

	Investigation report: Dymista 6.4 g Nasal Spray Stability results	Code: CQA-UB-0039/01
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		Department
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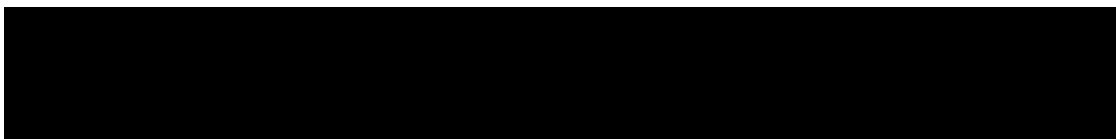
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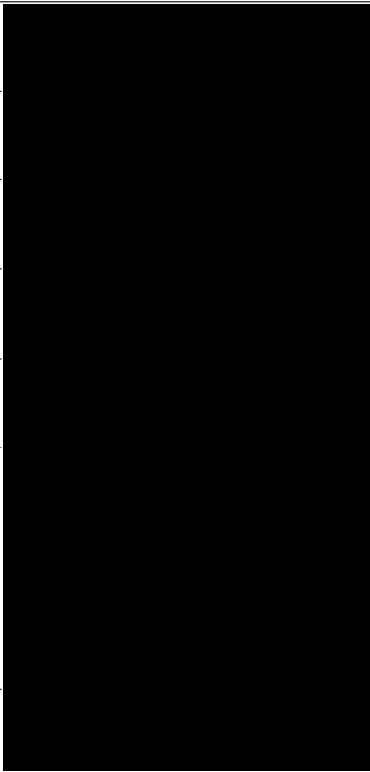
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1. Description of Incident

Observations during stability studies:



Specifications of parameters, where oos results have been observed:

Parameter	Specification	
Assay Azelastine HCl		release and shelf-life
Assay Fluticasonpropionate		release and shelf-life
Assay Benzalkonium chloride		shelf-life
Assay Phenylethylalcohol		shelf-life
Assay Disodium EDTA		release and shelf-life
Delivered Dose Uniformity		release and shelf-life
Weight loss		shelf-life



All imported batches are undergoing EU-testing and all batches met the release specification and were released to the market.

After the first oos report for the validation batches has been received, batch release for this product and manufacturing has been put on hold.

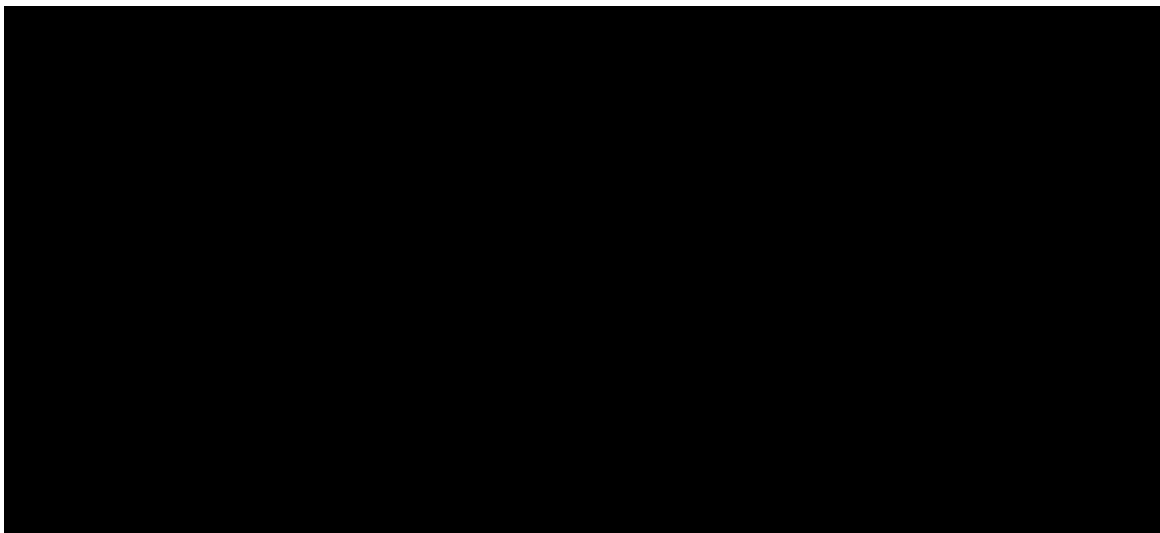
A shelf life of 36 months is registered for the 6.4g and the 23g form as well.

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Product: Dymista Nasal Spray 6.4g

Bulk batch and manufacturing date	Finished Product batch	Countries
FC2100 06/2012	FC2100	
FC2102 07/2012	FC2102	
FC2106 07/2012	FC2106	
FC3188 05/2013	FC3188 FC3192 FC3297 FC3458	
FC4001 01/2014	FC4001	

Table 1: Finished product of Dymista 6.4g preparations with running stability studies





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Batch	Condition/ Orientation	Weight loss Max. 2.0%	Assay										Delivered dose uniformity individual values 75-125%		Osmolali ty mosmol/ kg
			Azelaštine (%) 95.0 - 105.0%		Fluticasone (%) 95.0 - 105.0%		BAC (%) 80.0 - 105.0%		PEA (%) 70.0 - 105.0%		EDTA (%) 90.0 - 110.0%		Azelastine	Fluticasone	
		24 m	0 m	24 m	0 m	24 m	0 m	24 m	0 m	24 m	0 m	24 m			
FC 2100	25°C/60%RH/ upright														
FC 2100	25°C/60%RH/ horizontal														
FC 2102	25°C/60%RH/ upright														
FC 2102	25°C/60%RH/ horizontal														
FC 2106	25°C/60%RH/ upright														
FC 2106	25°C/60%RH/ horizontal														
FC 2100	30°C/75%RH/ upright														
FC 2100	30°C/75%RH/ horizontal														
FC 2102	30°C/75%RH/ upright														
FC 2102	30°C/75%RH/ horizontal														
FC 2106	30°C/75%RH/ upright														
FC 2106	30°C/75%RH/ horizontal														

Table 2: Summary of results of batches FC2100, FC2102 and FC2106 after 24 months 25°C / 60% r.h. and 30°C / 75% r.h.

Spray is stored in upright and horizontal position.

Attachment 1: Complete stability tables of batches FC2100, FC2102 and FC2106 at 25°C, 60% r.h. up to 24 months

Batch	Condition	Weight loss Limit NMT 2.0%	Assay Azelaštine Limit 95.0 – 105.0%	Assay Fluticasone Limit 95.0 – 105.0%	Assay Benzalkoni mchloride Limit 80.0 – 105.0%	Delivered Dose Uniformity Fluticasone Not more than 2 out of 20 determinations are outside 80 - 120% of label claim, none is outside 75 - 125% of label claim for Azelaštine HCl and Fluticasonpropionate
FC3188	25°C/ 60%r.h. Upright 18 months					

Table 3: Summary of oos results of batch FC3188 (18 months storage)

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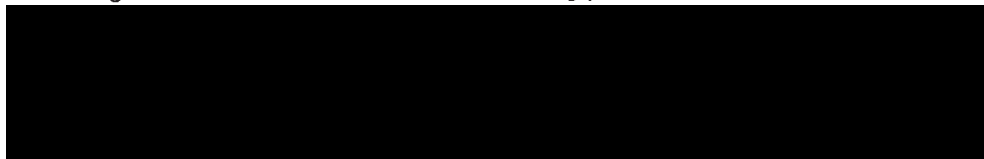
Batch	Condition	Assay Fluticasone Limit 95.0 – 105.0%
FC4001	25°C/ 60%r.h. Upright 9 months	

Table 4: Summary of oos results of batch FC4001 (9 months storage)

2. General Overview of the product and its processes

Dymista is a nasal spray with the two active pharmaceutical ingredients Azelastine HCl and Fluticasonepropionate. This fixed combination product was registered in the EU via a DCP submission and approved in January 2013 in EU. The product is marketed in two pack sizes. Vials with 6.4g (number of actuations >=28) and vials with 23g (number of actuations >= 120). The product is also registered in several Non-EU countries. The product manufacturing was first established at Cipla in Goa/ India in 2007 and transferred in 2012 to another Cipla manufacturing site of Cipla Indore/ India.

The following sites are involved in the manufacturing process:



All imported batches are undergoing EU-testing and all batches met the release specification and were released to the market.

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3. Composition of the Product

Component	Quality standard ¹	Function	Amount		
			% w/w	mg/g	mg/spray
Azelastine hydrochloride	Ph. Eur.				
Fluticasone propionate	Ph. Eur.				
Disodium edetate	Ph. Eur./ USP-NF				
Glycerol	Ph. Eur./ USP-NF				
Microcrystalline cellulose and carmellose sodium ²	Ph. Eur./ USP-NF				
Polysorbate 80	Ph. Eur./ USP-NF				
Benzalkonium chloride ³	Ph. Eur./USP-NF				
Phenylethyl alcohol	USP-NF				
Water, purified	Ph. Eur./ USP-NF				
Nitrogen ⁴	Ph. Eur./ USP-NF				
Total					

¹ The quality complies with the requirements of the monograph in its current version.

² Apparent viscosity [REDACTED]

³ Added as benzalkonium chloride solution [REDACTED]

⁴ Optionally, nitrogen may be used during compounding and as a processing aid during filling/pump application.

Primary packaging components:

Bottles:

Dymista Nasal Spray 6.4g, Suspension is filled into Ph. Eur. Type I amber glass bottles. Each bottle is fitted with a spray pump and a nasal applicator (actuator) assembled with a dust cap. The spray pump is crimped to the glass bottle and cannot be taken apart.

Information on the bottle can be found in the following table.

Pack size	Component	Material	Bottle size
6.4g	Bottle	Ph. Eur. Type I amber glass	10 mL (13.5 mL fill capacity)

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Spray pump:

A VP3/140 CS20 nasal spray pump with a nominal delivery volume of 140 µL is used for the dosing of Dymista Nasal Spray. A brief summary of the components of the spray pump and the materials employed is provided in the following table.

Component	Material
Body	Polypropylene blend
Floating gasket	Nitrile rubber
Spring support	Polypropylene blend
Spring cap	Polyoxymethylene (POM)
Return spring	Stainless steel
Stem	Polyoxymethylene (POM)
Piston	Low density polyethylene
Stem spring	Stainless steel
Stem gasket	Nitrile rubber
Ferrule	Aluminum
Neck gasket	Ethylene vinyl acetate (EVA)
Dip tube	Low density polyethylene

Nasal applicator:

An actuator with cap CB18 NAC/3/B + B25/A is used for the nasal application of Dymista Nasal Spray. A brief summary of the components of the nasal applicator and the materials employed is provided in the following table.

Component	Material
Head	Polypropylene blend
Captive insert	Polypropylene
Cap	Polypropylene

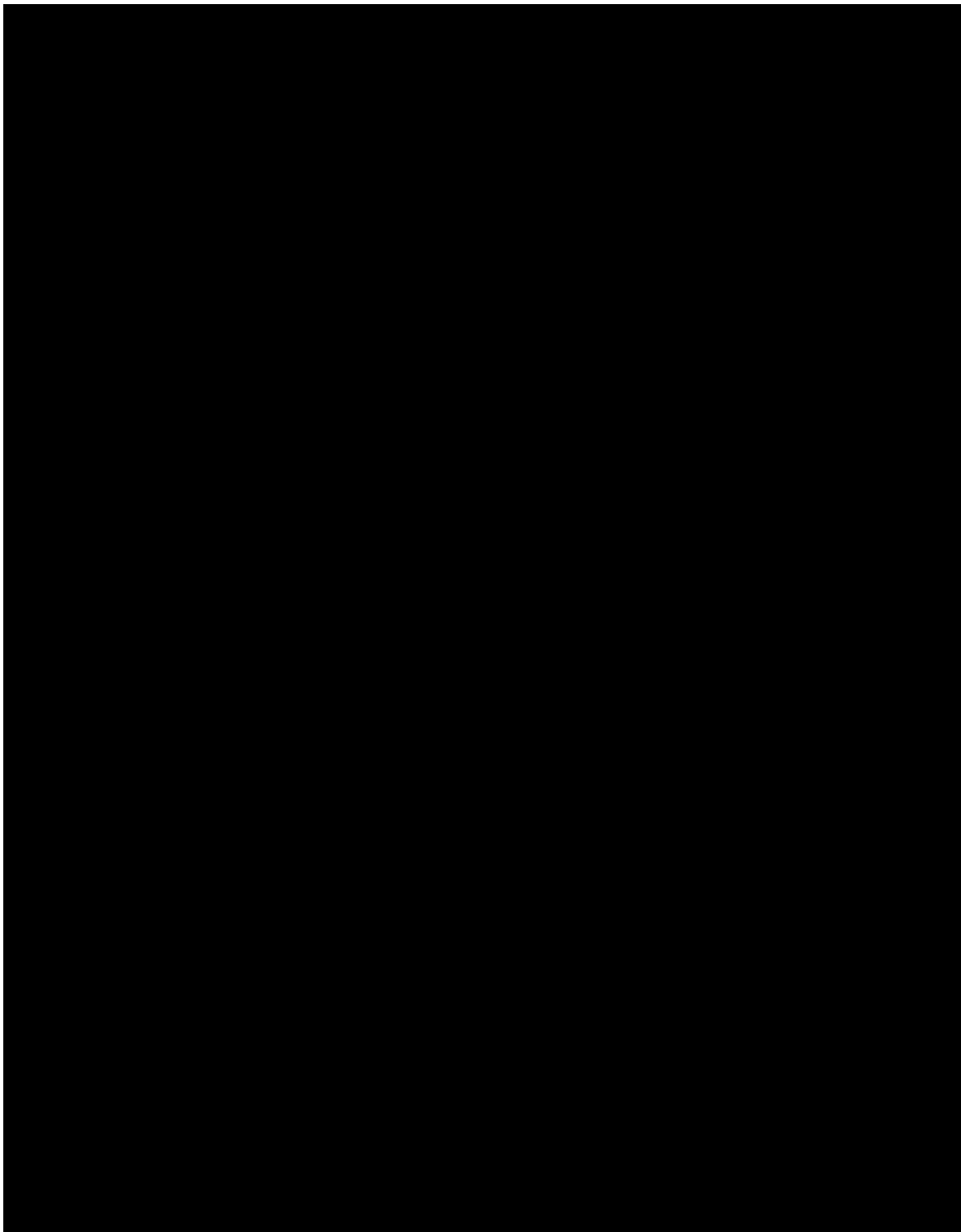
4. Manufacturing Flow

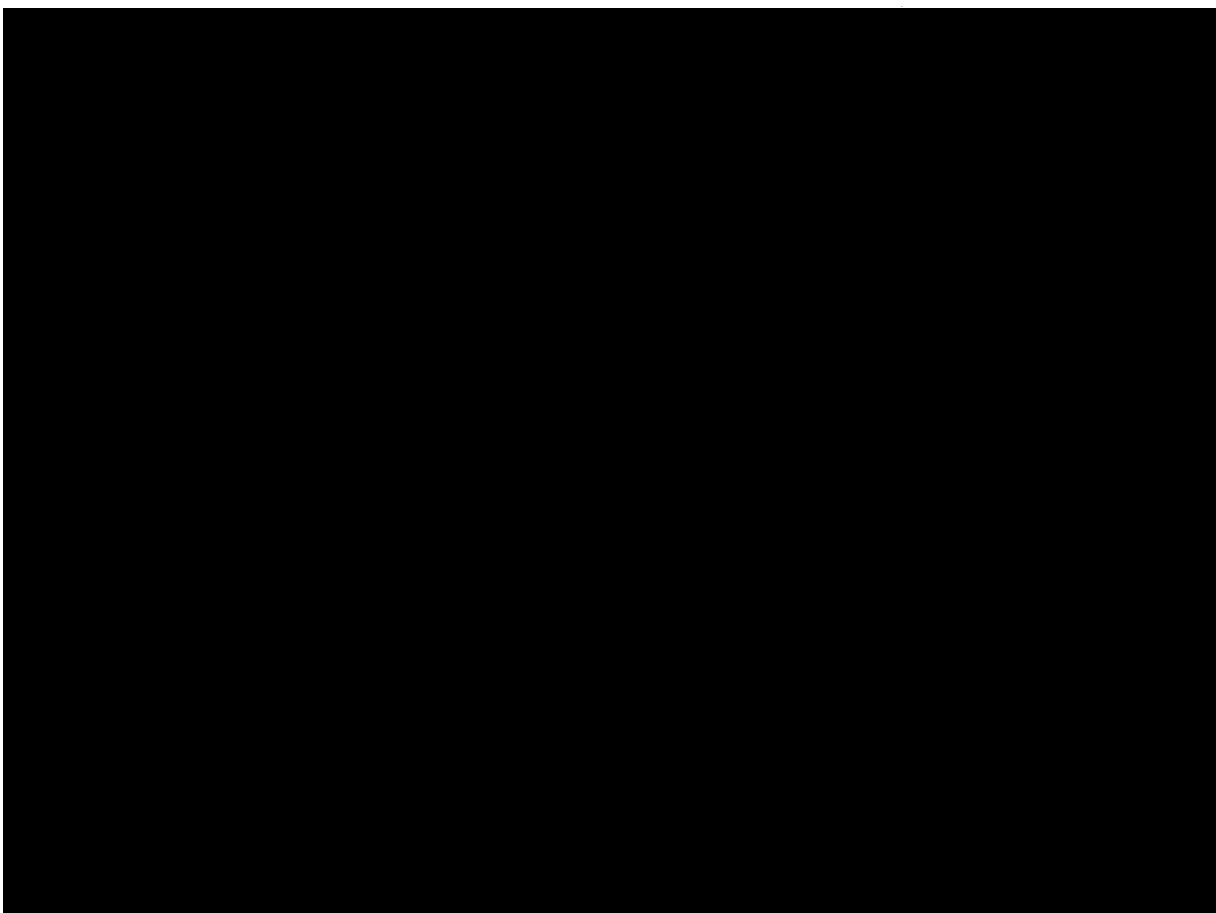
Diagram 1: Manufacturing flow chart of Dymista Nasal Spray (250kg batch size)



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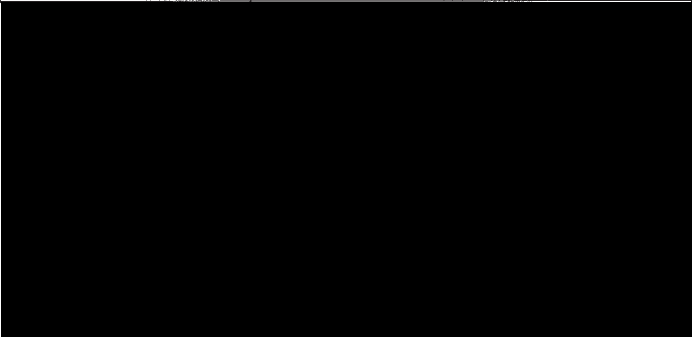
	Condition	Assay Azelastine Limit 95.0 – 105.0%	Assay Fluticasone Limit 95.0 – 105.0%	Assay Benzalkonium chloride Limit 80.0 – 105.0%
FC2100	23°C ~ 34 months			
FC2102	23°C ~ 34 months			
FC2106	23°C ~ 34 months			
FC3188	23°C ~ 22 months			
FC4001	23°C ~ 14 months			
FC4127	23°C ~ 11 months			

Table 6: Results of reference samples tested at Cipla Indore

Compared to the initial release results all stability results confirm the behaviour of the product during storage showing assay increase.

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Impact of starting Materials

Pump

The spray pumps for all batches manufactured have been supplied by the qualified manufacturer Aptar/USA.

The length of the dip tubes, diameter of ferrule and ferrule height has been checked as possible influence on the closing system for batches FC2100, FC2102 and FC2106. All results comply with the specification.

Vials

The bottles for all batches manufactured have been supplied by the qualified manufacturer Nuova Ompi, Italy.

No impact of the glass could be detected.

Nasal Applicator

The nasal applicators for all batches manufactured have been supplied by the qualified manufacturer Aptar/USA.

No impact of the nasal applicator could be detected.

Active Pharmaceutical Ingredients

The Active ingredients have been supplied by the qualified manufacturers Cipla, Kurkumbh, India and Evonik, Hanau, Germany. No impact of the API batches used could be detected.

Excipients

All excipients have been supplied by qualified manufacturers. No impact of the excipient could be detected.

5.3 Investigation in production / packaging

No deviations were reported in the respective packaging records.

Since 2012, when the manufacturing of the product was transferred from Cipla Goa to Cipla Indore and the process was validated, no changes in equipment and premises were done. The procedures remained unchanged.

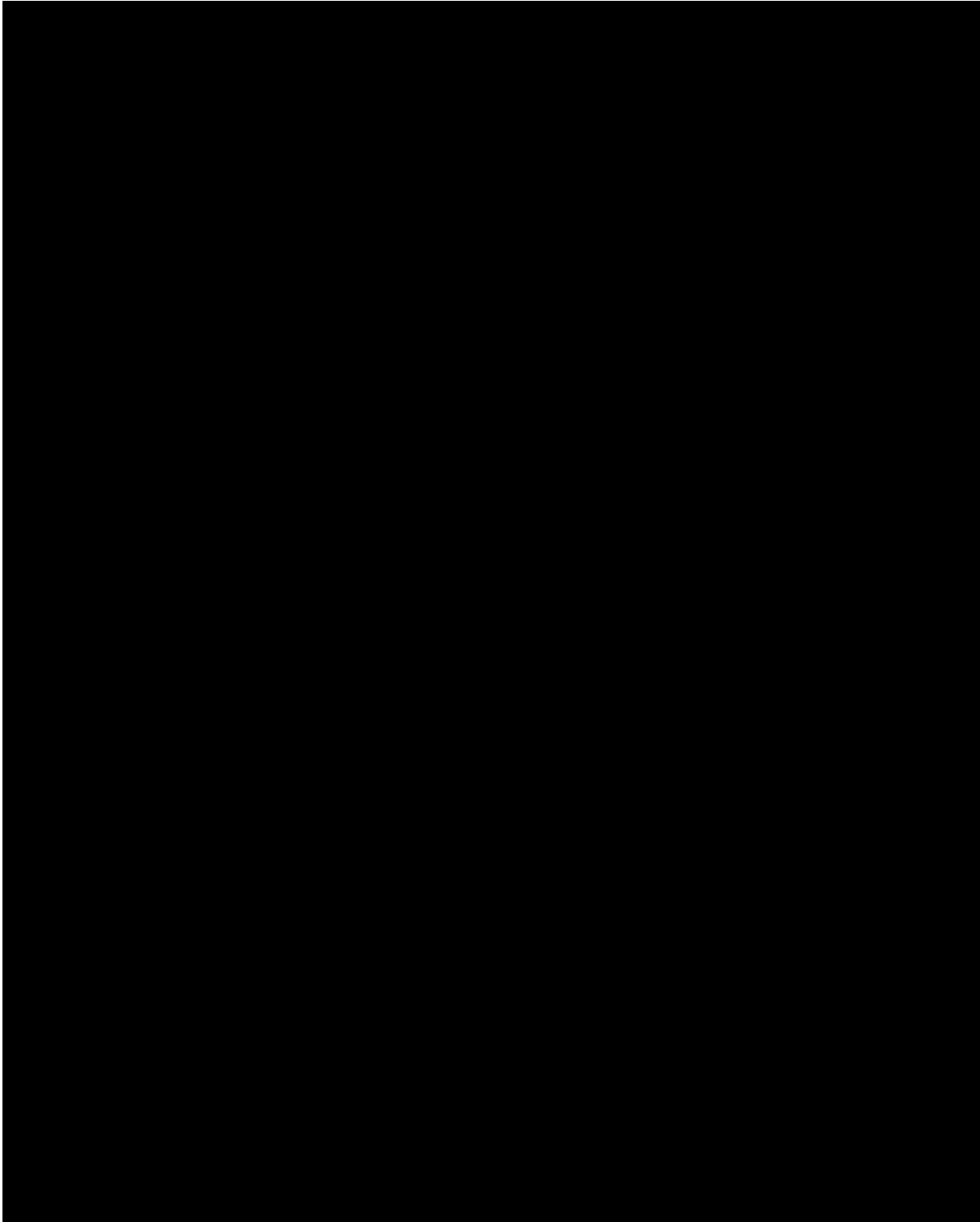
The difference between the former manufacturing site in Goa and the new manufacturer in Indore is the mechanism of closing of the vials, machine speed and filling process.

No significant difference could be seen for the stability data for both sites.



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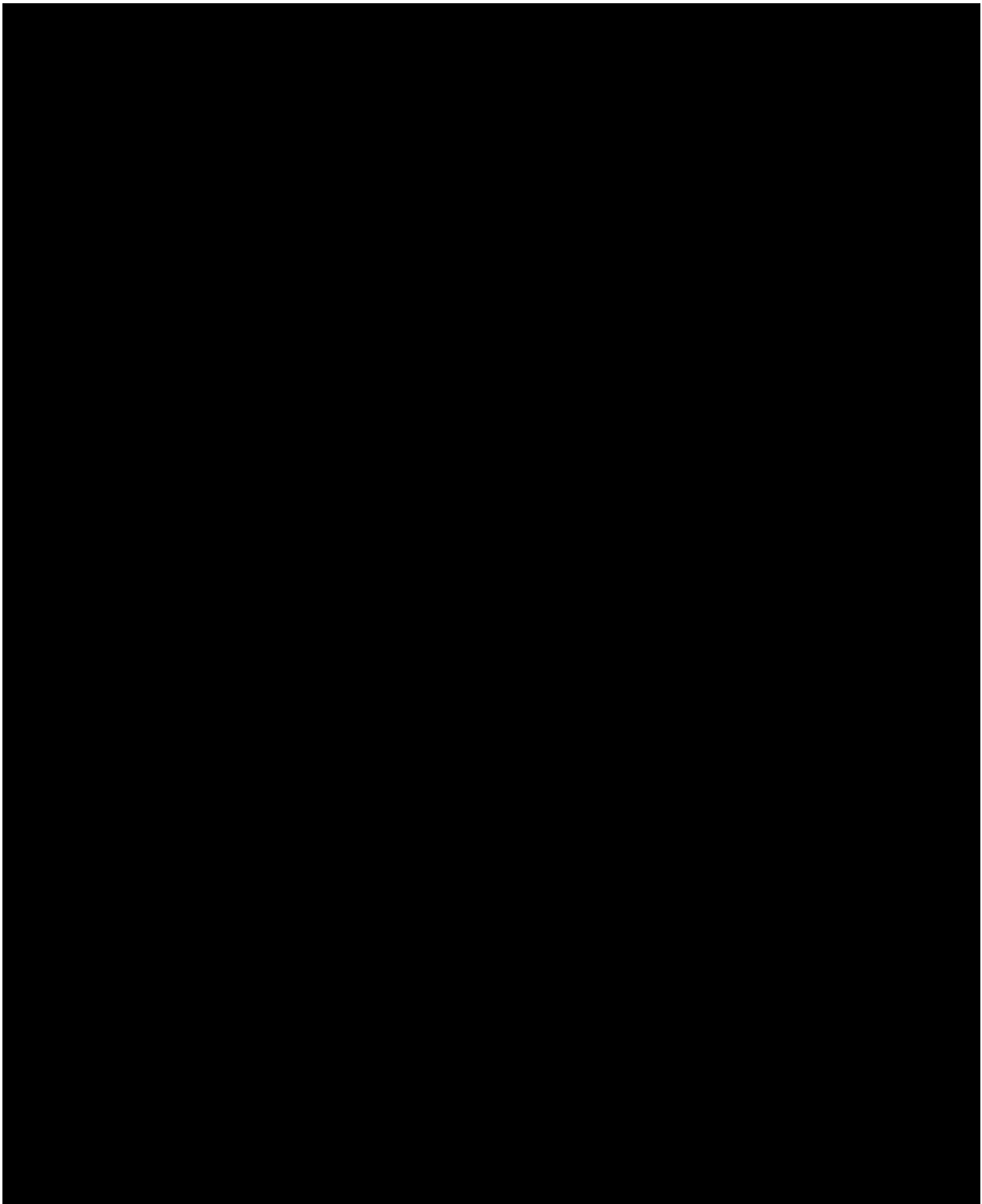
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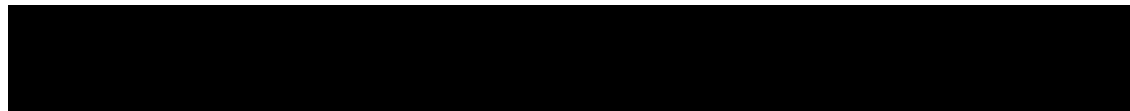
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7. Risk Assessment



A clinical assessment of API assay levels up to 125% was performed (attachment 2). The increase is considered as not clinically relevant with no risk for the patient.

8. CAPA

After [REDACTED] became available, manufacture and release of 6.4 g pack size was put on hold.

As CAPA the primary packaging material and sealing technology including increase of compression force is under evaluation.

Actual registered glass manufacturer had supplied vials for trials to support hypothesis. Trials have been executed, gasket compression is higher and weight loss results are lower compared to standard vials. Those results show that the sealing bead improves the tightness of the closing system.

A variation to reduce the shelf-life for 6.4g pack size to 18 months will be done in addition.

9. Distribution of product

A list of all Dymista 6.4g batches, that have been released since 03/2013 is available in attachment 3.

10. Conclusion

The [REDACTED] results have been confirmed on all batches that are currently part of stability studies. Deviation is not a batch specific issue. The clinical evaluation confirms that there is no risk to patient health and safety. CAPA will be established before manufacturing of new commercial batches.

List of attachments:

- Attachment 1: Compiled stability data for ICH validation batches FC2100, FC2102 and FC2106 at 25°C, 60% r.h. up to 24 months
- Attachment 2: Clinical Expert Statement
- Attachment 3: Distribution list of Dymista 6.4g

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Change Index

Version	Reason for update	Valid from	Registration, assessment and release in the framework of a Change Control Procedure	
			no	yes year/current No.
01	new edition	04.05.2015	X	

Attachment 1 to
 CQ4-UB-0039/09
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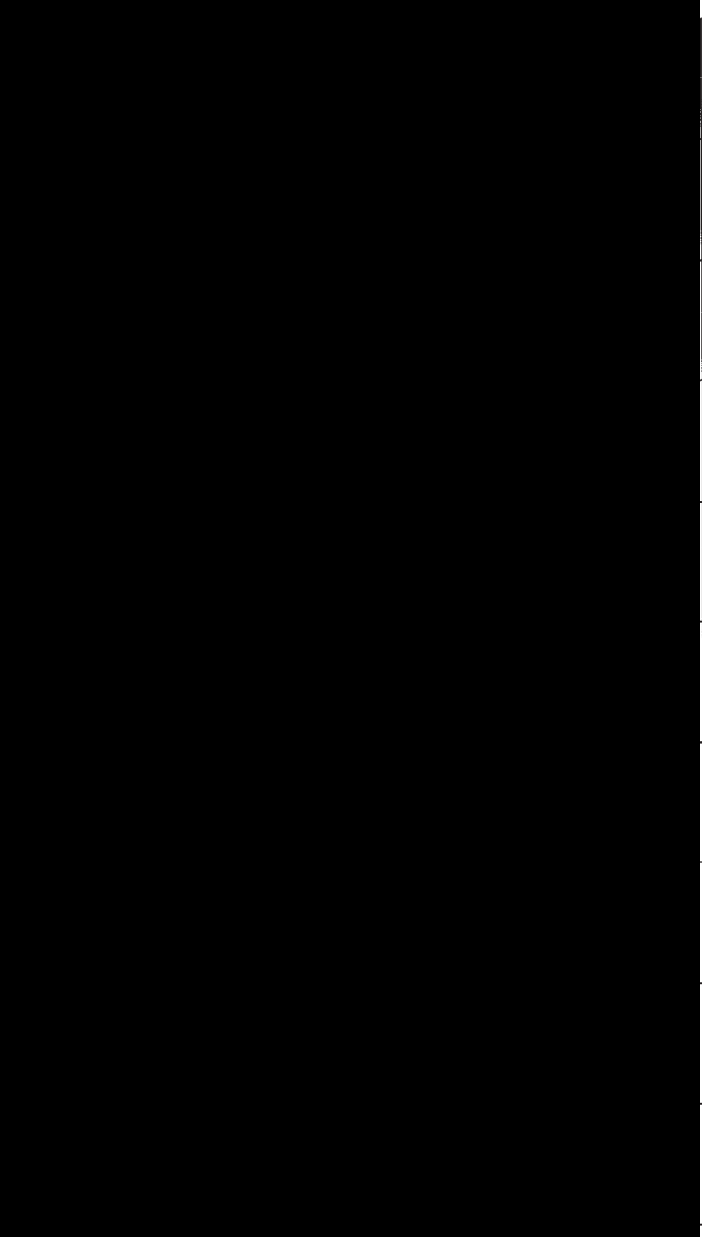
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3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 13: Stability data for batch FC2100 (4 mL, upright), at 25°C/60% RH

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Description	White, homogeneous redispersible suspension free from visible foreign matter in an amber glass bottle with a crimp seal pump and white actuator with a translucent dust cap										
pH	5.5 - 6.5										
Viscosity	20 - 60 mPa·s										
Osmolality	mosmol/kg (for data generation)										
Weight loss	≤ 5.0%										
Number of actuations ^{*)}	≥ 28 actuations										
Droplet size distribution	Mean D ₁₀ ^{*)}										
	Mean D ₅₀ 45-115 µm										
	Mean D ₉₀ ^{*)}										
	Span ^{*)}										
Particle size distribution	%Vol. < 10 µm ≤ 4%										
	≥ 50% ≤ 2.5 µm										
	≥ 80% ≤ 5 µm										
	≤ 20% > 5 µm and ≤ 10 µm										
	> 95% ≤ 10 µm										
	Any agglomeration, crystal growth or change in morphology should be absent.										

^{*)} for information only, no limit set.

^{*)} after initial priming of 6 actuations

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3.2. Body of Data

3.2.P Drug Product Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, Suspension

3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 13: Stability data for batch FC2100 (4 mL, upright) at 25°C/60% RH (continued)

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Del. dose uniformity Azelastine HCl - Range											
- Mean											
Fluticasone propionate - Range											
- Mean											
Related substances Azelastine HCl ¹⁾ Any impurity ²⁾ - Azel.-N-oxide A ⁵⁾ - Azel.-N-oxide B ⁵⁾ - Ph. Eur. Impurity D ⁵⁾ Total impurities											
Fluticasone propionate ³⁾ Any impurity ⁴⁾ - Ph. Eur. Impurity A ⁵⁾ - Ph. Eur. Impurity C ⁵⁾ - Ph. Eur. Impurity D ⁵⁾ Total impurities											

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3.2. Body of Data

3.2.P Drug Product Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, Suspension

3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 13: Stability data for batch FC2100 (4 mL, upright) at 25°C/60% RH (continued)

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Assay of benzalkonium chloride											
Assay of phenylethyl alcohol											
Assay of disodium edetate											
Assay of azelastine HCl											
Assay of fluticasone propionate											
Microbiological quality											

N/A = not applicable

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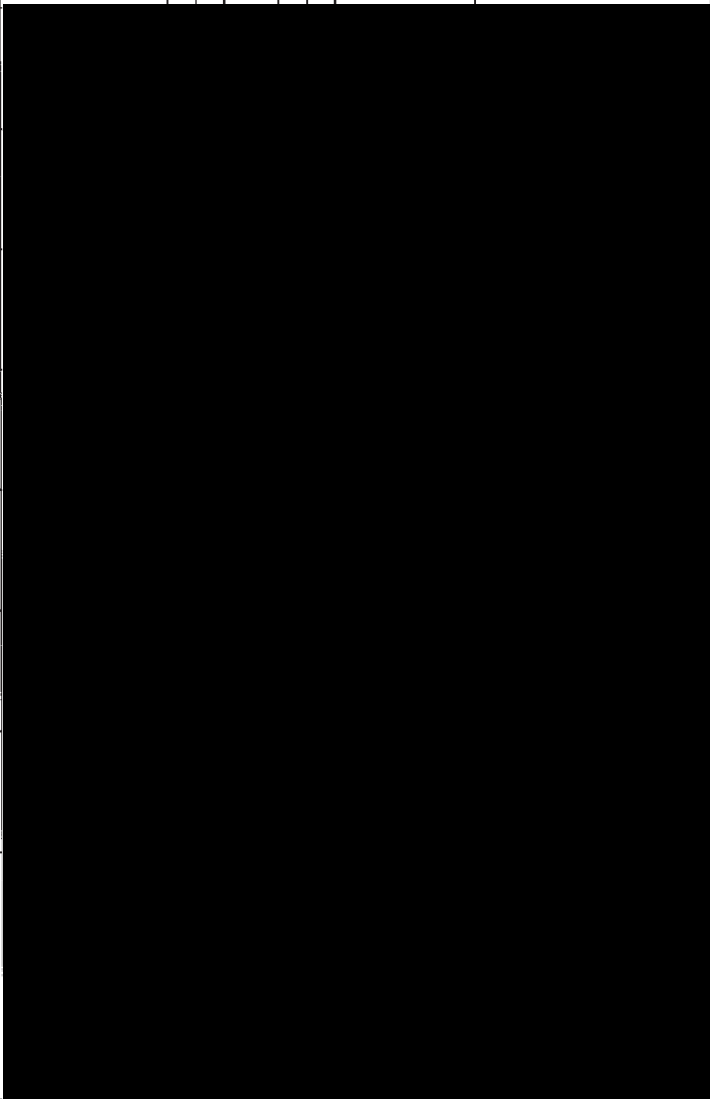
3.2. Body of Data

3.2.P Drug Product Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, Suspension

3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 14: Stability data for batch FC2100 (4 mL, horizontal) at 25°C/60% RH

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Description											
pH											
Viscosity											
Osmolality											
Weight loss											
Number of actuations ^{*)}											
Droplet size distribution											
Particle size distribution											

^{*)} for information only, no limit set.

^{**)} after initial priming of 6 actuations

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3.2. Body of Data

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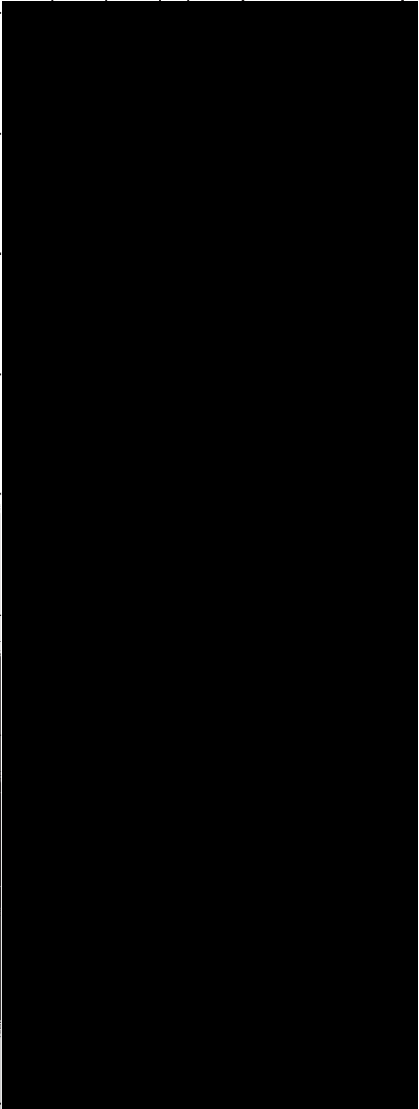
Table 14: Stability data for batch FC2100 (4 mL, horizontal) at 25°C/60% RH (continued)

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Del. dose uniformity Azelastine HCl - Range											
- Mean											
Fluticasone propionate - Range											
- Mean											
Related substances Azelastine HCl ¹⁾											
Any impurity ²⁾											
- Azel.-N-oxide A ⁵⁾											
- Azel.-N-oxide B ⁵⁾											
- Ph. Eur. Impurity D ⁵⁾											
Total impurities											
Fluticasone propionate ³⁾											
Any impurity ⁴⁾											
- Ph. Eur. Impurity A ⁵⁾											
- Ph. Eur. Impurity C ⁵⁾											
- Ph. Eur. Impurity D ⁵⁾											
Total impurities											



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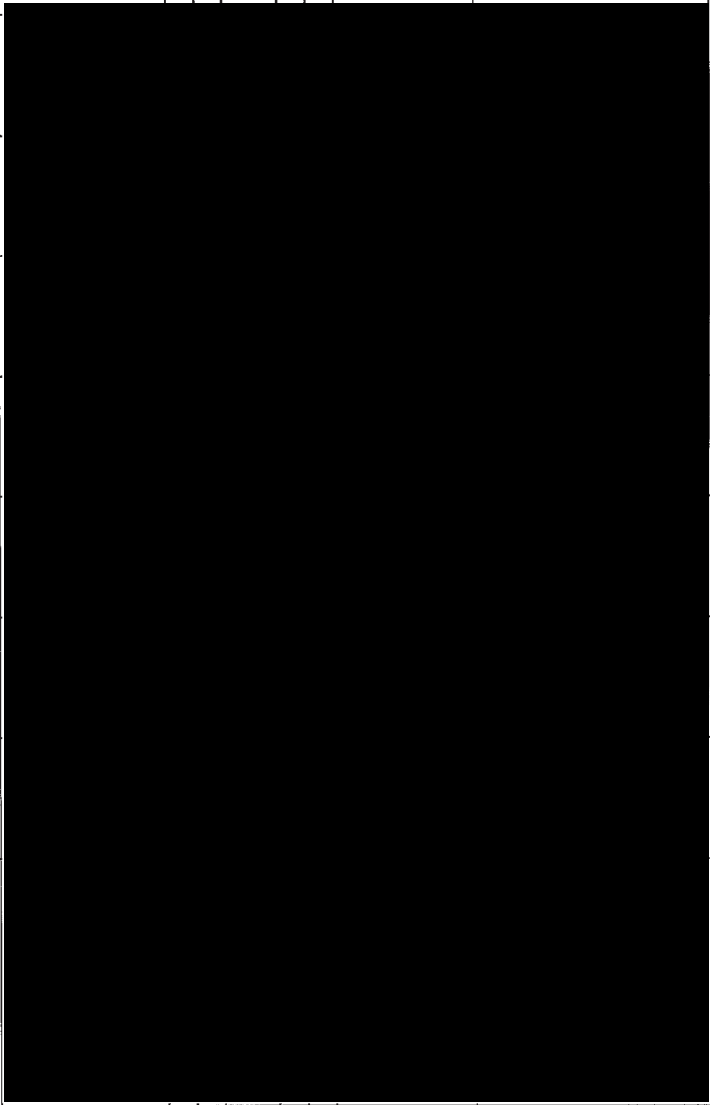
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Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Assay of benzalkonium chloride											
Assay of phenylethyl alcohol											
Assay of disodium edetate											
Assay of azelastine HCl											
Assay of fluticasone propionate											
Microbiological quality											

N/A = not applicable

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3.2.P.8.3	Stability Data

Table 15: Stability data for batch FC2102 (4 mL, upright) at 25°C/60% RH

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Description											
pH											
Viscosity											
Osmolality											
Weight loss											
Number of actuations ^{ns)}											
Droplet size distribution											
Particle size distribution											

^{ns)} for information only, no limit set.

^{ns)} after initial priming of 6 actuations

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Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Del. dose uniformity Azelastine HCl - Range											
- Mean											
Fluticasone propionate - Range											
- Mean											
Related substances Azelastine HCl ¹⁾											
Any impurity ²⁾											
- Azel.-N-oxide A ⁵⁾											
- Azel.-N-oxide B ⁵⁾											
- Ph. Eur. Impurity D ⁵⁾											
Total impurities											
Fluticasone propionate ³⁾											
Any impurity ⁴⁾											
- Ph. Eur. Impurity A ⁵⁾											
- Ph. Eur. Impurity C ⁵⁾											
- Ph. Eur. Impurity D ⁵⁾											
Total impurities											

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Table 15: Stability data for batch FC2102 (4 mL, upright) at 25°C/60% RH (continued)

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Assay of benzalkonium chloride											
Assay of phenylethyl alcohol											
Assay of disodium edetate											
Assay of azelastine HCl											
Assay of fluticasone propionate											
Microbiological quality											

N/A = not applicable

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3.2.P.8	Stability
3.2.P.8.3	Stability Data

Table 16: Stability data for batch FC2102 (4 mL, horizontal) at 25°C/60% RH

Test	Specification	0	3	6	9	12	18	24	30	36	-
Description											
pH											
Viscosity											
Osmolality											
Weight loss											
Number of actuations ^{*)}											
Droplet size distribution											
Particle size distribution											

^{*)} for information only, no limit set.

^{**)} after initial priming of 6 actuations

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Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Del. dose uniformity Azelastine HCl - Range											
- Mean											
Fluticasone propionate - Range											
- Mean											
Related substances Azelastine HCl ¹⁾ Any impurity ²⁾ - Azel.-N-oxide A ⁵⁾ - Azel.-N-oxide B ⁵⁾ - Ph. Eur. Impurity D ⁵⁾ Total impurities											
Fluticasone propionate ³⁾ Any impurity ⁴⁾ - Ph. Eur. Impurity A ⁵⁾ - Ph. Eur. Impurity C ⁵⁾ - Ph. Eur. Impurity D ⁵⁾ Total impurities											

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Table 16: Stability data for batch FC2102 (4 mL, horizontal) at 25°C/60% RH (continued)

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Assay of benzalkonium chloride											
Assay of phenylethyl alcohol											
Assay of disodium edetate											
Assay of azelastine HCl											
Assay of fluticasone propionate											
Microbiological quality											

N/A = not applicable

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3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 17: Stability data for batch FC2106 (4 mL, upright) at 25°C/60% RH

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Description											
pH											
Viscosity											
Osmolality											
Weight loss											
Number of actuations ^{*)}											
Droplet size distribution											
Particle size distribution											

^{*)} for information only, no limit set.

^{**)} after initial priming of 6 actuations

Module 3 Quality

3.2. Body of Data

3.2.P Drug Product Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, Suspension

3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 17: Stability data for batch FC2106 (4 mL, upright) at 25°C/60% RH (continued)

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Del. dose uniformity Azelastine HCl - Range											
- Mean											
Fluticasone propionate - Range											
- Mean											
Related substances Azelastine HCl ¹⁾ Any impurity ²⁾ - Azel.-N-oxide A ⁵⁾ - Azel.-N-oxide B ⁵⁾ - Ph. Eur. Impurity D ⁵⁾ Total impurities											
Fluticasone propionate ³⁾ Any impurity ⁴⁾ - Ph. Eur. Impurity A ⁵⁾ - Ph. Eur. Impurity C ⁵⁾ - Ph. Eur. Impurity D ⁵⁾ Total impurities											

Module 3 Quality

3.2. Body of Data

3.2.P Drug Product Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, Suspension

3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 17: Stability data for batch FC2106 (4 mL, upright) at 25°C/60% RH (continued)

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Assay of benzalkonium chloride											
Assay of phenylethyl alcohol											
Assay of disodium edetate											
Assay of azelastine HCl											
Assay of fluticasone propionate											
Microbiological quality											

N/A = not applicable

Module 3 Quality

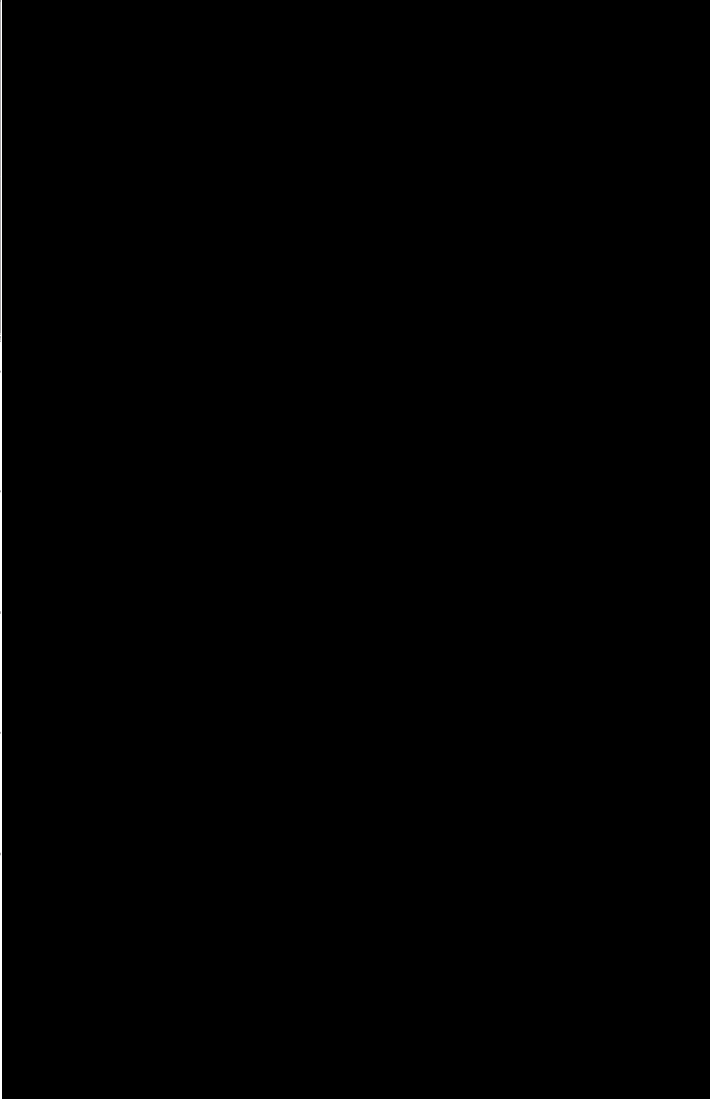
3.2. Body of Data

3.2.P Drug Product Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, Suspension

3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 18: Stability data for batch FC2106 (4 mL, horizontal) at 25°C/60% RH

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Description											
pH											
Viscosity											
Osmolality											
Weight loss											
Number of actuations **)											
Droplet size distribution											
Particle size distribution											

*) for information only, no limit set.

**) after initial priming of 6 actuations

Module 3 Quality

3.2. Body of Data

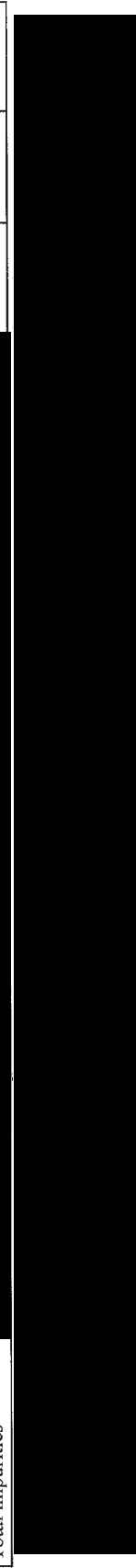
3.2.P Drug Product Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, Suspension

3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 18: Stability data for batch FC2106 (4 mL, horizontal) at 25°C/60% RH (continued)

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Del. dose uniformity Azelastine HCl - Range											
- Mean											
Fluticasone propionate - Range											
- Mean											
Related substances Azelastine HCl ¹⁾ Any impurity ²⁾ - Azel.-N-oxide A ⁵⁾ - Azel.-N-oxide B ⁵⁾ - Ph. Eur. Impurity D ⁵⁾											
Total impurities											
Fluticasone propionate ³⁾ Any impurity ⁴⁾ - Ph. Eur. Impurity A ⁵⁾ - Ph. Eur. Impurity C ⁵⁾ - Ph. Eur. Impurity D ⁵⁾											
Total impurities											



Module 3 Quality

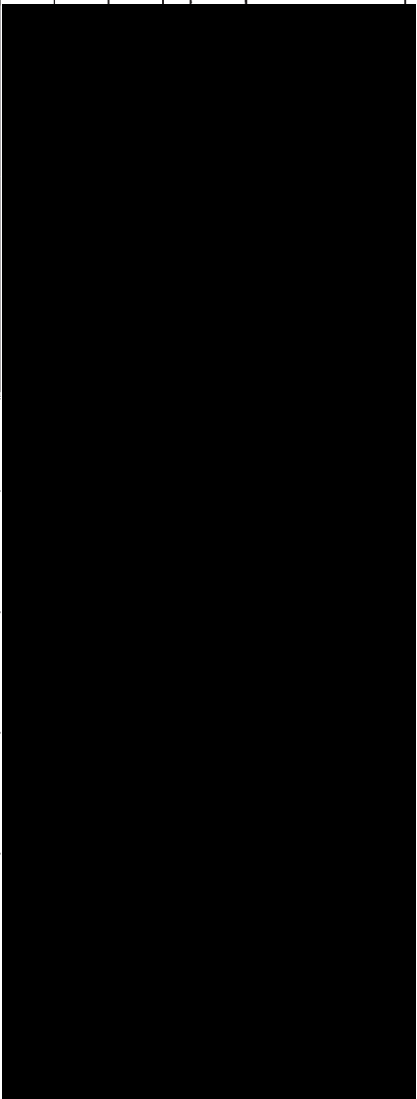
3.2. Body of Data

3.2.P Drug Product Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, Suspension

3.2.P.8 Stability

3.2.P.8.3 Stability Data

Table 18: Stability data for batch FC2106 (4 mL, horizontal) at 25°C/60% RH (continued)

Test	Specification	Time points (months)									
		0	3	6	9	12	18	24	30	36	-
Assay of benzalkonium chloride											
Assay of phenylethyl alcohol											
Assay of disodium edetate											
Assay of azelastine HCl											
Assay of fluticasone propionate											
Microbiological quality											

N/A = not applicable