EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Budesonide SUN and associated names

INN/active substance: budesonide

Procedure number: EMEA/H/A-29(4)/1492

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

An application in accordance with Article 10(3) of Directive 2001/83/EC was submitted under the decentralised procedure for Budesonide SUN and associated names, 250 microgram/2 ml nebuliser suspension, 500 microgram/2 ml nebuliser suspension and 1000 microgram/2 ml nebuliser suspension.

The application was submitted to the Netherlands, as reference member state (RMS) and to the following concerned member states (CMS): Germany, Italy, Poland, Spain, Sweden and the United Kingdom.[1]

The decentralised procedure NL/H/4194/001-003/DC started on 19 February 2018.

On day 210 of the procedure, potential serious risk to public health with regards to the demonstration of the equivalence of the reference and test product raised by Italy and the UK remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by the RMS. The CMDh referral procedure was initiated on 30 July 2019.

No agreement could be reached and the objections raised by Italy and the UK regarding the *in-vitro* data submitted in support of the equivalence between the reference and the test product were considered to be a potential serious risk to public health.

The RMS therefore triggered on 27 September 2019 a referral under Article 29(4) of Directive 2001/83/EC, for the CHMP to adopt an opinion on the concerns that the authorisation of Budesonide SUN and associated names, 250 microgram/2 ml nebuliser suspension, 500 microgram/2 ml nebuliser suspension and 1000 microgram/2 ml nebuliser suspension might present a potential serious risk to public health.

2. Scientific discussion

2.1. Introduction

The applicant Sun Pharmaceuticals has submitted an application in accordance to Article 10(3) of Directive 2001/83/EC under the decentralised procedure for Budesonide SUN 250 microgram/2 ml nebuliser suspension, Budesonide SUN 500 microgram/2 ml nebuliser suspension, Budesonide SUN 1000 microgram/2 ml nebuliser suspension and associated names (NL/H/4194/001-003/DC). The reference medicinal product for this application is Pulmicort Respules (250 microgram /2 ml, 500 microgram /2 ml, 1000 microgram /2 ml) registered by AstraZeneca.

Budesonide Sun is an inhalation medicinal product consisting of a nebuliser suspension containing the active substance in insoluble form. The medicinal product is a sterile, non-preserved aqueous suspension for nebulisation, containing 250, 500 or 1000 microgram budesonide per 2 ml in each single-dose ampoule. The different strengths are dose proportional. The excipients include polysorbate 80, sodium chloride, sodium citrate dehydrate, citric acid monohydrate disodium edetate and water for injections.

Budesonide nebuliser suspension is a glucocorticosteroid with a high local anti-inflammatory action. The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood, however it is believed that anti-inflammatory actions such as inhibition of inflammatory

[1] The United Kingdom (UK) formally left the European Union (EU) on 31 January 2020 and became a third country. A transition period began on 1 February 2020, during which EU pharmaceutical law remains applicable to the UK as if it were a Member State. This is due to end on 31 December 2020. However, during the transition period, the UK no longer participates in EU decision making/shaping

mediator release and inhibition of cytokine-mediated immune response are playing a vital role. The incidence and the severity of the adverse events of inhaled corticosteroids are much lower than those observed with oral formulations.

The applicant has applied for the below indications:

- adults and children, in particular children aged 4 years and above, with bronchial asthma, who should be treated with corticosteroids and for whom other local dosage forms are unsatisfactory or inappropriate
- children aged 6 months to 4 years with recurrent or persistent complaints of coughing and/or wheezing, in whom a diagnosis of asthma is suspected.
- very serious pseudocroup (Laryngitis subglottica) in which hospitalisation is indicated.

The referral was raised as an agreement could not be reached among the MS with regards to which *in-vitro* data are considered pivotal for the assessment of the equivalence of the reference and the test product for this application.

2.2. Assessment of the issues raised as a potential serious risk to public health

The *"Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents."* CPMP/EWP/4151/00 Rev.1, referred as 'OIP equivalence guidance' hereafter, provides that:

"For suspensions for nebulisation therapeutic equivalence should be demonstrated through in-vivo studies, unless justification is provided for the use of other types of studies to demonstrate equivalence." in Section 4.3 and

"For abridged applications therapeutic equivalence to a reference medicinal product must be substantiated. In some cases, the use of only comparative in vitro data, obtained with an accepted method (e.g. multistage impactor/impinger), may be considered acceptable if the product satisfies all of the following criteria (compared with the reference product)" in Section 5.2. The criteria listed to substantiate the equivalence include:

- same active substance;
- identical dosage form;
- active substance in the solid state; differences in crystalline structure/polymorph should not affect dissolution or performance characteristics;
- any qualitative and/or quantitative differences in excipients should not influence the performance of the product and should not change its safety profile;
- the target delivered dose should be similar (within +/- 15%);
- aerodynamic particle size distribution (APSD) comparisons of the test/reference ratio (T/R) should be within +/- 15% (CI 90%), with at least 4 groups of stages. Justification should be based on the expected deposition sites in the lungs.

On the basis of the OIP equivalence guidance, the applicant did not conduct any clinical studies to support the application and instead provided the results of in-vitro tests.

All the requirements of the guidance were met apart from the requirement of the aerodynamic performance of the test product as compared to the reference product performed per impactor stage or justified group of stages. All strengths were tested, and differences were observed for some grouped stages of the APSD comparison as the T/R ratio 90% confidence intervals fell outside the pre-defined maximum allowed range of variability of +/- 15% (0.85, 1.176).

To justify the observed difference, the applicant provided an extensive characterisation of the test and reference product. The *in-vitro* tests performed with the test and reference product as suspension for nebulisation prior to nebulisation demonstrated that the nebuliser suspensions have equivalent chemical and physical characteristics, such as the same critical quality attributes (CQA) that might have an impact on the dissolution and absorption of the active substance in the lung (including density, viscosity, surface tension, resuspendability, sedimentation rate, pH, osmolality and particle size distribution [PSD] of the suspended particles).

Two CMSs, the UK and Italy, considered that equivalence could not be confirmed for the following reasons:

- With regards the PSD in the suspension for nebulisation before nebulisation, it was considered that the data and information provided for the used method (Morphology G31D) is not adequate to demonstrate equivalence of the test and reference product. The CMSs were of the opinion that insufficient information has been provided with regards to sample preparation for the particle size data with and without agglomerate, the validity of the sample size and method validation is missing.

- The APSD comparison between test and reference, which is considered as a CQA, fell outside the maximum allowable pre-defined variability range of 85.00-117.65% and therefore the OIP equivalence guidance criteria are not fulfilled, thus the equivalence has not been demonstrated.

- Furthermore, it was considered that the justifications provided for the observed differences for the APSD results are not acceptable and that the arguments and data provided may raise additional concerns related to the quality of the test product. The CMS argued that since the sensitivity of sample storage and transferring steps have an effect on the quality of the test product when compared to the reference product, it should be adequately demonstrated that this will not lead to clinical relevant differences.

In conclusion, IT and UK considered that the therapeutic equivalence of the products has not been demonstrated since no robust data has been provided to adequately substantiate that the test and reference product are equivalent in terms of APSD and that they will result in similar nebulisation behaviour even when administered with the same nebulisation medical device.

As part of this referral procedure, the applicant was requested by the CHMP to further substantiate the suitability of the Malvern Morphology G3SE-ID method for the PSD comparison. Additionally, the applicant was asked to discuss the APSD results, justify the observed lower side results which fell outside of the pre-defined acceptance criteria and finally explain that the observed differences will not lead to clinically relevant differences. Furthermore, the CHMP asked the Quality Working Party (QWP) to provide their views on the suitability of the comparison of APSD results obtained with cascade impactor equipment for the assessment of therapeutic equivalence of the test and reference product (see section 3).

Particle size distribution (PSD) assessment of the suspension prior to nebulisation

For the PSD comparison, the applicant has used the Malvern Morphology G3SE-ID.

The study was performed using 3 batches of test and 3 batches of reference product of 0.25mg/2ml and 1mg/2ml strength with 3 different lots of API used to produce the batches of each strength. Total 9 observations per strength (3 set of observation per batch) were evaluated.

The applicant was asked to justify the suitability of the Morphology G3-ID method for the PSD characterization of the suspension for nebulisation before nebulisation (i.e. as present in the ampoule). Concerns were also raised with regards to the sample preparation and validity of the sample size, the lack of particle size data with and without agglomerates and the accuracy of the validation data.

The applicant submitted validation data for the determination of particle shape and PSD of the active substance, with and without agglomerates and the description of the analytical method including sample preparation and its validation. The advantages and the suitability of the Morphology G31D method in comparison to light scattering (Laser Diffraction Technique) technique for testing PSD in suspensions, with and without agglomerates have been summarised and presented by the applicant.

The applicant also presented an FDA article [FDA Embraces Emerging Technology for Bioequivalence Evaluation of Locally Acting Nasal Spray (on Mometasone furoate Nasal spray)][2], the draft guidance on Triamcinolone Acetonide Nasal Spray[3] and on Azacitidine for Injection[4], which all support the use of the Malvern Morphology G3SE-ID technique to substantiate the equivalence of PSD between test and reference products.

Taking into consideration the submitted justifications and validation data, the CHMP concluded that the Morphology G31D is an acceptable technique for testing particle size distribution in suspensions. The sample preparation has been clearly described and the method has adequately been validated. Overall, the CHMP was of the view that the applicant demonstrated the suitability of the Malvern Morphology G3SE-ID and that consequently equivalence between the test and the reference product in terms of PSD has been demonstrated.

Aerodynamic particle size distribution (APSD) assessment

The applicant conducted a comparison of the APSD of the Pulmicort Respules and Budesonide SUN by Cascade impactor.

Differences were noted in stages 1, 2 and 3 for Sum of mass for Group 1, which fell outside the pre-defined maximum allowed range of variability of +/- 15% for the 90% CI of the T/R ratio, as defined for in-vitro similarity in the OIP equivalence guidance (CPMP/EWP/4151/00/Rev.1). The APSD data and comparison are presented in Tables 1, 2 and 3 below.

[2] https://www.fda.gov/media/97705/download
[3] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Triamcinolone%20acetonide%20nasal%20spray%20NDA%20020468%20RV%20Feb%202019.pdf
[4] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Azacitidine_subcutaneous%20and%20IV%20infusion%20powder_NDA%20050794_RV04-17.pdf

Table 1

B. *In-Vitro* Bioequivalence Statistical Analysis.
Budesonide Nebuliser Suspension BP, 0.5 mg/2 ml (EU)

	Geo. LS Means			90% CI	
Parameter	**Test**	**Reference**	**% Ratio**	**Lower**	**Upper**
Active substance delivery rate (infant)	3.79	4.00	94.76	91.97	97.64
Total active substance delivered (infant)	23.94	24.60	97.32	93.94	100.82
Active substance delivery rate (child)	11.88	12.42	95.71	93.64	97.82
Total active substance delivered (child)	69.01	73.83	93.46	91.72	95.25
Aerodynamic assessment by NGI					
Group 1	59.72	68.61	87.04	81.97	92.42
Group 2	27.76	30.77	90.22	87.98	92.51
Group 3	13.87	16.28	85.20	82.98	87.47
Group 4	1.86	1.94	95.71	91.40	100.22

Table 2

A. *In-Vitro* Bioequivalence Statistical Analysis.
Budesonide Nebuliser Suspension BP, 1 mg/2 ml (EU)

	Geo. LS Means			90% CI	
Parameter	**Test**	**Reference**	**% Ratio**	**Lower**	**Upper**
Active substance delivery rate (adult)	44.39	47.47	93.51	91.56	95.51
Total active substance delivered (adult)	220.51	235.92	93.47	91.38	95.61
Aerodynamic assessment by NGI					
Group 1	124.20	144.86	85.74	81.84	89.82
Group 2	55.18	61.18	90.20	86.96	93.55
Group 3	24.15	27.28	88.50	85.20	91.93
Group 4	2.08	2.12	97.81	94.30	101.44

Table 3

C. In-Vitro **Bioequivalence Statistical Analysis.**
Budesonide Nebuliser Suspension BP, 0.25 mg/2 ml (EU)

	Geo. LS Means			90% CI	
Parameter	**Test**	**Reference**	**% Ratio**	**Lower**	**Upper**
Active substance delivery rate (infant)	2.24	2.20	101.88	99.79	104.02
Total active substance delivered (infant)	13.88	13.42	103.42	100.97	105.93
Active substance delivery rate (child)	6.06	5.99	101.22	98.97	103.53
Total active substance delivered (child)	36.64	36.43	100.59	99.24	101.95
Aerodynamic assessment by NGI					
Group 1	31.78	35.48	89.55	86.54	92.67
Group 2	15.20	15.54	97.82	95.39	100.31
Group 3	9.04	9.43	95.87	93.23	98.59
Group 4	1.82	1.90	95.80	92.10	99.64
Droplet size distribution					
D50	4.33	4.20	103.13	101.76	104.52
SPAN	2.15	2.18	98.68	96.74	100.65
Mean Nebulization Time	6.81	6.86	99.31	97.17	101.49

The CHMP considered that the APSD is a CQA and its assessment allows to predict the aerodynamic behaviour of the particles when measured through a validated impaction method (e.g. cascade impactor). The APSD assessment results fell outside the maximum allowable pre-defined variability range of 85.00-117.65% for the middle and highest strengths (0.5mg/2mL and 1mg/2mL).

The applicant argues that that the test and reference products are suspensions for nebulisation, where the active substance does not dissolve in the medium and hence they can be considered as 'simple' suspension. Like for solutions for nebulisation, also for the aqueous suspension for nebulisation, the aerosol deposition is determined by the transformation of bulk liquid into droplets. In that respect, the PSD similarity shown in the nebulised droplet size distribution additionally supports the in-vitro similarity of the reference and the test product, in such a way that it would be sufficient to conclude on the equivalence. The applicant claimed that any variation between the test and the reference product can only be due to a difference in the polymorphic form or of the active substance or particle size distribution before nebulisation (i.e. as present in the ampoule). Both aspects were demonstrated to be equivalent, hence the applicant argued that the APSD comparison with cascade impactor will not have any additional contribution to the conclusion of equivalence as the product is a suspension with well characterised physiochemical properties including PSD comparison both in the solution and when aerosolised. In addition, the applicant has argued that the APSD characterisation by cascade impactor is known to be over-discriminative and hardly suitable to confirm therapeutic equivalence.

The CHMP acknowledged that the comparative PSD data, with and without agglomerates, measured by laser diffraction and image analysis, before and after nebulisation have shown similarity between test and reference product, in addition to the similarity of the physical characteristics in terms of shape and extent of aggregates, which are relevant for the functionality of the product.

However, the CHMP noted that the only recommended method for post-nebulisation assessment by the OIP equivalence guidance is the APSD assessment by cascade impaction, where the mass of particles deposited at each stage is assayed and quantitatively determined. According to the European monograph 2.9.44. Preparations for nebulisation characterisation, cascade impactors enable the aerosol to be characterised unambiguously in terms of the mass of active substance as a function of

aerodynamic diameter. The OIP equivalence guidance recommend PSD measurement with laser diffraction (during the aerosolization) only in case of homogeneous solutions, while in case of suspensions, laser diffraction may be used only if validated against a cascade impaction method. In addition, the APSD by cascade impactors is considered the standard technique for the characterisation of inhalation products and for their comparison, due to its ability to provide the required degree of resolution in the aerodynamic performance of the particles in the range of greatest interest for inhalation products (0.5 to 5 microns).

In addition, the applicant was requested to justify that the observed lower side APSD results which fell outside of the pre-defined acceptance criteria observed with the cascade impaction method would not result in different lung deposition and/or absorption characteristics of the test product.

The applicant indicated that the observed lower side results of T/R ratio's below 1 in APSD are attributed to the fact that, although the delivered dose comparison meets the requirements of the OIP equivalence guidance, the delivered dose of the test samples is lower than the delivered dose of the reference product samples. Additionally, the APSD analysis involves various steps of sample handling that would have resulted in the observed differences in the delivered dose, though there are no significant differences in the assay content in ampoule. The lower side results of deposited fractions in the cascade impactor may have occurred due to differences in the sample storage orientation and the content transferring steps. The storage and handling orientation of the test samples were not the same as that of the reference product samples which were obtained from the market and already being stored upright according to the labelling instruction.

Another argument from the applicant was that the APSD analysis by next generation impactor (NGI) does not include whole content of drug product in ampoule where only a fraction of drug content is aerosolized during the analysis. The sampling period was reduced from 10 to 2 minutes, during analytical method development, as recommended in European Pharmacopoeia monograph 2.9.44, "Aerodynamic Assessment of Nebulised Aerosols", to avoid impactor over loading. It was argued that, when test and reference products are nebulised in conditions as intended to use by patients, i.e. for 10 minutes, the observed marginal difference in APSD analysis would not lead to significant differences in the delivery of the active substance and in the lung deposition.

The CHMP noted the above argument, however, based on the differences in delivered dose expressed as percentage of the label claim (12-13% higher in the reference product for the middle and higher strength, as shown in Table 4) due to higher amount of active substance retained in the ampoule of the test product, it was assumed that the substance losses during transference into the nebuliser might be due to caking during storage and that the 2-minute nebulisation would indeed result in different amount of delivered substance between the two formulations.

Table 4: Comparative Net fill weight (range and mean), Mean assay, Mass balance and actual delivered dose of test and reference product used in characterization study

Strengths	Test Product					Reference Product					% difference in delivered dose (R-T/R) * 100
	Net fill weight range (ml)	Mean Net fill weight (ml)	Mean assay (%)	Mass balance (%)	Actual delivered dose (mcg)	Net fill weight range (ml)	Mean Net fill weight (ml)	Mean assay (%)	Mass balance (%)	Actual delivered dose (mcg)	
0.25mg/2ml (N=30)	1.98 to 2.21	2.12	98.63	103	59.67	2.10 to 2.17	2.13	95.66	104	64.38	7.32
0.5mg/2ml (N=30)	2.03 to 2.18	2.11	98.26	102	107.06	2.09 to 2.17	2.14	96.76	105	121.45	11.85
1mg/2ml (N=30)	2.02 to 2.18	2.11	98.46	102	212.82	2.05 to 2.19	2.13	96.63	104	243.56	12.62

The mean percentage difference in delivered dose is around 12-13% lower for the test product for the middle and higher strengths as compared to the reference product. The data demonstrate that the percentage difference in terms of micrograms of active substance retained in the ampoule between reference and test product is 22.35% for the 0.25 mg strength, 25.38% for the 0.5 mg strength and 39.62% for the 1 mg strength. Pooling of data is not considered appropriate as the similarity between the test and the reference product needs to be confirmed for the individual applied strengths in line with the intended use of the product. The different strengths are recommended for use in different target populations and have been studied with different flow rates (infant, child, adults).

The CHMP noted that equivalence with the reference product should be established for each one of the individual strengths.

With reference to the claimed inherent variability and limitation of the APSD assessment, the CHMP noted that the analytical method should be sufficiently evaluated and validated to limit variability and to allow obtaining sufficient amount of API on the stage in order to measure it. The APSD deviation cannot be imputed only as incidental nature as a real quality difference between the test and the drug product was identified.

As a corrective action for the identified quality issues, the applicant proposed to apply an overfill of the nebuliser suspension in the ampoule of the test product. However, the issue should have been addressed as part of the pharmaceutical development. Furthermore, results of tests applying such overfill have not been provided and therefore have not be taken into account in the benefit/risk assessment of this product.

3. Quality Working Party responses

In the context of this procedure, the Quality Working Party (QWP) advice was sought on the suitability of the comparison of APSD results obtained with cascade impactor equipment for the assessment of therapeutic equivalence of the test and reference product.

The QWP considered that comparison of APSD with cascade impactor is a suitable method to demonstrate comparability of the aerosolised suspension. This technique has been used widely for a long time and the NGI is recommended by Ph. Eur. 2.9.44 Ph. for characterisation of products for nebulisation and thereby considered as suitable for use, if performed in accordance with Ph. Eur. recommendations (i.e. flow rate, cooling, sampling time etc.).

The QWP acknowledged that for comparison of test and reference product via cascade impactors, the method may be over-discriminatory, leading to observation of *in-vitro* differences which might not be clinically relevant. The interpretation of any APSD deviations is challenging; with multiple comparisons the increase of type II errors (risk of false negative conclusions) can be expected. However, the QWP noted that this should not be used as a sole justification by the applicant for not being able to conclude similarity as this increased error rate could have been addressed *a priori* (e.g. increasing the power of the hypotheses). In addition, no systematic deviations by the active substance, product strength or particle size group should be acceptable.

The QWP views were also sought on the deviation of the APSD results from the OIP equivalence guidance and from the European monograph 2.9.44. on Preparations for nebulisation (characterisation), taking into consideration the physiochemical properties and quality characteristics of the reference and test products.

In line with the above conclusion, the QWP acknowledged that cascade impactors are sensitive analytical procedures, thus deviations of the APSD should be carefully assessed and interpreted.

For the reference and the test products, a comparison of the APSD has been performed and evaluated with grouped stages of NGI. All mean ratios (test/reference) were below 1 with some confidence intervals outside the acceptance criteria (85-117.65). The deviations are unexpected, since a comparison of two suspensions for nebulisation having identical qualitative and quantitative compositions, with comparable physico-chemical characteristics (i.e. particle size distribution and morphology of the active substance) using the same nebulisation system, are expected to show similarity.

Based on the data provided, since the suspension in the vial prior to nebulisation is considered equivalent for test and reference product and the same nebulisation system is used; the recorded difference in APSD could be due to analytical method variability or variability of the reference product batches. The data provided do not indicate a significant variability of the reference product batches; hence, the variability could be attributed to the analytical method. However, this has not been proven and therefore this hypothesis is not confirmed.

The deviations in the APSD comparison appear in different groups of particle size, hence there are no systematic deviation among the different product strengths. However, the fact that the ratios are all below 1 and that the failures are only in the lower confidence interval could be a systematic deviation. Submitted data demonstrate that a larger fraction of the active substance remains in the vial compared to the reference product, hence, a larger fraction of the active substance of the test product compared to the reference product is not nebulised and would not be administered to the patient. The difference however is small and applying the acceptance criteria in the OIP equivalence guidance (±15%) equivalence is demonstrated for the delivered dose. Nevertheless, this small difference indicates that a lower fraction is available for distribution in the cascade impactor and could explain the lower mean ratio for the APSD comparison.

The QWP concluded that for the APSD comparison some deviations are slightly outside the acceptance criteria. There are some possible explanations for the observed differences (e.g. method variability and larger fraction of active substance remaining in the vial for the test compared to the reference product), however since no data has been provided by the applicant to support these possible justifications, these hypotheses cannot be investigated.

4. Benefit-risk balance

4.1. Initial benefit-risk balance assessment

Budesonide Sun is a medicinal product intended to be administered into the lung and consisting of a nebuliser suspension containing the only active substance in insoluble form.

According to the OIP equivalence guidance, in order to demonstrate therapeutic equivalence between two suspensions for nebulisation clinical studies are required unless other types of studies are able to demonstrate therapeutic equivalence. In order for abridged applications to rely on *in-vitro* data only, the criteria in section 5.2 in the OIP equivalence guidance need to be fulfilled. Amongst the criteria listed in the guidelines "*Data from the complete particle size distribution profile of individual stages or justified group of stages of a validated multistage impactor/impinger method should be provided*." The 90% confidence intervals for the observed *in-vitro* differences per impactor stage or justified group of stages must be calculated and demonstrated to fall within the acceptable variability criteria of +/- 15%.

Based on submitted data, the CHMP was of the view that it was adequately demonstrated that the nebuliser suspensions of test and reference products have similar chemical and physical characteristics such as same qualitative and quantitative composition, same polymorphic form of the active substance, same CQAs that might have an impact on the dissolution and absorption of the active substance in the lung including density, viscosity, surface tension, resuspendability, sedimentation rate, pH, osmolality, particle size distribution of the suspension prior to nebulisation, with and without agglomerates and particle shape.

The CHMP was of the view equivalence between the test and the reference product in terms of PSD has been demonstrated, since the applicant demonstrated the suitability of the Malvern Morphology G3SE-ID, the sample preparation has been clearly described and the method has been adequately validated**.**

However, some results of the comparative assessment in terms of APSD, which is the CQA that more than any other parameters allows to predict the aerodynamic performance of a product, as measured through a validated impaction method, failed to support the equivalence between the test and the reference product. The lower side of the 90% CI of the mean T/R ratio was observed outside the acceptable variability range of +/- 15% (85-117.65) for some grouped stages and is below 1 for almost all grouped stages. As the failures are only in the lower side of the CI, a systematic deviation can be identified, resulting in a lower fraction of active substance available during nebulisation for the test product.

It can be observed that the amount of active substance retained in the ampoules is larger for the test product than for the reference product, and therefore it is considered that the amount retained on the surface of the ampoules after pouring the content (from the vial to the nebuliser), may have an impact on the amount of active substance nebulised. It has been argued by the applicant that the observed differences in APSD can be attributed to the fact that the delivered dose of the test samples is lower than the delivered dose of the reference product samples. However, this cannot be confirmed since evidence to support this hypothesis has not been submitted.

The QWP has been consulted in the context of this procedure. The QWP concluded that APSD by cascade impactor is a suitable method to demonstrate comparability of the aerosolised suspension. While it was acknowledged that the method can be over-discriminatory and could potentially detect differences which are not always of clinical relevance, the QWP also highlighted, that the increased error rate should have been addressed *a priori* (e.g. increasing the power of the hypotheses) and no systematic deviations by the active substance, product strength or particle size group should be acceptable. With regards to the observed APSD differences, the impact of two potential factors (i.e. method variability and residual suspension in the vial) that could be responsible for the deviation observed, have not been fully investigated and discussed by the applicant. This position was endorsed by the CHMP.

The applicant has proposed to apply an overfill of the nebuliser suspension in the ampoule of the test product as a corrective action for the identified quality issues. However, introducing an overfill should be clearly justified during the pharmaceutical development and cannot be a mean to mitigate *a posteriori* a quality issue, thus this approach is not deemed acceptable by the CHMP in the context of this referral procedure. In addition, in the absence of supportive data generated with the product containing the overfill, it cannot be concluded that applying such overfill would indeed result in similar delivered doses poured from the ampoules and subsequently no structural trend of APSD ratio T/R < 1.

Overall, the CHMP was of the view that therapeutic equivalence between the reference and test product has not been demonstrated. In particular, it has not been proven that the aerodynamic performance of Budesonide Sun is equivalent to that of the reference medicinal product, and therefore it cannot be excluded that this would not lead to clinically relevant differences. The CHMP therefore concluded that the benefit-risk balance of Budesonide SUN is not favourable.

4.2. Re-examination procedure

Following the adoption of the CHMP opinion during March CHMP meeting, the applicant requested a re-examination of the procedure on 02 April 2020.

It is noted that the CHMP is a scientific committee and while it operates within the framework of the Union legislation regulating medicinal products, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the CHMP, and therefore the re-examination of the referral procedure under Article 29(4) of Directive 2001/83/EC focuses only on the scientific grounds for re-examination.

4.2.1. Detailed grounds for re-examination submitted by the applicant/MAH

Having received a negative opinion after finalisation of the CHMP referral procedure under Article 29(4) of Directive 2001/83/EC, the applicant requested a re-examination based on the following grounds:

In the initial assessment the CHMP concluded that the results of the comparative assessment in terms of APSD on the lower side of the 90% CI of the mean T/R ratio observed are outside the acceptable variability range of +/- 15% (85.00 - 117.65) for some grouped stages and below 1 for almost all grouped stages. The applicant disagrees with said conclusion for the reasons explained below.

It is claimed by the applicant that these results are due to the differences in the reference product higher net content per ampoule, though the assay content per mL of suspension of both test and reference products are the same and the marginal difference in the ampoule retention is not the contributing factor for the observed lower APSD results.

The applicant has argued that the justifications provided for the observed differences for the APSD results are well supported by the delivered dose studies done in different orientation on the test and reference products that was observed to be within the acceptance range.

In addition, the applicant claimed that the APSD study results of lowest strength are within the acceptable variability range of +/- 15% (85.00-117.65) and this should be considered in relation to higher and middle strengths that are dose proportional with same composition with only different drug substance concentrations.

The last ground presented by the applicant was referring to the PSD in the suspension for nebulisation before and after nebulisation. It was claimed that the validated data and information provided for the used method (Morphology G31D) is adequate to demonstrate equivalence between the test and the reference product.

4.2.2. CHMP discussion on grounds for re-examination

The CHMP considered the grounds submitted by the applicant within this re-examination procedure and the scientific data underlying these grounds.

Ground 1

The applicant argued that the differences observed in the comparative APSD assessment (i.e. the lower side of the 90 % CI of the mean T/R ratio < 1 and outside $\pm$ 15 %) were caused by the higher net content per ampoule of the reference product and, in turn, by the lower delivered dose of the test product. The amount of residue in the ampoule were similar for the test (6.01 – 10.35 %) and the

reference product (4.54 – 10.00%). Therefore, the applicant rejected the position that differences in the fractions of drug substance in the vial mainly contributed to the differences in APSD assessment.

Indeed, with respect to the data submitted by the applicant, the net content (%) of the reference product batches seems to be slightly higher (103 – 106 %) compared to the test product batches (100 – 105 %). However, the observed ranges of the net content of both products seem to be comparable likewise observed for the amount of suspension retained in the ampoules.

In support of this justification, the applicant has referred to the APSD results of the middle and highest strength, which have been re-calculated by data normalisation after delivered dose has been corrected. The re-calculated 90 % CI for grouped impactor stages for the middle and highest dosage strength complied with equivalence criteria. However, while it is evident that the delivered dose of the test product batches was lower compared to the reference product batches, the CHMP concluded that the higher net content of the reference product is not considered to be the contributing factor which led to the differences in delivered dose and APSD behaviour.

In the initial assessment, the applicant had proposed to apply an overfill of the nebuliser suspension in the ampoule of the test product as a corrective action for the identified quality issues. The CHMP noted that introducing an overfill should be clearly justified during the pharmaceutical development and cannot be a mean to mitigate *a posteriori* a quality issue, thus this approach was not deemed acceptable. In the re-examination procedure, the applicant argued that the intention to adjust the fill weight towards the nominal fill i.e. 2.1mL of the filling range defined (2.0 -2.2ml) observed for the reference product filling range would not be an overfill per se.

The CHMP is of the opinion that for each drug product for inhalation, the minimum fill justification is part of the drug product characterisation during pharmaceutical development. The development studies aim to define the target fill as well as the acceptable fill weight range, which ensures adequate drug product performance as per defined specifications. Once the formulation and the manufacturing process development, including up-scaling, has been completed the process is subject to validation. The manufacturing process fully validated should ensure adequate pre-defined filling of the ampoules. The CHMP also noted that during the decentralised procedure, the minimum fill volume of test and reference product was found comparable and the applicant did not consider this an issue in terms of the lower delivered dose of the test product. Overall, the adjustment of the fill weight towards the nominal fill of 2.1 mL can therefore not be endorsed by the CHMP as this should have been established during the development and process validation and this post-protocol adjustment of the drug product is not acceptable.

In the initial assessment, the CHMP and the QWP noted that the observed APSD differences could have been attributed to various factors such as the methodology of the impaction method and corresponding transferring steps including a reduced sampling time during nebulisation, which could lead to a higher variability of the analytical method. However, these factors were not addressed by the applicant in the re-examination procedure.

In the light of the above considerations, the applicant's first ground re-examination referring to the justification of differences in the APSD assessment and the reasons for applying an overfill to the ampoules is not endorsed by the CHMP.

Ground 2

The applicant has argued that the justifications provided for the observed differences for the APSD results are well supported by the delivered dose studies done in different orientation on the reference and the test product, which was observed to be within the acceptance range.

To support the observed lower side differences in test product during APSD testing, the applicant performed an orientation study to measure any impact of storage orientation on delivered dose.

Vials of test and reference product were kept in upright or on the side orientation for 7 days and the content of active substance was analysed by pouring the content from the vial into an analytical container. The content remained in the vial was determined and the actual content per vial was calculated for the test and reference product.

The applicant concluded that the study results confirmed that the differences concerning the delivered dose and the resulting APSD behaviour was caused by a higher net content of the reference product. However, the CHMP is of the opinion that the results from the orientation study demonstrated that the amount of the active substance delivered from a vial of the test product deviated from the amount delivered from the vial of the reference product. Also, the results showed that the difference remains at approximately 5%, confirming the results from the *in-vitro* performance test. Therefore, the CHMP concluded that the storage orientations upright and on the side will not have any impact on the delivered dose which is confirmed at a level marginally lower than the reference product.

In view of the considerations in the paragraph above, the applicant's second ground for re-examination referring to the justification of the observed APSD differences is not endorsed by the CHMP.

Ground 3

The applicant claimed that current submitted APSD results for the lowest strength of the medicinal product (0.25mg/2ml) satisfactorily comply with all the requirements as laid down in the OIP equivalence guidance and the results for this strength are found within the acceptable range of +/- 15% (85.00 - 117.65) and is of the view that the results for the lowest strength can support the similarity of the reference and the test products in the middle and highest strength as well. The applicant's argumentation is based on the rationale that for a suspension product, the particle size distribution of input API in suspension defines the *in-vivo* deposition of insoluble drug substance. On this basis, the applicant made reference to the similarity of the reference and test products to a solution in which only drug substance is in insoluble form and therefore the particle size distribution of suspension alone is sufficient to claim therapeutic equivalence between two products.

Therefore, taking into consideration the same physico-chemical properties of the reference and the test products, according to the applicant it is expected that the drug substance deposition should be similar in all strengths irrespective of the strength as the same input material. The APSD differences observed for the middle and highest strengths are attributed by the applicant to the inherent analytical variability, sensitivity of the technic and difference in the net content of test and reference products of middle and highest strengths.

Furthermore, to support the claim of dose proportionality of different strengths, the applicant has provided and statistically evaluated the pooled APSD data for respective groups for all the three strengths demonstrating equivalence within the acceptance criteria for all groups.

The CHMP acknowledged that the lowest strength (0.25mg/2ml) of the test product has demonstrated comparable APSD results which fall within the acceptable range of +/- 15% (85.00 - 117.65) and comply with all the requirements of the OIP equivalence guidance. However, the CHMP considered that the results of the pooled analysis do not satisfactory support the dose proportionality rationale claimed by the applicant, for the following reasons.

Firstly, summing up data for each strength is not acceptable in an equivalence setting as it can diminish differences between test and reference products. Hence, the probability to wrongly conclude on equivalence in case there are in fact differences between products is increased.

Secondly, the CHMP noted that it is a rather arbitrary decision which batches are grouped in the different sets and which data are summed for the different strengths. Especially, in case the data are known beforehand, it cannot be excluded that this knowledge could have influenced the grouping and the pooling towards concluding equivalence.

Finally, although there is no information available on how the 90% confidence intervals are calculated, based on limited re-analysis of the data, it seems that the standard approach assuming independence of all measurements was used. This is not acceptable since the 10 measurements within each set are dependent. This dependence structure should have been taken into account when calculating the confidence intervals. As it seems reasonable to assume that repeated measurements per batch are more similar when compared to measurements from different batches, ignoring the dependence structure (i.e. assuming independence of all observations as seems to be done for the analysis provided by the applicant) may actually underestimate the variability. This would again result in an increased probability to wrongly conclude on equivalence.

Overall, the post-hoc pooled analysis submitted by the applicant in the re-examination procedure is not considered appropriate by the CHMP due to the above-mentioned methodological limitations. In addition to dose proportionality of all three strengths, a comparable APSD behavior should be demonstrated between the individual strengths. Similarity in view of the APSD assessment should be confirmed for each individual strength of the test and reference products and should be analysed by different breathing profiles. The CHMP also noted that the different strengths are recommended for use in different target populations (infants, children, adults) with different breathing patterns.

Based on the above argumentation, the applicant's third ground for re-examination referring to the dose proportionality of all three dosage strengths taking into account that APSD assessment of the lowest dosage strength only complied with the equivalence criteria of the OIP guideline is not endorsed by the CHMP.

Ground 4

The applicant claimed that the PSD characterisation method by Morphology G3ID used for demonstration of the PSD equivalence of the suspension before and after nebulisation, with complete method validation package, is adequate to demonstrate equivalence between the test and reference product.

In the initial assessment the CHMP acknowledged that the choice of image analysis technique over laser diffraction has been sufficiently justified by the applicant. The CHMP also acknowledged that the PSD results, with and without agglomerates, measured by laser diffraction and image analysis, before and after nebulisation have shown similarity between the reference and the test products.

The applicant has claimed that the established PSD similarity before and after nebulisation between the reference and the test products should be taken into consideration when the equivalence is assessed.

Whilst the CHMP noted that the PSD results concerning the suspension in the ampoules can be considered similar, the conclusion that the PSD results after nebulisation obtained by Malvern Morphology G3SE-ID technology can replace the APSD assessment by impactor is not endorsed. As already noted by the CHMP during the initial assessment, the APSD assessment by cascade impaction is the only recommended method for post-nebulisation assessment. This is not only highlighted by the OIP equivalence guidance, but it is also required as per Ph. Eur. monograph 2.9.44 'Preparations for nebulisation characterisation'. The relation between PSD and APSD remains unknown, which does not enable a correlation of results of completely different analytical techniques.

Overall, the suitability of the PSD assessment after nebulisation by Malvern Morphology G3SE-ID technology as surrogate for APSD assessment by impaction method is questioned. In the absence of similar APSD behaviour between the test product and reference products batches, therapeutic equivalence should have been substantiated by clinical studies following the stepwise approach of the OIP equivalence guidance.

As a conclusion, the applicant's fourth ground for re-examination referring to the adequacy of the PSD assessment only, before and after nebulisation by Morphology G31D, to demonstrate equivalence between the test product and the reference products is not endorsed by the CHMP.

4.2.3. Conclusion of the re-examination procedure

Having received a negative opinion after finalisation of the CHMP referral procedure under Article 29(4) of Directive 2001/83/EC, the applicant has requested a re-examination based on the following grounds:

First, the justification for the observed differences in the APSD assessment based on the higher net content of the reference product and the resulting justification to adjust the fill volume; second, the justifications provided for the observed differences for the APSD results are well supported by the delivered dose orientation studies; third, the acceptability of the middle and higher dosage strength based on the dose proportionality to the lowest dosage strength, for which acceptable comparative APSD behaviour to the reference product has been demonstrated; fourth, the suitability of the determination of similar PSD in the suspension for nebulisation before and after nebulisation by Morphology G31D method as surrogate of APSD assessment by impaction method.

In the first ground for re-examination the applicant argued that the differences observed in the comparative APSD assessment are attributed to the higher net content per ampoule of the reference product and in the lower delivered dose of the test product, and proposed again the adjustment of the fill weight towards the nominal fill of 2.1 mL. The CHMP did not consider that it is adequately demonstrated that the observed APSD differences are attributed to the higher net content of the reference product and therefore the adjustment of the fill weight is not justified. In addition, the CHMP confirmed its initial position that introducing an overfill should be clearly justified during the pharmaceutical development and cannot be a mean to mitigate *a posteriori* a quality issue.

With regards to the second ground, the applicant made reference to a storage orientation study and concluded that the study results confirmed that the differences concerning the delivered dose and the resulting APSD behaviour were caused by a higher net content of the reference product. However, the CHMP considered that the provided data do not support the rationale that a higher net fill for the reference product accounts for the differences observed in the APSD assessment.

In the third ground, the applicant emphasised that all *in-vitro* similarity criteria have been fulfilled for the lowest dosage strength and that in view of dose proportionality between all strengths this should be taken into account in view of the therapeutic equivalence between the reference and the test product. In addition, a *post-hoc* pooled analysis of the APSD data for all the three strengths has been submitted demonstrating equivalence within the acceptance criteria apart from pooled group 1. The CHMP concluded that a *post-hoc* pooled analysis is not acceptable due to methodological limitations. In addition, apart from the dose proportionality of all three dosage strengths, a comparable APSD behavior should be demonstrated between the individual strengths of the reference and the test products.

The CHMP noted that the lowest strength complies with all the acceptance criteria as set out by the OIP equivalence guidance and therefore the *in-vivo* similarity is demonstrated for this strength only, in contrast with the middle and highest strengths. The CHMP discussed the possibility of approving only the lowest strength of 0.25 mg/2 ml, for which equivalence criteria were fulfilled. However, after a thorough assessment, this approach was not endorsed since the lowest strength alone is not suitable to reach the recommended range of therapeutic doses. The medicinal product Budesonide Sun is indicated for the management of asthma in children and adults where other local dosage forms are unsatisfactory or inappropriate and in the treatment of serious pseudocroup. The recommended initial and maintenance dose in adults for the treatment of asthma is usually 0.5-1 mg twice daily. To administer 0.5-1 mg of budesonide suspension 2-4 ampoules of the lowest strength of 0.25 mg/2 ml should be nebulised with a mean nebulisation time of 20-40 minutes (according to the mean nebulisation time of 10 minutes indicated for 2 ml of suspension). The long time required for nebulisation might seriously compromise the compliance of the patients. For the treatment of pseudocroup in infants and children 2 mg of nebulised budesonide are recommended as a single administration or two 1 mg doses separated by 30 minutes. The lowest strength is not suitable for the intended use due to the long nebulisation time required for the administration of 8 ampoules of 0.25 mg/2 ml that would be needed to reach the 2 mg dose.

Finally, in the fourth ground for re-examination, the applicant claimed that the PSD in the suspension for nebulisation before and after nebulisation, the validated data and information provided for the used method (Morphology G31D) are adequate and scientifically sound explanations to demonstrate equivalence between the reference and the test products. However, the CHMP did not agree that the PSD results after nebulisation obtained by Malvern Morphology G3SE-ID technology can replace the APSD assessment by impactor and therefore the PSD assessment after nebulisation by Malvern Morphology G3SE-ID technology cannot be considered as a surrogate for APSD assessment by impaction method.

In conclusion, the reasons for the observed APSD differences remain uncertain and from a quality perspective not all the requirements as per OIP equivalence guidance have been fulfilled. In this re-examination procedure, no new argumentation or explanation for justifying the recorded differences have been provided by the applicant. In the absence of demonstration of therapeutic equivalence based on all requirements of the OIP equivalence guidance, the CHMP confirms its initial conclusion that the benefit-risk balance of the medicinal product Budesonide SUN is not favourable.

5. Grounds for Opinion following the re-examination procedure

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC;
- The Committee considered the totality of the data submitted by the applicant in relation to the objections raised as potential serious risk to public health, in particular the data provided in support of the demonstration of the similarity between the physiochemical properties and the quality characteristics of the reference medicinal product and those of the test medicinal product;
- The Committee noted that the results of the aerodynamic particle size distribution (APSD) comparison, which is a critical quality attribute for the particle aerodynamic performance, fell outside the pre-defined maximum allowed range of variability of +/- 15% for some grouped stages, hence the APSD results did not meet the requirements of the OIP equivalence guidance

(CPMP/EWP/4151/00 Rev.1.), therefore the Committee was of the view that the equivalence of the aerodynamic performance of Budesonide Sun to that of the reference medicinal product has not been proven;

- The Committee considered the response of the Quality Working Party;
- The Committee took into consideration the grounds for re-examination submitted by the applicant and the subsequent assessment by the (Co-)Rapporteurs
- Taken together, the Committee was of the view that the available data were not sufficient to demonstrate equivalence between the reference and test product and that clinically relevant differences could not be excluded;

The Committee, as a consequence, considers that the benefit-risk balance of Budesonide SUN and associated names is not favourable.

Therefore, the Committee recommends the refusal of the marketing authorisation application of Budesonide SUN and associated names in the reference and concerned Member State(s).