reference suspension II

0		< II	
3	< II		< II
6	< II		< II
9	< II		
12	< II		
18	< II		

Melting behaviour

265 - 270°C (DSC at 3 K/min)

0		267°C	
3	268°C		268°C
6	268°C		268°C
9	267°C		
12	269°C		
18	267°C		

Water content

Not more than 1 %

0		0.3 %	
3	0.3 %		0.3 %
6	0.4 %		0.3 %
9	0.3 %		
12	0.3 %		
18	0.4 %		

Batch No.: S96013

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time	Storage conditions
[months] 25°C/60 %	40°C/75 %

Impurities and degradation of BIWG 98 SE	Imp. I not more than 0.3 %, Imp. II not more than 0.3 %, any unspecified impurity (degradation) up to 0.1%, total impurities not more than 0.7 %
0	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
3	Imp. I 0.2 %; Imp. II 0.2 %; no unspecified impurity (degradation)
6	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
9	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
12	Imp. I 0.2 %; Imp. II 0.3 %; no unspecified impurity (degradation)
18	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)

Assay of BIWG 98 SE	98.0 - 101.0 %
0	100.16 %
3	99.45 % 98.58 %
6	99.60 % 100.23 %
9	100.20 %
12	100.42 %
18	100.83 %

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Batch No.: S96013

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time

Storage conditions

[months] 25°C/60 %

40°C/75 %

**Assessment of
packaging material**

Appearance unchanged.

0		faultless	
3	unchanged		unchanged
6	unchanged		unchanged
9	unchanged		
12	unchanged		
18	unchanged		

Batch No.: S96014

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time	Storage conditions
[months] 25°C/60 %	40°C/75 %

Appearance	White to off-white substance
0	White to off-white substance
3	unchanged
6	unchanged
9	unchanged
12	unchanged

Odour	Almost imperceptible
0	Almost imperceptible
3	unchanged
6	unchanged
9	unchanged
12	unchanged

Colour of the solution	Not more intensely coloured than reference solution Y 4
0	Y 5 - Y 4
3	Y 5 - Y 4
6	Y 5 - Y 4
9	Y 5 - Y 4
12	Y 5 - Y 4

Batch No.: S96014

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time	Storage conditions
[months] 25°C/60 %	40°C/75 %

Clarity of the solution	Not more opalescent than reference suspension II
0	< II
3	< II
6	< II
9	< II
12	< II

Melting behaviour	265 - 270°C (DSC at 3 K/min)
0	267°C
3	268°C
6	267°C
9	266°C
12	268°C

Water content	Not more than 1 %
0	0.4 %
3	0.3 %
6	0.4 %
9	0.4 %
12	0.4 %

Batch No.: S96014

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time	Storage conditions
[months] 25°C/60 %	40°C/75 %

Impurities and degradation of BIWG 98 SE	Imp. I not more than 0.3 %, Imp. II not more than 0.3 %, any unspecified impurity (degradation) up to 0.1%, total impurities not more than 0.7 %
0	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
3	Imp. I 0.2 %; Imp. II 0.2 %; no unspecified impurity (degradation) Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
6	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation) Imp. I 0.2 %; Imp. II 0.3 %; no unspecified impurity (degradation)
9	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
12	Imp. I 0.2 %; Imp. II 0.3 %; no unspecified impurity (degradation)

Assay of BIWG 98 SE	98.0 - 101.0 %
0	100.25 %
3	100.94 % 98.50 %
6	100.68 % 100.00 %
9	100.28 %
12	99.10 %

Assessment of container closure system	Appearance unchanged.
0	faultless
3	unchanged unchanged
6	unchanged unchanged
9	unchanged
12	unchanged

Batch No.: S96015

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time	Storage conditions
[months] 25°C/60 %	40°C/75 %

Appearance	White to off-white substance
0	White to off-white substance
3	unchanged
6	unchanged
9	unchanged
12	unchanged

Odour	Almost imperceptible
0	Almost imperceptible
3	unchanged
6	unchanged
9	unchanged
12	unchanged

Colour of the solution	Not more intensely coloured than reference solution Y 4
0	Y 5 - Y 4
3	Y 5 - Y 4
6	Y 5 - Y 4
9	Y 5 - Y 4
12	Y 5 - Y 4

Batch No.: S96015

Container closure system 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time

Storage conditions

[months] 25°C/60 %

40°C/75 %

Clarity of the solution

Not more opalescent than reference suspension II

0		< II	
3	< II		< II
6	< II		< II
9	< II		
12	< II		

Melting behaviour

265 - 270°C (DSC at 3 K/min)

0		267°C	
3	268°C		268°C
6	267°C		268°C
9	268°C		
12	269°C		

Water content

Not more than 1 %

0		0.3 %	
3	0.4 %		0.3 %
6	0.4 %		0.3 %
9	0.3 %		
12	0.4 %		

Batch No.: S96015

Container closure system: 500 ml glass flask with twist-off closure lined with polyethylene foil

Storage time	Storage conditions
[months] 25°C/60 %	40°C/75 %

Impurities and degradation of BIWG 98 SE	Imp. I not more than 0.3 %, Imp. II not more than 0.3 %, any unspecified impurity (degradation) up to 0.1%, total impurities not more than 0.7 %
0	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
3	Imp. I 0.2 %; Imp. II 0.2 %; no unspecified impurity (degradation)
6	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
9	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
12	Imp. I 0.2 %; Imp. II 0.3 %; no unspecified impurity (degradation)

Assay of BIWG 98 SE	98.0 - 101.0 %
0	99.98 %
3	99.88 %
6	99.63 %
9	99.59 %
12	100.32 %

Assessment of Container closure system	Appearance unchanged.
0	faultless
3	unchanged
6	unchanged
9	unchanged
12	unchanged

Batch No.: S96013

Container closure system Open petri-dish

Storage time	Storage conditions
[hours]	Xenon lamp

Appearance	
	White to off-white substance
0	White to off-white substance
22	unchanged

Colour of the solution	
	Not more intensely coloured than reference solution Y 4
0	Y 5 - Y 4
22	Y 5 - Y 4

Clarity of the solution	
	Not more opalescent than reference suspension II
0	< II
22	< II

Impurities and degradation of BIWG 98 SE	
	Imp. I not more than 0.3 %, Imp. II not more than 0.3 %, any unspecified impurity (degradation) up to 0.1%, total impurities not more than 0.7 %
0	Imp. I 0.3 %; Imp. II 0.2 %; no unspecified impurity (degradation)
22	Imp. I 0.2 %; Imp. II 0.3 %; no unspecified impurity (degradation)

Assay of BIWG 98 SE	
	98.0 - 101.0 %
0	100.16 %
22	99.89 %

4.3 Evaluation

The three registration batches packed in polyethylene bags in 500 ml glass flasks with twist-off closure were investigated. The samples had been stored up to 18 respectively 12 months at 25°C/60 % r.h. and up to 6 months at 40°C/75 % r.h.. The analytical procedures were stability indicating and completely validated.

4.3.1 Organoleptical properties:

During the storage no change in appearance or odour took place.

4.3.2 Physico-chemical properties:

During the storage at both conditions no change in colour of solution, clarity of solution, melting behaviour and loss on drying occurred.

4.3.3 Chemical properties:

During the storage no fall in assay took place. No degradation > 0.05 % was detected. Two known impurities did not change.

Since no decomposition or fall in assay took place, the statistical evaluation was deleted. This is underlined by the graphical presentation of the data of assay of BIWG 98 SE. These data scatter slightly.

4.3.4 Container closure system properties:

No interaction was found with the polyethylene foil.

4.3.5 Photostability:

The Photostability was investigated applying the Suntest CPS (Atlas Corp.). After 22 hours (Confirmatory Testing) no change in any test criteria took place. According to the results BIWG 98 SE is not light sensitive.

5 Conclusion

The NCE BIWG 98 SE is a stable drug substance. The Accelerated and Long-Term Stability test results with the three registration batches confirmed fully the data of the Stress-testing with the drug substance.

No change took place in the organoleptical, physico-chemical, chemical and container closure system properties.

Due to the hygroscopicity a slight increase in loss on drying was indicated.

The drug substance is not sensitive to light according to the Photostability investigation. The tested polyethylene foil can be used for storage and shipment.

The drug substance must be stored in tight containers. Special precautions for handling during production are not required.

A preliminary re-test period of 24 months can be derived from the primary and supportive data. the stability testing will be continued up to 60 months with the expectation to extend the re-test period up to 60 months. It means all stability data are within release specifications.

6 Statements

Storage instructions: - Keep the container tightly closed
- Store in a dry place

In the EU and Japan no further storage instructions are necessary.

USA: Store at 25°C, excursions permitted (15 - 30°C)

During shipment 30°C can be exceeded (3 months 70°C have been investigated)