Australian Government
Department of Health
Therapeutic Goods Administration

Pharmaceutical Chemistry Section
Scientific Evaluation Branch

Milestone 3 evaluation report of chemical, pharmaceutical and biopharmaceutical data

Type of submission:	Type D: New generic medicine
Submission number:	PM-2017-03103-1-5
eSubmission Identifier:	e002646
Drug substance:	tiotropium bromide
Dose form:	Dry Powder for Inhalation, hard capsules
Strength(s):	13 microgram
Sponsor:	Teva Pharma Australia Pty Ltd
Proposed trade name(s):	BRALTUS
Chemistry file number:	E18-211908
Associated DMF file(s):	E17-24557
Evaluator:	[redacted]
Report status:	This report requires censoring before release to the sponsor

Contents

I Introduction

Teva Pharma Australia Pty Ltd has applied to register 13 microgram tiotropium (as bromide) capsules for dry powder inhalation (10 micrograms tiotropium as the delivered dose) under the trade name *BRALTUS*. ***The trade name will be referred to the clinical delegate for comment and further questions may arise.***

The new drug product is intended to be a new generic of *Spiriva* tiotropium 18 micrograms powder for inhalation (in capsule) blister pack sponsored by Boehringer Ingelheim Pty Ltd (AUST R 81525). There are no generic versions of *Spiriva* on the market.

Tiotropium, a N-quaternary anticholinergic agent, is topically (broncho-) selective when administered by inhalation. The high potency (IC50 approximately 0.4 nM for M3) and slow receptor dissociation is associated with a significant and long-acting bronchodilation in patients with chronic obstructive pulmonary disease (COPD). The bronchodilation following inhalation of tiotropium is primarily a local effect on the airways, not a systemic one.

Tiotropium is indicated for the long term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD). Tiotropium is indicated for the prevention of COPD exacerbations.

The maximum recommended daily dose for tiotropium is inhalation of the contents of one capsule, at the same time each day (13 µg delivered dose).

Tiotropium Bromide Monohydrate is the subject of a BP/Ph. Eur. monograph. However, the product is not subject to a BP or USP monograph.

II. Evaluation of the data as originally submitted

Module 1: Administrative and prescribing information

1.3 Medicine information and labelling

1.3.1 Australian Product Information (PI)

The sponsor has submitted a draft of the intended Product Information.

The sponsor should ensure that the following issues are addressed in the PIs:

- ***Please include the capsule as an excipient with the proprietary ingredient names and include the proprietary ingredient number in brackets adjacent to the name. The sponsor may need to submit a notification of a new proprietary ingredient form if the ingredient is not listed in the database.[1] This information will be added to the PARs once it is confirmed.***

1.3.3 Australian labelling

The applicant has submitted colour mock-ups of the proposed labelling.

The labelling complies with Labelling Order TGO 91 except for the following issues:

- ***It is unclear how the product strength should be expressed given the innovator product is labelled as an 18 microgram dose which the sponsor claims to be bioequivalent to their 13 microgram dose. This will be referred to the clinical delegate.***
- ***Please express the strength of the product as Tiotropium (as bromide) 13 micrograms.***
- ***It is unclear of the layout of the labels, for example it appears that the barcode on the box will not be visible. Please provide a physical sample pack.***

Note: The labelling has not been assessed for compliance with Australian State requirements.

1.6 Master files and Certificates of suitability

A letter of authorisation from the drug substance manufacturer (Industriale Chimica) to access the Tiotropium bromide drug master file number E17-24557 has been provided.

[1] Notification of a proprietary ingredient – https://www.tga.gov.au/form/notification-proprietary-ingredient

1.9 Biopharmaceutic studies

The sponsor has provided a summary form for the bioequivalence study to be evaluated as part of the assessment of the quality data for this product. This study is titled:

- Randomized, open, three-way, semi-replicate, crossover pharmacokinetic study in a two-stage design for evaluation of the systemic safety of Tiotropium 10 µg delivered dose inhalation powder, hard capsule (Test) compared to SPIRIVA® 18 microgram, inhalation powder, hard capsule (10 µg delivered dose) (Reference) each one administered as a single dose of 20 µg delivered dose of tiotropium (2 capsules) in healthy subjects

A justification for performing the biopharmaceutics studies on an overseas reference product has been provided and is discussed in section 5.3.

1.11 Foreign regulatory information

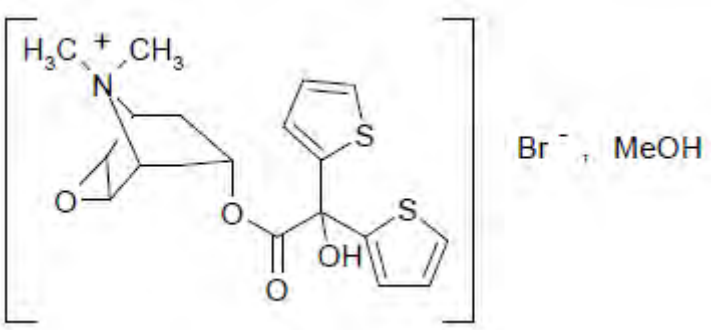
This product has been submitted and approved in the EU.

The sponsor should liaise with Manufacturing Quality Branch (gmpclearance@tga.gov.au) to ensure GMP clearance for all overseas manufacturing sites are maintained beyond the expected decision date.

Provisional ARTG Record (PAR)

The sponsor will be asked to review the PARs in the S.31 request and advise the TGA of any errors or omissions.

Module 3.2.S: Drug substance

Drug substance name	**Tiotropium bromide (methanol solvate)**
Structure	
Chemical formula	$C_{19}H_{22}NO_4S_2 \bullet CH_4O \bullet Br$
CAS Number	913719-58-1
Monographs	BP monograph

Manufacture and quality control by drug substance manufacturer

The manufacture, quality (according to in-house specification) and stability of the active ingredient are described in the associated Drug Master File which is the subject of a separate evaluation report (See D18-10385267). ***Questions have been raised.***

Aspects of the drug substance relevant to the drug product

Particle size distribution

Particle size is not controlled by the drug substance manufacturer.

Crystallinity/Polymorphism

There are known polymorphs of Tiotropium bromide. The drug substance manufacturer produces the methanol solvate form and tests for this form in the specification.

Control of the drug substance by finished product manufacturer

Specification

Proposed drug substance specification applied by the finished product manufacturer are the same as the drug substance manufacture specification except the finished product manufacturer does not control microbial purity. ***A control for microbial purity should be added to the specification as per the drug substance manufacture's specification.***

Analytical procedures

It is assumed that the drug substance analytical methods applied by the finished product manufacturer are the same as that applied by the drug substance manufacturer, however, details of the analytical methods applied by the finished product manufacturer have not been provided. ***The sponsor should provide details of the analytical methods applied by the finished product manufacturer. If these are the same as the drug substance manufacturer, this should be stated.***

Batch analyses

Batch data have been provided for three batches of the drug substance analysed by the drug substance and drug product manufacturer. The results show that the drug substance can be manufactured to a consistent quality.

Retest period

No stability data has been provided. ***The sponsor should confirm that they will test the drug substance immediately before use.***

Module 3.2.P: Drug product

There are no relevant drug product monographs.

3.2.P.1 Description and composition of the drug product

Description

Tiotropium 10 microgram (delivered dose) Dry Powder Inhalation (DPI) product consists of a capsule containing a blend of tiotropium bromide and lactose monohydrate and a single-dose inhaler device.

Formulation

Ingredient	Purpose	Quality standard	Quantity (mg)
Tiotropium bromide methanol solvate	Active ingredient	Ph. Eur.	0.0156[a]
Lactose monohydrate	Stabilizing agent, carrier, diluent	Ph. Eur.	[redacted]
HPMC capsule	Capsule	Ph. Eur.	
[redacted]			

[a] Tiotropium Bromide Methanol Solvate quantity is adjusted depending on Methanol content to produce the equivalent to 0.0156 mg of Tiotropium Bromide (0.013 mg of Tiotropium) during Spray drying

3.2.P.2 Pharmaceutical development

3.2.P.2.1 Components of the drug product

3.2.P.2.1.1 Drug substance

Tiotropium bromide methanol solvate is used in the manufacture of the product. [redacted]

3.2.P.2.1.2 Excipients

Lactose monohydrate

Lactose monohydrate is the only excipient used in the drug product. Particle size was determined to be a critical parameter and as such is controlled as follows:

[redacted]

[redacted]

3.2.P.2.2 Drug product

3.2.P.2.2.1 Formulation development

Formulation

The proposed 13 µg Tiotropium dry powder inhalation product is designed to be therapeutically equivalent to Spiriva® HandiHaler® 18 µg.

[redacted]

Physical characterisation

[redacted]

[redacted]

Minimum fill justification

[redacted]

Delivered dose uniformity & fine particle mass through container life

[redacted]

Delivered dose uniformity & fine particle mass over patient flow rate range

[redacted]

Single dose fine particle mass

[redacted]

Particle / droplet size distribution

[redacted]

Actuator / mouthpiece deposition

Drug substance is seen to accumulate on the mouthpiece of the drug product throughout the life of the product in a similar amount to the reference product.

Cleaning requirements

There are no cleaning instructions for the device as it is to be discarded after the use of 30 capsules. Studies have shown that the correct delivered dose is given throughout this period.

Effect of environmental moisture

Humidity did not result in brittleness of capsules and no capsule breakages were observed. However, high humidity conditions were seen to cause less of the drug substance dose to be received (below the specification limit). ***The sponsor should provide adequate justification for the reduced dose received at high humidity conditions as a significant proportion of Australia is considered to be in high humidity environments.***

Robustness

The sponsor has investigated the robustness of the product to device actuation, dropping, transport and inhalation orientations. The device was seen to be robust in all situations.

Delivery device development

It is unclear if the changes to the device described were undertaken after clinical and in vitro studies were performed. If they were comparison of the products performance characteristics (e.g., delivered dose, fine particle mass, etc.) should be investigated.

3.2.P.2.2.2 Overages

There are no overages in any of the manufacture of the product.

3.2.P.2.3 Manufacturing process development

The manufacturing process involves spray drying the drug substance with lactose and filling the blend in empty capsule shells.

3.2.P.2.4 Container closure system

See section 3.2.P.7 for details on the container closure system.

3.2.P.2.5 Microbiological attributes

Not applicable.

3.2.P.2.6 Compatibility

Not applicable.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Refer to Module 1.7 of this report.

3.2.P.3.2 Batch formula

[redacted]

3.2.P.3.3 Description of manufacturing process and process controls

Manufacturing process

[redacted]

Hold times are claimed by the sponsor as seen in the diagram above. However, ***in order to claim holding times the sponsor is required to provide full analysis on batches that have been held for the claimed periods, the data provided only tested for appearance, assay and homogeneity. Assurance should also be provided that the shelf life will be calculated in compliance with "CPMP/QWP/072/96 Annex: Start of Shelf-life of the finished product".***

3.2.P.3.4 Controls of critical steps and intermediates

Critical steps

[redacted]

3.2.P.3.5 Process validation and/or evaluation

[redacted]

3.2.P.4 Control of excipients

Lactose monohydrate is controlled according to the current version of the Ph. Eur. In addition the sponsor controls microbial quality and particle size distribution.

The capsule shell is controlled according to in-house specifications. The individual ingredients comply with the Ph. Eur.

The sponsor states that all excipients are free from the risk of TSE/BSE.

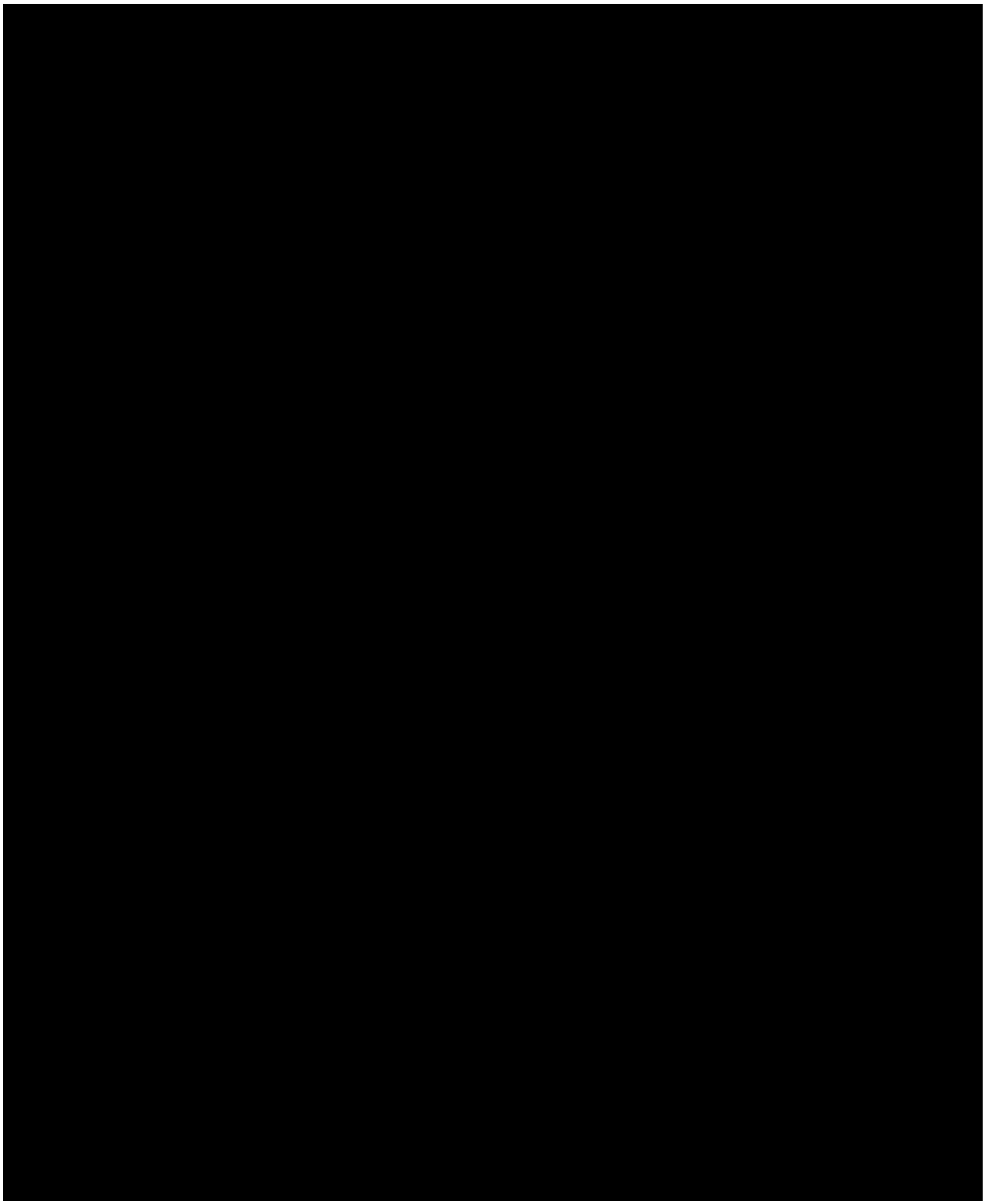
No novel excipients are used in the manufacturing of the proposed drug product.

3.2.P.5 Control of drug product

3.2.P.5.1 Specifications

The drug product specifications have been included below.

Drug product specifications



[redacted]

Please include all tests in the expiry specifications for regulatory testing purposes.

[redacted]

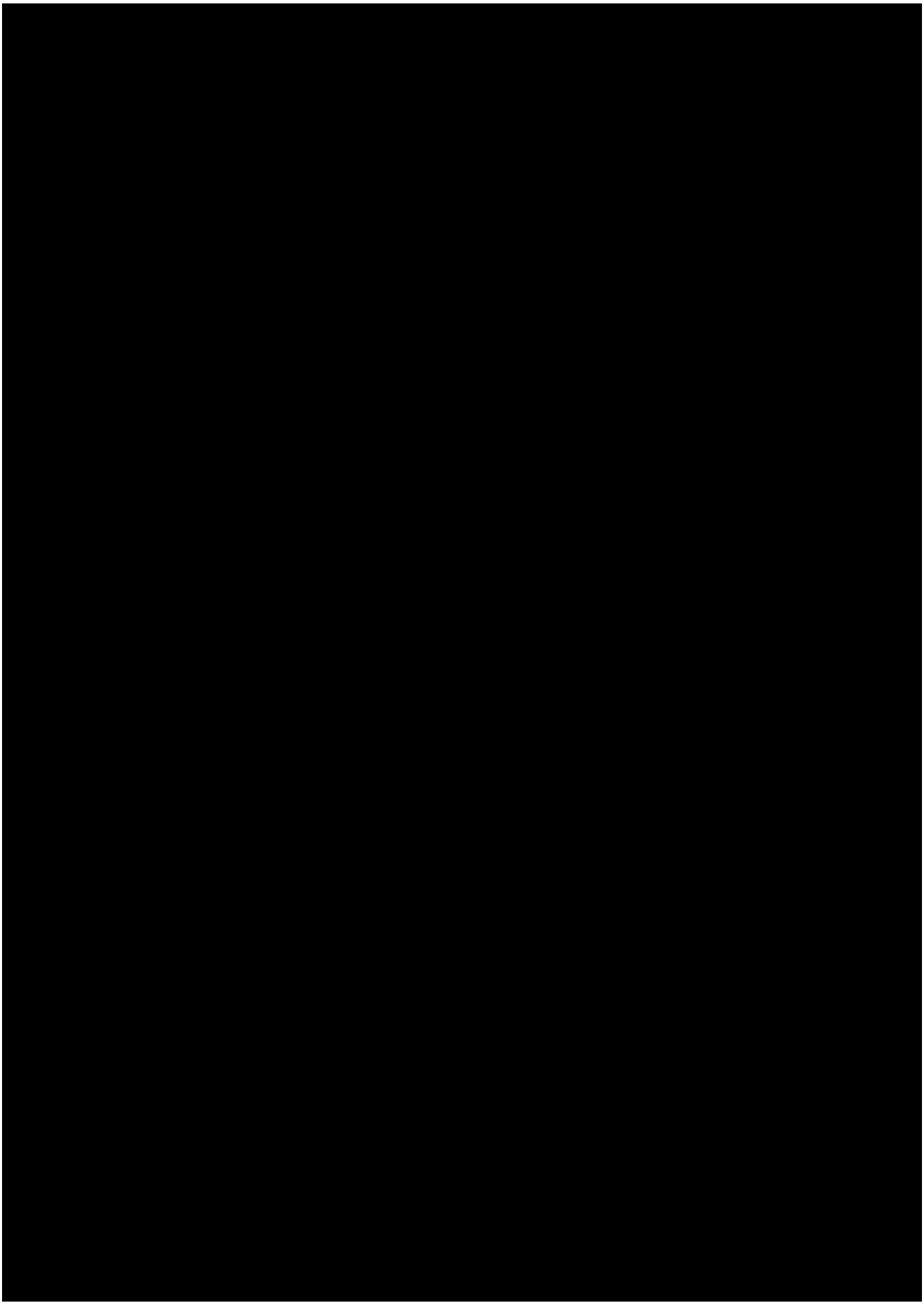
No justification has been provided for the particle size distribution limits. This should be provided, including discussion on the lack of an upper limit for the fine particle dose.

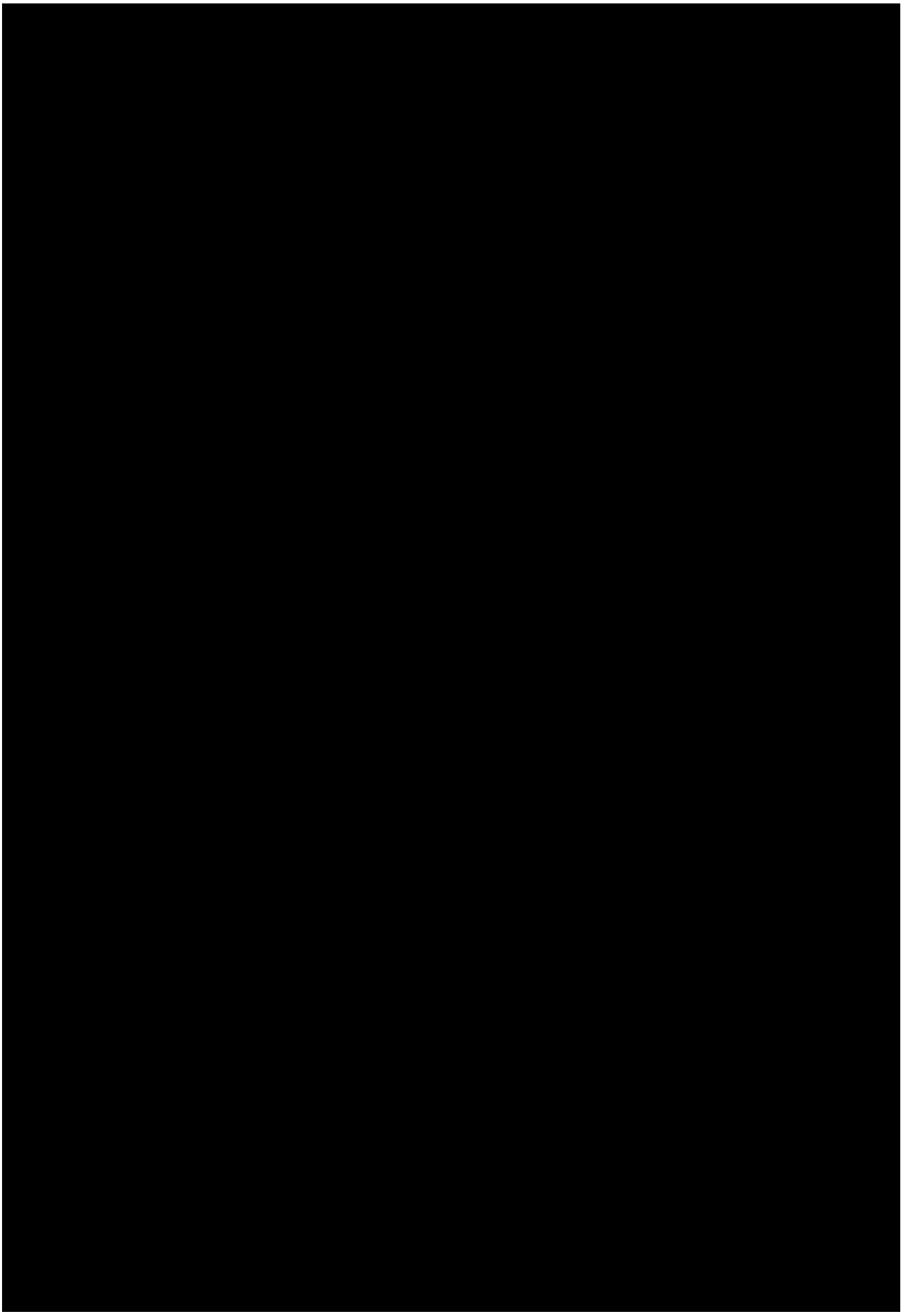
3.2.P.5.2 Analytical procedures

Test methods [redacted]

3.2.P.5.3 Validation of analytical procedures

[redacted]





3.2.P.5.4 Batch analyses

Batch data generated by the finished product manufacturer have been provided for multiple batches [redacted] The test results meet the proposed specifications and show that the product can be manufactured to a consistent quality.

3.2.P.5.5 Characterisation of impurities

Refer to the BP monograph for Tiotropium.

3.2.P.5.6 Justification of specification(s)

See Section 3.2.P.5.1, above.

3.2.P.6 Reference standards or materials

The working standards for tiotropium bromide monohydrate and impurities were provided by [redacted]

3.2.P.7 Container closure system

The capsules are packed in HDPE bottles with a child resistant caps containing a desiccant.
Assurance should be provided that the child resistant closure complies with TGO80.

[redacted]

Assurance that the packaging materials are suitable for contact with foodstuffs has also been provided.

The colour of the delivery device is different to that of the reference product, therefore, the sponsor should provide a clinical justification for the colours used and discuss any safety issues around how a user will recognise the difference between different medicines.

3.2.P.8 Stability

3.2.P.8.1 Stability summary and conclusion

The stability of the product has been investigated at 25 °C/60% RH, 30 °C/75% RH and 40 °C/75% RH storage conditions as summarised below in Section 3.2.P.8.3.

All methods used during stability studies are the same as analytical methods described in Section 3.2.P.5.2.

The proposed shelf life for the unopened tablets is 24 months with the conditions 'Keep the bottle tightly closed. Store in the original package to protect from moisture'. It is proposed that this medicinal product does not require of any special temperature storage conditions in the proposed HDPE bottles.

3.2.P.8.2 Post-approval stability protocol and stability commitment

The sponsor has provided a commitment to place 1 production batch annually on long-term stability studies.

3.2.P.8.3 Stability data

Stability of the unopened product

Details of the tiotropium capsule batches placed on stability are provided in the table below. Stability data has been provided for up to 24 months at 25°C/60% RH, 12 months at 30 °C/75% RH and 6 months at 40 °C/75% RH.

Summary of batches used in stability tests

[redacted]

All results are within specification throughout the shelf life and did not exhibit any significant trends [redacted]

Stability in use

The tables above indicate that in use stability was conducted, however, this information could not be located. Please identify the location of this data.

Photostability

[redacted] ***Either way from the degradation studies provided for the substance and product, it would appear that the product is susceptible to light and the labels and Pi should include the condition to 'Protect from light'.***

Recommended shelf-life

Provided the issues outlined above can be satisfactorily resolved, a shelf life 24 months is supported by the stability data provided.

Module 5.3: Pharmacokinetics and biopharmaceutics

a. Summary of human pharmacokinetics

Source of information

Innovator PI

Rate and extent of absorption

Following inhalation in young healthy volunteers, the absolute bioavailability of 19.5% suggests that the proportion reaching the lung is highly bioavailable. The bioavailability is the apparent bioavailability, which is dependent upon the amount of tiotropium that is effectively inhaled. It is expected from the chemical structure of the compound that tiotropium is poorly absorbed from the gastro-intestinal tract. This was confirmed in a study in young healthy volunteers, with a low bioavailability of 2-3% for oral solutions. Food is not expected to influence the absorption of tiotropium for the same reason. Maximum tiotropium plasma concentrations were observed 5 – 7 minutes after inhalation. At steady state, peak tiotropium plasma concentrations in patients with COPD were 12.9 pg/mL and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.71 pg/mL.

Metabolism and distribution

Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent. Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg.

Metabolism does not occur to any great extent in young healthy volunteers, as indicated by 74% renal excretion of unchanged drug after an intravenous dose. The major metabolic pathway is nonenzymatic ester cleavage to the alcohol N-methylscopine and dithienylglycolic acid that are inactive on muscarinic receptors.

Mode, route and rate of elimination

The effective half-life of tiotropium ranges between 27 to 45 h following inhalation by patients with COPD. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. Urinary excretion of unchanged substance in young healthy volunteers is 74% of an intravenous dose. Following inhalation of tiotropium by patients with COPD to steady state, urinary excretion is 7% (1.3 µg) of the unchanged dose over 24 hours, the remainder being mainly non-absorbed drug in the gut that is eliminated via the faeces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic, once daily inhalation by patients with COPD, pharmacokinetic steady state was reached by day 7, with no accumulation thereafter.

Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

Effects of age (if any)

As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (365 mL/min in patients with COPD < 65 years to 271 mL/min in patients with COPD > 65 years) This did not result in a corresponding increase in AUC0-6,ss or Cmax,ss values.

Effects of food

Food is not expected to influence the absorption of tiotropium.

b. Justification submitted for non-supply of bioequivalence data

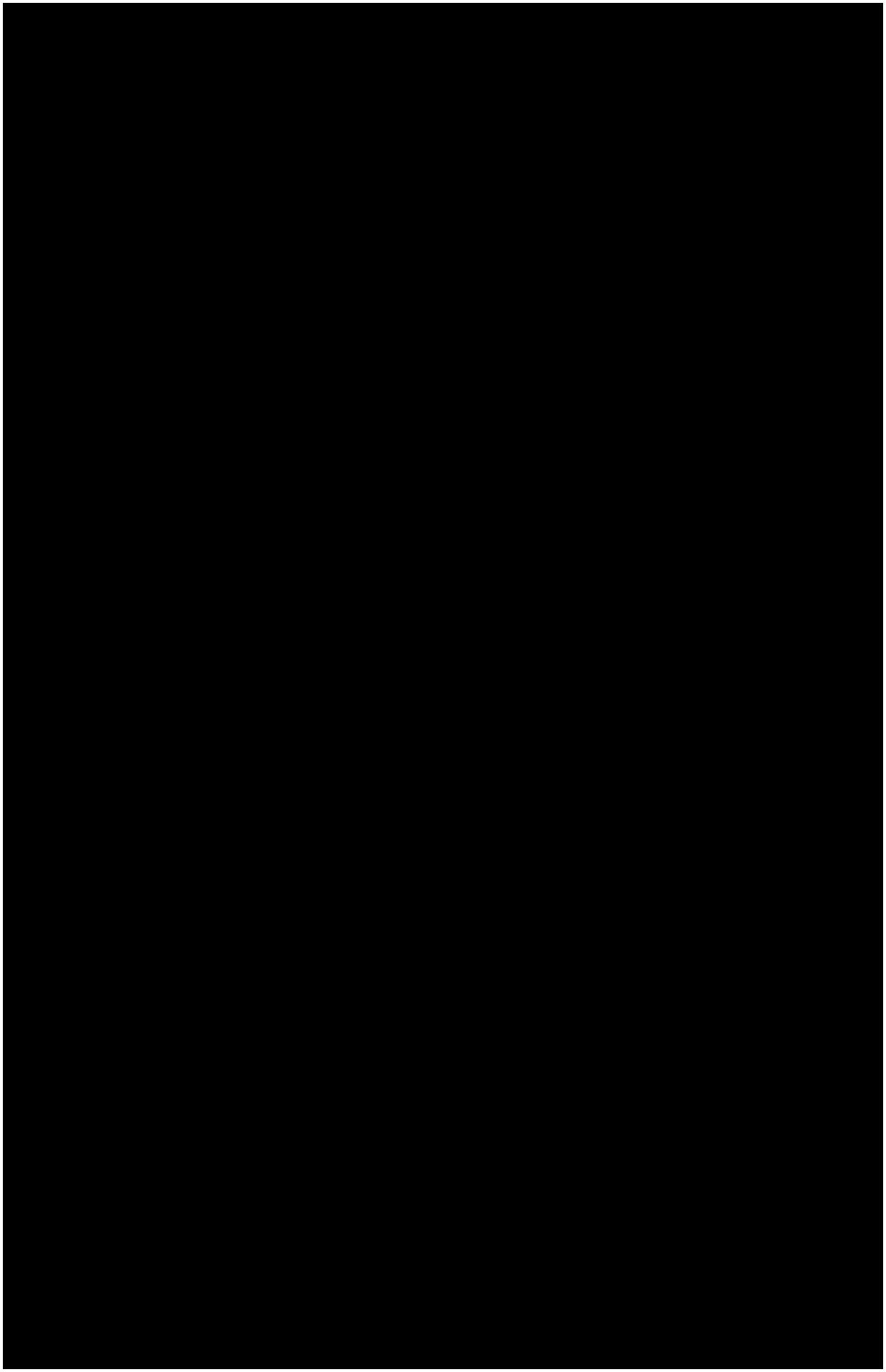
Overseas Reference

Bioequivalence studies has been provided comparing the test tiotropium inhalation powder with the reference product sourced from the EU.

[redacted]

The sponsor has submitted a justification for establishing bioequivalence on a reference product sourced from the EU based on EMA guidance CPMP/EWP/4151/00 Rev. 1.

[redacted]



[redacted]

In order to demonstrate identicality of the reference products the sponsor would be required to demonstrate that the particle size distribution of tiotropium is the same across the reference products as well as demonstrating that the delivered doses are the same.

d. Summary of bioavailability and bioequivalence studies

Study CLL11002

Study Title

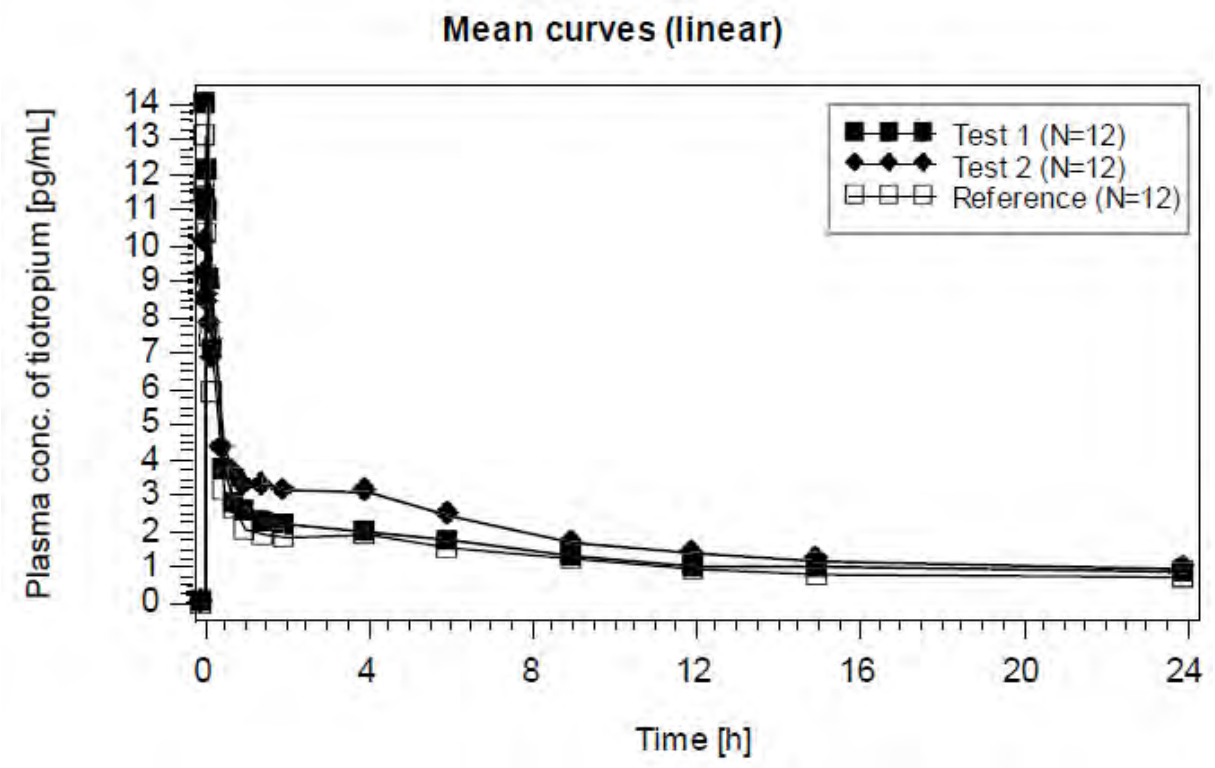
[redacted]

Summary

This study was initiated to investigate the differences between 2 test products, a 12 µg inhalation powder and an 18 µg inhalation powder, to the reference product sourced from the EU. The study was conducted 12 [redacted] Caucasian subjects under fasting conditions. Each subject received a single dose of each product with at least 7 days between testing of each product.

Blood samples were collected pre-dose and 0:02, 0:04, 0:06, 0:08, 0:10, 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 4:00, 6:00, 9:00, 12:00, 15:00 and 24:00 hours after inhalation.

[redacted]



TIOTROPIUM (n=12)				
TEST 1 vs. REFERENCE				
Variable	**method**	**point estimator**	**confidence intervals**	**CV(%)**
AUC(0-t) (ratio test 1/reference)	ANOVA-log	122.35%	100.57% - 148.85%	28.39%
Cmax (ratio test 1/reference)	ANOVA-log	91.32%	70.21% - 118.77%	38.67%
TEST 2 vs. REFERENCE				
Variable	**method**	**point estimator**	**confidence intervals**	**CV(%)**
AUC(0-t) (ratio test 2/reference)	ANOVA-log	158.01%	129.88% - 192.23%	28.39%
Cmax (ratio test 2/reference)	ANOVA-log	75.24%	57.85% - 97.86%	38.67%

Study CLL12003

Study Title

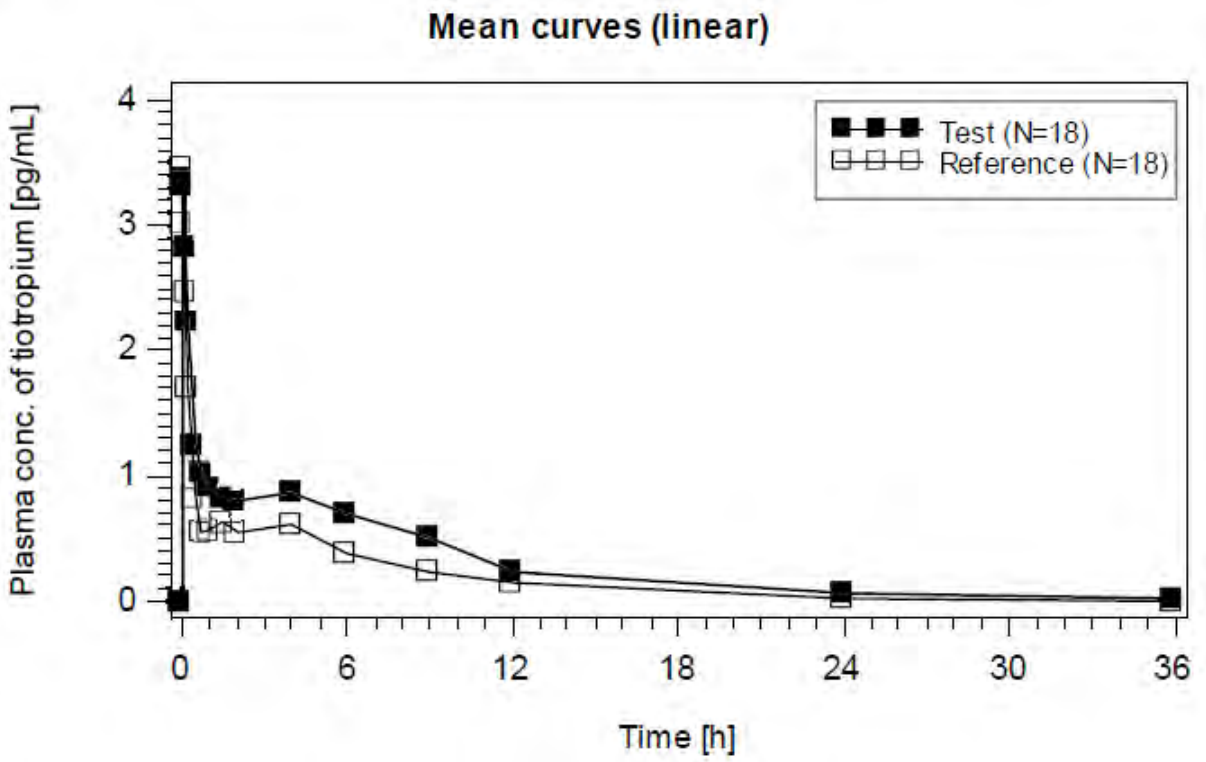
Randomized, double-blind, double-dummy, three-way, semi-replicate, crossover pharmacokinetic study in a two-stage design for evaluation of the systemic safety of Tiotropium 10 µg delivered dose inhalation powder, hard capsule (Test) compared to SPIRIVA® 18 microgram, inhalation powder, hard capsule (10 µg delivered dose) (Reference) each one administered as a single dose in healthy subjects

Summary

This study was initiated to investigate the differences between a 10 µg inhalation powder (batch number DG1300900) and the reference product sourced from the EU. The study was conducted 18 male and female Caucasian subjects under fasting conditions. Each subject received a single dose of each product with at least 10 days between testing of each product.

Blood samples were collected pre-dose and 0:03, 0:06, 0:09, 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 4:00, 6:00, 9:00, 12:00, 24:00; 36:00 and 48:00 hours after inhalation.

Results of the study are summarised below. As the interim analysis showed that the products were not bioequivalent the study was discontinued.



TIOTROPIUM (n=18 subjects)				
Variable	method	point estimator	confidence intervals	CV(%) (T/R)
AUC(0-t) (ratio test /reference)	ANOVA	193.26%	92.11% - 405.47%	undef. / 103.20%
Cmax (ratio test /reference)	ANOVA	99.57%	66.53% - 149.03%	undef. / 41.50%

Study CLL13002

Study Title

Randomized, open, three-way, semi-replicate, crossover pharmacokinetic study in a two-stage design for evaluation of the systemic safety of Tiotropium 10 µg delivered dose inhalation powder, hard capsule (Test) compared to SPIRIVA® 18 microgram, inhalation powder, hard capsule (10 µg delivered dose) (Reference) each one administered as a single dose of 20 µg delivered dose of tiotropium (2 capsules) in healthy subjects

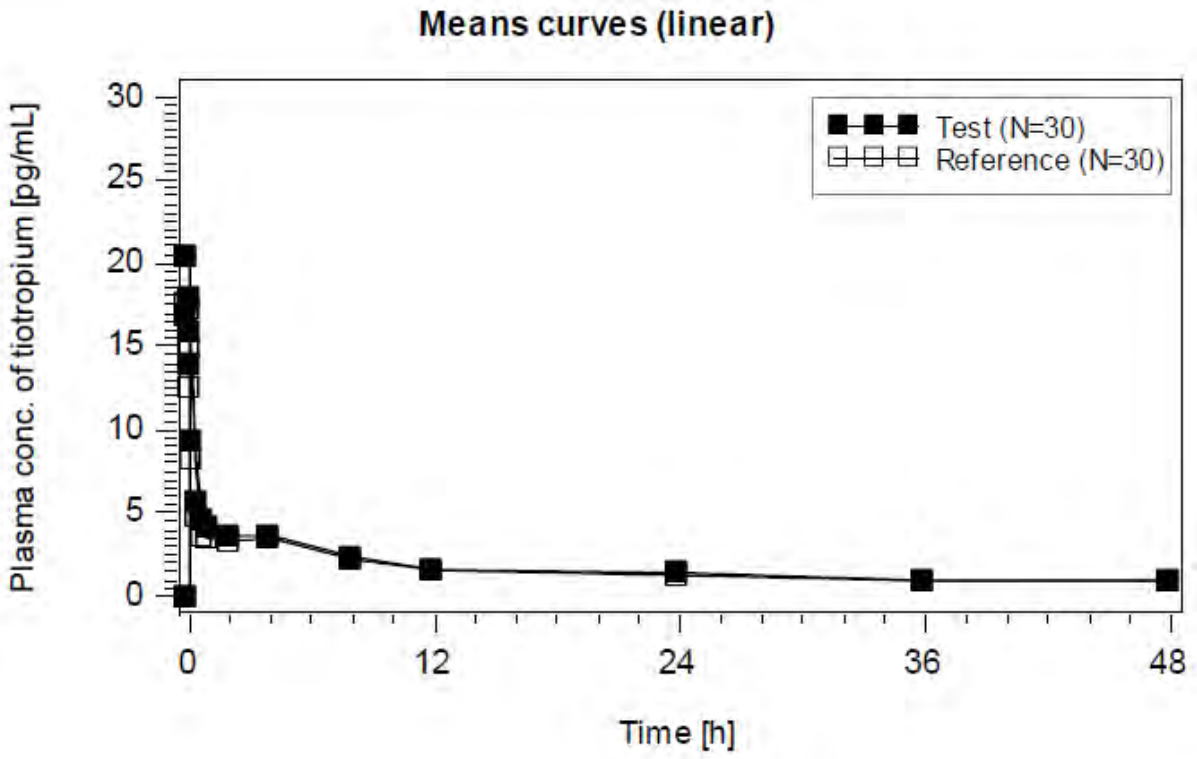
Summary

This study was initiated to investigate the differences between a 10 µg inhalation powder (batch number DG1300900) and the reference product sourced from the EU. The study was planned as a two stage design with 18 male and female Caucasian subjects in the first stage with a total of 30 subjects on completion of the second stage. Each subject received a single dose of two capsules of each product with at least 14 days between testing of each product. ***It is unclear why***

two capsules of the test and reference products should be considered acceptable as the PI recommends a single capsule once per day. The sponsor should provide a justification for using two capsules given the instructions in the PI and why the results of this bioequivalence study can be relied upon. Discussion should include reference to study CLL 12003which concluded bioinequivalence for the same batch number.

Blood samples were collected pre-dose and 0:01, 0:02, 0:04, 0:06, 0:08, 0:15, 0:30, 0:45, 1:00, 2:00, 4:00, 8:00, 12:00, 24:00, 36:00; and 48:00 hours after inhalation.

After the interim analysis of the first stage it was determined that a total of 30 subjects were required to reach a power of 90%. Therefore, an additional group of 12 subjects were introduced to the study. The 90.20% confidence intervals for the pooled first and second stages are summarised below. ***The sponsor should provide a justification for choosing 90.20% confidence intervals for the pooled samples.***



TIOTROPIUM (n=30 subjects)				
Variable	**method**	**point estimator**	**confidence intervals**	**within subject CV%**
AUC(0-t) (ratio test /reference)	ANOVA-log	106.36%	101.33% - 111.64%	11.92% (R)
Cmax (ratio test /reference)	ANOVA-log	96.45%	87.26% - 106.60%	22.40% (R)

It should also be noted that while the intra subject variability is quoted for the reference product above, the true intra subject variability for the reference product may only be calculated if the reference product is tested twice and thus each subject acts as their own control.

III Summary of Evaluation

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

Assessment

A number of significant deficiencies in the application data were identified during the assessment. Registration of the product for distribution in Australia is not recommended until each of the S31 questions listed below is satisfactorily resolved.

[redacted]

Office of Scientific Evaluation

4 April 2018

Section 31 questions

The following questions should be put to the company:

Module 1

Tradename:

1. The trade name, BRALTUS, will be referred to the clinical delegate for comment and further questions may arise.

Labels:

2. Regarding the submitted labels please address the following:

    2.1. It is unclear how the product strength should be expressed given the innovator product is labelled as an 18 microgram dose which the sponsor claims to be bioequivalent to their 13 microgram dose. This will be referred to the clinical delegate.

    2.2. Please express the strength of the product as Tiotropium (as bromide) 13 micrograms.

    2.3. It is unclear of the layout of the labels, for example it appears that the barcode on the box will not be visible. Please provide a physical sample pack.

Product Information (PI):

3. Regarding the submitted PIs please address the following:

    3.1. Please include the capsule as an excipient with the proprietary ingredient names and include the proprietary ingredient number in brackets adjacent to the name. The sponsor may need to submit a notification of a new proprietary ingredient form if the ingredient is not listed in the database. This information will be added to the PARs once it is confirmed.

Provisional ARTG records (PARs):

[redacted]

5. The sponsor will be asked to review the PARs in the S.31 request and advise the TGA of any errors or omissions.

Module 3:

Drug Substance:

6. The DMF has been separately evaluated and issues identified will be raised directly with the DMF holder. You should liaise with the DMF holder to ensure that timely responses to issues raised are provided and that any consequential changes are made to the finished product dossier.
7. A control for microbial purity should be added to the specification as per the drug substance manufacture's specification.
8. Please provide details of the analytical methods applied by the finished product manufacturer. If these are the same as the drug substance manufacturer, this should be stated.
9. As no stability data has been provided, please confirm that the drug substance will be tested immediately before use.
10. [redacted]

Drug Product:

11. Please provide a physical sample of your delivery device.

[redacted]

17. Humidity did not result in brittleness of capsules and no capsule breakages were observed. However, high humidity conditions were seen to cause less of the drug substance dose to be

received (below the specification limit). The sponsor should provide adequate justification for the reduced dose received at high humidity conditions as a significant proportion of Australia is considered to be in high humidity environments.

18. It is unclear if the changes to the delivery device described were undertaken after clinical and in vitro studies were performed. If they were comparison of the products performance characteristics (e.g., delivered dose, fine particle mass, etc.) should be investigated.

19. Hold times have been claimed by the sponsor in the manufacture of the product. However, in order to claim holding times the sponsor is required to provide full analysis on batches that have been held for the claimed periods, the data provided only tested for appearance, assay and homogeneity. Assurance should also be provided that the shelf life will be calculated in compliance with "CPMP/QWP/072/96 Annex: Start of Shelf-life of the finished product".

20 [redacted]

21. In regard to the finished product specifications, please address the following issues:

    21.1. Please include all tests in the expiry specifications for regulatory testing purposes.

    21.2. No justification has been provided for the particle size distribution limits. This should be provided, including discussion on the lack of an upper limit for the fine particle dose.

[redacted]

22. The capsules are packed in HDPE bottles with a child resistant caps containing a desiccant. Assurance should be provided that the child resistant closure complies with TGO80.

23. The colour of the delivery device is different to that of the reference product, therefore, the sponsor should provide a clinical justification for the colours used and discuss any safety issues around how a user will recognise the difference between different medicines.

24. The stability tables indicate that in use stability was conducted, however, this information could not be located. Please identify the location of this data.

[redacted]

Either way from the degradation studies provided for the substance and product, it would appear that the product is susceptible to light and the labels and Pi should include the condition to 'Protect from light'.

Biopharmaceutics:

26. As identicality of the Australian and European reference products has not been established, the biowaiver justification for using an overseas reference product is not considered acceptable. [redacted]

[redacted]

27. Bioequivalence study CLL13002 involved a single dose of two capsules. It is unclear why two capsules of the test and reference products should be considered acceptable as the PI recommends a single capsule once per day. The sponsor should provide a justification for using two capsules given the instructions in the PI and why the results of this bioequivalence study can be relied upon. Discussion should include reference to study CLL 12003which concluded bioinequivalence for the same batch number.
28. Please provide a justification for choosing 90.20% confidence intervals for the pooled samples.