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Research paper

Equivalence testing and equivalence limits of metered-dose inhalers and dry powder inhalers measured by in vitro impaction ☆

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Abstract

In this study, criteria for the acceptability of comparative in vitro equivalence testing are proposed. Furthermore, the following equivalence limits for in vitro impaction methods are postulated: the 90% confidence interval (CI) of the in vitro deposition ratio of the test product and the reference product should lie within 0.80–1.20. The aim of this study was to challenge these limits by applying them to in vitro impaction results of several groups of pressurized metered-dose inhalers and dry powder inhalers containing salbutamol and beclomethasone dipropionate. The deposition results were obtained with the Twin Impinger. All products had a marketing authorization in the Netherlands and were considered therapeutically equivalent within each group. The postulated equivalence limits/group were challenged by fictitiously assigning a preparation as a test product or reference product and calculating the 90% CI of the deposition ratio of the test and reference products. All possible combinations of products within a group were tested. The products were considered equivalent if the 90% CI of the quotient lay within 0.80–1.20. In most cases, the quotient of the test product and reference product remains within 0.80–1.20, but due to a high variability in the deposition results of several products, the 90% CI of the quotient sometimes falls outside the proposed equivalence limits. It is concluded that the equivalence limits postulated are rather conservative, with respect to accepting equivalence. The limits can therefore serve as a prudent predictor of equivalence within the acceptability criteria proposed, but have to be further validated.

Keywords: Equivalence; Dry powder inhalers; Metered-dose inhalers; Impaction; Twin Impinger

1. Introduction

Equivalence testing is an important part of the development of a medicinal product. If the clinical trial formulation differs from the commercial product, equivalence between the two formulations has to be demonstrated. Furthermore, during marketing of the product, the marketing authorization holder may wish to change the formulation and/or the production process. Again, equivalence between the 'old' and the 'new' formulation must be proven. Lastly, in an application for a generic product, equivalence to the innovator needs to be substantiated.

In general, two medicinal products are therapeutically equivalent if they contain the same active substance and show the same efficacy and safety. For orally administered drugs, equivalence can usually be demonstrated by comparing the products at issue with respect to the concentration of drug in the plasma over time in a bioequivalence study [1]. For inhaled products, this approach is generally difficult to apply, because systemic levels are the result of the absorption of the drug deposited in the lungs and of the drug swallowed and taken up from the gastrointestinal tract. The therapeutic benefit of preparations for inhalation is effected by local rather than systemic action. Therefore, plasma levels do not necessarily correlate with efficacy, and consequently, are inappropriate for establishing therapeutic equivalence.

Several methods are currently available for the equivalence testing of inhaled products [2]. Comparative clinical

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trials are considered as the 'gold standard', but they are not always easy to perform. There is no consensus on the clinical endpoints to be used. Clearly-defined equivalence limits are therefore lacking. Furthermore, the day-to-day variability in the state of asthmatic disease hampers the statistical proof of equivalence [3]. Pharmacodynamic studies are an alternative approach [4,5]. However, for clinical trials there is no consensus on the endpoints to be used and equivalence criteria have not been established. In addition, pharmacodynamic tests are not available for every class of antiasthmatic.

As already mentioned, comparative pharmacokinetic studies have a major drawback concerning the correlation with the efficacy of inhaled products. However, pharmacokinetic studies can be of use with regard to safety. Furthermore, if the amount of drug swallowed and absorbed from the gastrointestinal tract can be neglected, or if the drug swallowed is blocked from entering the absorption pathway by the charcoal-block method, comparative pharmacokinetic trials might be usable [6,7].

In recent years, a lot of work has been published on in vivo radioaerosol distribution studies. The formulations intended to be administered by inhalation are radiolabelled, and gamma scintigraphy is subsequently used to compare the whole-lung dose and the amount of drug deposited in central, intermediate and peripheral lung zones [8]. This method may be suitable to demonstrate the equivalence of inhaled products. Nevertheless, comparable lung deposition and distribution do not necessarily imply equivalence in clinical effects [9]. Furthermore, equivalence criteria need to be defined.

In vitro impaction methods may also be used in equivalence testing [5]. It is generally believed that lung deposition depends on the aerodynamic particle-size distribution, which can be measured in vitro by impactors and impingers. Based on the mass deposited on the different stages, an arbitrary division is made between 'respirable' and 'non-respirable' fractions. Only fine particles (below approximately 5–7 μm) are thought to reach the lower airways. The relative ease of operation, the high power to detect differences and the relatively low variability in measurement makes in vitro impaction an attractive method in equivalence testing. However, it is not known which differences between two products can be reliably assessed by in vitro impaction methods. Furthermore, in vitro equivalence limits must still be defined.

In this study, criteria for the acceptability of comparative in vitro equivalence testing are proposed. Furthermore, the following equivalence limits for in vitro impaction methods are postulated: the 90% confidence interval (CI) of the in vitro deposition ratio of the test product and the reference product should lie within 0.80–1.20. These limits are based on bioequivalence limits applied for orally-administered drugs. The aim of this study was to challenge the equivalence limits postulated, by applying them to in vitro impaction results of several groups of inhalation products. The impaction results were obtained with the Twin Impinger, i.e. Apparatus A (Ph. Eur.), because at the time of the investigation this impinger was generally used.

2. Materials and methods

2.1. Samples

Pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) containing salbutamol (base) and beclomethasone dipropionate as the active substance were included in this study. The groups investigated were pMDIs salbutamol, 100 μg/dose; pMDIs salbutamol, 200 μg/dose; pMDIs beclomethasone dipropionate, 50 μg/dose; pMDIs beclomethasone dipropionate, 250 μg/dose; DPIs beclomethasone dipropionate, 100 μg/dose; and DPIs beclomethasone dipropionate, 200 μg/dose. A summary of the products included is given in Tables 1–6. For some products, more than one batch was tested.

All products had a marketing authorization in the Netherlands and were commercially available at the time of the investigation. Based on identical active substance, label claim, dosing advice and inhalation device, the products within each group were assumed to be therapeutically equivalent. Until measurement of the in vitro impaction, the samples were stored at 18 ± 2°C and 40–80% RH. These storage conditions fall within the registered storage conditions for each of the products. The products had not passed their expiry date at the end of the study.

2.2. In vitro impaction measurements

The Twin Impinger described as Apparatus A in the European Pharmacopoeia was used [10]. The apparatus was supplied by Erweka, Heusenstamm, Germany. For determination of the fine-particle dose, 7 ml solvent was introduced into the upper impingement chamber and 30 ml solvent into the lower impingement chamber. Methanol was used as a solvent for salbutamol, and a mixture of methanol/water (72:28 v/v) was applied for beclomethasone dipropionate. The air flow through the apparatus, as measured at the inlet to the throat, was adjusted to 60 ± 5 l/min. For determination of the flow rate, a calibrated flow meter (Model 1307, Brooks Instruments, Veenendaal, the Netherlands) was used.

The measurements were carried out according to the instructions for pMDIs and DPIs as described in the European Pharmacopoeia [10]. The inhaler devices used for Becotide Rotacaps and Beclomethasone Cyclocaps were the Rotahaler® and the Cyclohaler®, respectively. Before sampling, each pMDI was shaken for 5 s and primed five times. Subsequently, the actuator of the pMDI was cleaned. The pMDIs and DPIs were attached to the inlet port of the Twin Impinger with a rubber gasket. After the discharge of ten doses (or four doses when sampling Beclomethasone 200 Cyclocaps), the inner surface of the inlet

Table 1
Deposition results and quotients of pMDIs salbutamol 100 μg/dose

	Product name	RVG number[a]	Stage 2 deposition[b]	
			μg/dose ± SD	RSD (%)
I	Salbutamol CF (dose-aerosol 0.1 mg/dose)	16922 = 12697	57 ± 5.1	8.9
II	Salbutamolum (dose-aerosol 0.1 mg/dose)	56750	61 ± 1.5	2.4
III	Salbutamolum 100 'pharbita' (aerosol 100 μg/dose)	14607 = 11743	66 ± 1.6	2.5
IV	Ventolin 100 Inhalator (aerosol 100 μg/dose)	06005	54 ± 2.0	3.8
V	Ventolin 100 Inhalator (aerosol 100 μg/dose)	06005	58 ± 4.7	8.1
VI	Ventolin 100 Inhalator (aerosol 100 μg/dose)	06005	50 ± 0.5	1.0
Test	Reference	Quotient	90% CI of quotient	Equivalent
I	II	0.93	0.86–1.00	Yes
I	III	0.85	0.79–0.92	No
I	IV	1.05	0.97–1.14	Yes
I	V	0.98	0.90–1.06	Yes
I	VI	1.14	1.04–1.24	No
II	III	0.92	0.85–0.98	Yes
II	IV	1.13	1.04–1.22	No
II	V	1.05	0.97–1.13	Yes
II	VI	1.22	1.15–1.30	No
III	IV	1.23	1.14–1.33	No
III	V	1.15	1.06–1.23	No
III	VI	1.33	1.23–1.44	No
IV	V	0.93	0.86–1.01	Yes
IV	VI	1.08	0.99–1.18	Yes
V	VI	1.16	1.06–1.26	No

[a] Dutch registration number. Different Roman numerals having the same RVG number are different batches of the same product.
[b] Pooled SD, 3.1 μg; d.f., 12.

tube to the lower impingement chamber and its outer surface which projects into the chamber were rinsed with methanol. The washings were collected in a volumetric flask and diluted with methanol. This fraction was designated as the stage 2 deposition.

The samples containing salbutamol were analyzed by high performance liquid chromatography (HPLC). The amount of beclomethasone dipropionate was determined by ultraviolet-spectrophotometry (UV). Before analysis, all samples were filtered through a 0.45-μm filter (Type Spartan 30/B, Schleicher & Schuell, 's-Hertogenbosch, the Netherlands). The in vitro impaction was calculated in μ/dose. The measurements were carried out in triplicate.

2.3. Assay

2.3.1. Salbutamol

The HPLC method for the assay of salbutamol samples was based on the method described by Croes et al. [11]. The chromatographic system consisted of an injector (Type SPH 125, Sparks, Emmen, the Netherlands), a pump (Type 2150, LKB, Pharmacia-LKB, Zoetermeer, the Netherlands),

Table 2
Deposition results and quotients of pMDIs salbutamol 200 μg/dose

	Product name	RVG number[a]	Stage 2 deposition[b]	
			μg/dose ± SD	RSD (%)
VII	Ventolin 200 Inhalator (aerosol 200 μg/dose)	14497	105 ± 3.8	3.6
VIII	Ventolin 200 Inhalator (aerosol 200 μg/dose)	14497	98 ± 1.8	1.8
Test	Reference	Quotient	90% CI of quotient	Equivalent
VII	VIII	1.08	1.02–1.13	Yes

[a] Dutch registration number. Different Roman numerals having the same RVG number are different batches of the same product.
[b] Pooled SD, 3.0 μg; d.f., 4.

Table 3
Deposition results and quotients of pMDIs beclomethasone dipropionate 50 μg/dose

	Product name	RVG number[a]	Stage 2 deposition[b]	
			μg/dose ± SD	RSD (%)
IX	Aldecin, inhalator (50 μg/dose)	06782	28 ± 3.1	11.3
X	Becotide 50 Inhalator (aerosol 50 μg/dose)	06824	29 ± 8.1[c]	28.0
XI	Becotide 50 Inhalator (aerosol 50 μg/dose)	06824	33 ± 0.8	2.4
XII	Becotide 50 Inhalator (aerosol 50 μg/dose)	06824	36 ± 2.0	5.6
XIII	Becotide 50 Inhalator (aerosol 50 μg/dose)	06824	24 ± 1.2	5.0

Test	Reference	Quotient	90% CI of quotient	Equivalent
IX	X	0.96	0.67–1.24	No
IX	XI	0.83	0.75–0.91	No
IX	XII	0.77	0.69–0.84	No
IX	XIII	1.14	1.01–1.27	No
X	XI	0.87	0.61–1.12	No
X	XII	0.80	0.56–1.04	No
X	XIII	1.19	0.83–1.56	No
XI	XII	0.93	0.85–1.01	Yes
XI	XIII	1.38	1.23–1.53	No
XII	XIII	1.49	1.33–1.64	No

[a] Dutch registration number. Different Roman numerals having the same RVG number are different batches of the same product.
[b] Pooled SD, 2.0 μg; d.f., 10.
[c] This was not used for calculation of the pooled SD, because the SD appeared to be significantly different from the other members of the group.

a guard column (Adsorbosphere S5 SCX, 7.4 × 4.6 mm, Hewlett–Packard, Amstelveen, the Netherlands), a reversed-phase column (Spherisorb S5 SCX, 10 cm × 4.6 mm, Hewlett–Packard, Amstelveen, the Netherlands), a UV-VIS detector set at a detection wavelength of 276 nm (Type Uvicord VW 2251, Pharmacia–LKB, Zoetermeer, the Netherlands) and an integrator (Type SP 4400, Spectra Physics, H.I. Ambacht, the Netherlands). The column was kept at a temperature of 35 ± 2°C using a column oven (Croco-cil, Spectra Physics, H.I. Ambacht, the Netherlands). The mobile phase consisted of methanol containing 40 mM $NaClO_4 \cdot H_2O$. The injection volume was 100 μl, and a flow rate of 1.4 ml/min was applied. All solvents were of analytical grade. The amount of salbutamol in the samples was established by means of a calibration curve prepared with salbutamol (in house standard, Sigma, St. Louis, MO). The method was validated with regard to variability (within-day and day-to-day), recovery, specificity/selectivity, linearity, detection limit and range, and proved to be suitable according to internal GLP standards. Data are available on request.

Table 4
Deposition results and quotients of pMDIs beclomethasone dipropionate 250 μg/dose

	Product name	RVG number[a]	Stage 2 deposition[b]	
			μg/dose ± SD	RSD (%)
XIV	Becloforte 250 Inhalator (aerosol 250 μg/dose)	10434	83 ± 5.1	6.2
XV	Becloforte 250 Inhalator (aerosol 250 μg/dose)	10434	96 ± 7.6	8.0

Test	Reference	Quotient	90% CI of quotient	Equivalent
XIV	XV	0.86	0.75–0.97	No

[a] Dutch registration number. Different Roman numerals having the same RVG number are different batches of the same product.
[b] Pooled SD, 6.5 μg; d.f., 4.

Table 5
Deposition results and quotients of DPIs beclomethasone dipropionate 100 μg/dose

	Product name	RVG number[a]	Stage 2 deposition[b]	
			μg/dose ± SD	RSD (%)
XVI	Becotide 100 Rotacaps (capsules with powder for inhalation)	09208	13 ± 2.6	20.4
XVII	Becotide 100 Rotacaps (capsules with powder for inhalation)	09208	12 ± 1.5	12.8
XVIII	Becotide 100 Rotacaps (capsules with powder for inhalation)	09208	16 ± 2.3	14.5
Test	Reference	Quotient	90% CI of quotient	Equivalent
XVI	XVII	1.09	0.78–1.39	No
XVI	XVIII	0.81	0.61–1.02	No
XVII	XVIII	0.75	0.55–0.95	No

[a] Dutch registration number. Different Roman numerals having the same RVG number are different batches of the same product.
[b] Pooled SD, 2.2 μg; d.f., 6.

2.3.2. Beclomethasone dipropionate

A UV-spectrophotometer (Type Lambda 16, Perkin Elmer, Nieuwerkerk a/d IJssel, the Netherlands), set at a detection wavelength of 239 nm, was used. The solvent consisted of methanol/water (72:28 v/v). The amount of beclomethasone dipropionate in the samples was determined by means of a calibration curve prepared with beclomethasone dipropionate (in house standard, Sigma, St. Louis, MO). The method was validated with regard to variability (within-day and day-to-day), recovery, specificity/selectivity, linearity, detection limit and range, and proved to be suitable according to internal GLP standards. Data are available on request.

2.4. Testing the proposed in vitro equivalence limits.

Normal distribution of the deposition results of the largest group of preparations was tested using the Martinez–Iglewicz test [12]. Normality could not be rejected. Based on these findings, a normal distribution for the other groups of preparations was assumed.

Within each group, the homogeneity of variance was tested using Cochran's test [13,14]: the test value is calculated by dividing the largest variance by the sum of variances. If the test value was smaller than the critical value for Cochran's test at the 5% significance level, it was concluded that there was no significant difference between the variances, and hence, between the standard deviations (SD). SDs that appeared not to be significantly different (see above) were pooled (pooled SD), with each SD being weighted by its degrees of freedom (d.f.) [13,14].

The quotients of the deposition results of all possible combinations of products within each group were calculated by fictitiously assigning a preparation as a test or reference product. Subsequently, using the pooled SD, the 90% CI of the quotients were calculated. Two products were consid-

Table 6
Deposition results and quotients of DPIs beclomethasone dipropionate 200 μg/dose

	Product name	RVG number[a]	Stage 2 deposition[b]	
			μg/dose ± SD	RSD (%)
XIX	Beclomethason 200 cyclocaps (capsules with powder for inhalation)	13391	23 ± 0.8	3.5
XX	Beclomethason 200 cyclocaps (capsules with powder for inhalation)	13391	24 ± 3.3	13.9
XXI	Beclomethason 200 cyclocaps (capsules with powder for inhalation)	13391	26 ± 4.6	17.7
Test	Reference	Quotient	90% CI of quotient	Equivalent
XIX	XX	0.95	0.74–1.17	No
XIX	XXI	0.86	0.68–1.05	No
XX	XXI	0.90	0.71–1.09	No

[a] Dutch registration number. Different Roman numerals having the same RVG number are different batches of the same product.
[b] Pooled SD, 3.3 μg; d.f., 6.

ered equivalent if the 90% CI of the quotient lay within the postulated in vitro equivalence limits of 0.80–1.20.

3. Results

The results obtained for the in vitro impaction in the Twin Impinger are summarized in Tables 1–6. The average results ($n = 3$) are shown, including SDs and relative standard deviations (RSD), as well as pooled SD and d.f./group. Within each group, for all possible combinations of products, the quotient, as well as the 90% CI of the quotient, of the deposition results of the test and reference products are given. Based on the 90% CI of the quotient, a decision was made regarding the equivalence of the two products. In Table 7, the proposed criteria for the acceptability of in vitro equivalence testing are mentioned.

4. Discussion

In Table 7, criteria for the acceptability of comparative in vitro equivalence testing are proposed. The rationale for these criteria is discussed below. It is evident that identical amounts of the same active substance must be present. With regard to interchangeable inhaled products, it would be reasonable to apply an 'identical amount' to the delivered dose, because this is the amount of drug received by the patient. Obviously, if the declared delivered doses of the test and reference products are identical, equivalence testing is allowed. However, at present, the label claim of preparations is generally expressed as a metered dose and not always as a delivered dose. According to the British Pharmacopoeia, the content of active ingredients in preparations for inhalation should be 80–120%, delivered by actuation of the valve [15,16]. Based on these limits, we therefore propose that, at the 5% significance level, the delivered dose of the test product must not differ by more than 20% from the delivered dose of the reference product in order to allow equivalence testing.

Furthermore, it should be borne in mind that impactors are only suitable for measurement of the physical properties of inhaled products. The interaction between the patient and the product is not taken into account. Therefore, in vitro impaction results should only be used in equivalence testing if the test product and reference product do not differ in the physical state of the active substance, in pharmaceutical dosage form and in inhalation device [17,18]. In addition, any qualitative or quantitative difference in excipients must not influence the inhalation behaviour of the patient. Therefore, the test product at issue should only be formulated from well-known excipients, used previously in inhalation products [19]. We suggest that within the criteria summarized in Table 7, comparative in vitro equivalence testing is acceptable.

The acceptability criteria in Table 7 were applied to the various groups of pMDIs and DPIs. Each product within a group complied with the criteria when compared to any other member of the group. Therefore, according to the acceptability criteria proposed, comparative in vitro testing is allowed.

In this paper, the following equivalence limits for comparative in vitro deposition studies are postulated: the 90% CI of the in vitro deposition ratio of the test product and the reference product should lie within 0.80–1.20. As already mentioned, for orally-administered drugs, therapeutic equivalence can usually be substantiated by demonstration of bioequivalence. In the Note for Guidance on the investigation of bioavailability and bioequivalence, acceptance criteria are defined for the area under the curve (AUC); the 90% CI of the AUC-ratio of the test product and the reference product should lie within 0.80–1.25 [1]. The AUC is used as a measure for the amount of active substance delivered to the site of action. For inhaled products, the site of action is the lung. The aerodynamic particle-size distribution, measured by in vitro impaction, determines the in vivo lung deposition. If impactor deposition results can be considered as predictive for the efficacy and safety of preparations for inhalation, the same equivalence limits are possibly applicable for comparative in vitro tests. However, the bioequivalence of orally-administered drugs is based on log-transformed data, and the acceptance range of the AUC-ratio is the result of exponential calculations. For impaction, a normal distribution is assumed and untransformed data are used. Based on these considerations, the above-mentioned equivalence limits are proposed.

The postulated in vitro equivalence limits of 0.80–1.20 were challenged using the various groups of pMDIs and DPIs. For pMDIs containing salbutamol, the results in Tables 1 and 2 reveal that the in vitro deposition of different products within one group varies considerably. However, in most cases, the quotient remains within 0.80–1.20. Moreover, the quotient of different batches of one product always stays within 0.80–1.20. Nevertheless, in eight out of 16 combinations of test and reference products, in vitro equivalence cannot be proven. Due to the high variability in the deposition results of product I and product V, the 90% CI of several quotients falls outside the proposed equivalence limits.

Table 7
Criteria for the acceptability of comparative in vitro equivalence testing

Criteria
● Same active substance, including physical state
● Same declared delivered dose, or, at the 5% significance level, the delivered dose of the test product differs by not more than 20% of the delivered dose of the reference product
● Same pharmaceutical dosage form
● Identical inhalation device
● Qualitative and/or quantitative differences in excipients are known to have no influence on the inhalation behaviour of the patient

From Tables 3 and 4, it can be seen that for pMDIs containing beclomethasone dipropionate, the quotient generally remains within 0.80–1.20 also. However, the high RSD in the deposition values of several products again results in a 90% CI outside the proposed equivalence range. The same is true for DPIs with beclomethasone dipropionate, as shown in Tables 5 and 6.

According to their summary of product characteristics (SmPC), the products within each group have an identical label claim and dosing advice, contain the same active substance and have the same pharmaceutical dosage form and inhalation device. Therefore, we consider the products as therapeutically equivalent. In fact, in practice the products are used as interchangeable products. If therapeutic equivalence within each group is assumed, it is clear from the data presented that equivalence cannot always be proven by in vitro impaction studies when applying equivalence limits of 0.80–1.20. The results of this study and the above-mentioned considerations do not, however, negate the proposed in vitro equivalence limits, but emphasize the primary concern of erroneously accepting equivalence. The deposition ratio of the test and reference products and the RSD in the deposition results determine the 90% CI. If the ratio is outside the proposed limits of 0.80–1.20 and/or the variability in the deposition results is relatively high, equivalence cannot be proven by in vitro impaction. However, in cases of high variability, it is possible to increase the number of measurements in order to narrow the 90% CI. If this has no advantageous effect, other (in vivo) methods have to be used in order to provide evidence of therapeutic equivalence.

Furthermore, beclomethasone dipropionate has a flat dose-response curve compared with the dose-response curve of salbutamol [20]. It is therefore plausible that the equivalence limits of 0.80–1.20 are unnecessarily strict for beclomethasone dipropionate. In cases of a flat dose-response curve, wider equivalence limits could therefore be justifiable, provided that safety remains unaffected. In fact, this solution has already been accepted for the AUC-ratio in the Note for Guidance on the investigation of bioavailability and bioequivalence [1]. Of course, in cases of an especially narrow therapeutic range, the equivalence limits need to be tightened.

The results of this study indicate that the proposed equivalence limits for in vitro impaction are rather conservative with respect to accepting equivalence. The proposed general equivalence limits can therefore serve as a prudent predictor of equivalence. The limits are, however, only established based on deposition results obtained with the Twin Impinger, and pMDIs and DPIs containing salbutamol and beclomethasone dipropionate. Additional research has to be carried out to investigate the applicability of the proposed general in vitro equivalence limits for other impactors and classes of products. Furthermore, the assumption was made that the products/group are therapeutically equivalent. This assumption was merely based on identical label claim and dosing advice in the SmPC. The correlation between clinical performance of inhaled products and in vitro impaction results should be established in order to further validate the proposed equivalence test and equivalence limits. Such a study is now in progress.

5. Conclusions

We suggest that in vitro impaction data of pMDIs and DPIs can be used in equivalence testing within each of the following acceptability criteria.

- The same active substance (including physical state).
- The same declared delivered dose or, at the 5% significance level, the delivered dose of the test product differs by not more than 20% of the delivered dose of the reference product.
- Identical inhalation device.
- The same pharmaceutical dosage form.
- Any qualitative and/or quantitative difference in excipients between test product and reference product is known to have no influence on the inhalation behaviour of the patient.

Within these acceptability criteria, we postulate that the 90% CI of the in vitro deposition ratio of the test product and the reference product should lie within 0.80–1.20. Wider limits may be acceptable if clinically justified. In cases of an especially narrow therapeutic range, the equivalence limits need to be tightened. The correlation between clinical performance of inhaled products and in vitro impaction results should be further established in order to fully validate the proposed equivalence limits.

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References

[1] The European Agency for the Evaluation of Medicinal Products, London, CPMP note for guidance on investigation of bioavailability and bioequivalence, 1992.
[2] N.J.C. Snell, Assessing equivalence of inhaled products, J. Pharm. Pharmacol. 49 (Suppl 3) (1997) 55–60.
[3] P. Zanen, J.-W.J. Lammers, Sample sizes for comparative inhaled corticosteroid trials with emphasis on showing therapeutic equivalence, Eur. J. Clin. Pharmacol. 48 (1995) 179–184.
[4] The European Agency for the Evaluation of Medicinal Products, London, CPMP Note for guidance on replacement of chlorofluorocarbons (CFC's) in metered dose inhalation products, 1993.
[5] The European Agency for the Evaluation of Medicinal Products, London, CPMP note for guidance on clinical requirements for locally-applied, locally-acting products containing known constituents, 1995.

[6] O.A. Aswania, S.A. Corlett, H. Chrystyn, Determination of the relative bioavailability of nedocromil sodium to the lung following inhalation using urinary excretion, Br. J. Clin. Pharmacol. 54 (1998) 475–478.
[7] L. Thorsson, S. Edsbäcker, T.-B. Conradson, Lung deposition of budesonide from Turbuhaler® is twice that from a pressurized metered-dose inhaler (p-MDI), Eur. Respir. J. 7 (1994) 1839–1844.
[8] R. Pauwels, S. Newman, L. Borgström, Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers, Eur. Respir. J. 10 (1997) 2127–2138.
[9] D. Newnhamd, D. McDevitt, B. Lipworth, Comparison of the extra-pulmonary beta2-adrenoreceptor responses and the pharmacokinetics of salbutamol given by standard metered-dose inhaler and modified actuator device, Br. J. Clin. Pharmacol. 36 (1993) 445–450.
[10] European Pharmacopoeia Convention, Council of Europe, European Pharmacopoeia, second ed., V.5.9.1., 1995.
[11] K. Croes, P.T. McCarthy, R.J. Flanagan, HPLC of basic drugs and quaternary ammonium compounds on microparticulate strong cation-exchange materials using methanolic or aqueous methanol eluents containing an ionic modifier, J. Chromatogr. 693 (1995) 289–306.
[12] N. Martinez, B. Iglewicz, A test for departure from normality based on a biweight estimator of scale, Biometrika 68 (1981) 331–333.
[13] R. Caulcutt, R. Boddy, Statistics for Aanalytical Chemists, Chapman and Hall, London, 1983, pp. 70.
[14] R. Caulcutt, R. Boddy, Statistics for Analytical Chemists, Chapman and Hall, London, 1983, pp. 72.
[15] The British Pharmacopoeia Commission, London, UK, British Pharmacopoeia, 1993, p. 1408.
[16] The British Pharmacopoeia Commission, London, UK, British Pharmacopoeia, 1993, p. 2083.
[17] K. Bauer, K. Sertl, B. Kaik, G. Kaik, Effect of solution and suspension type aerosol of formoterol on tremor, response and airways in patients with asthma, J. Allergy Clin. Immunol. 96 (1995) 495–501.
[18] L. Borgström, L. Asking, O. Beckman, E. Bondesson, A. Källén, B. Olsson, Discrepancy between in vitro and in vivo dose variability for a pressurized metered-dose inhaler and a dry powder inhaler, J. Aerosol Med. 11 (Suppl 1) (1998) S59–S64.
[19] J.G. Ayres, C. Benincasa, Acute bronchoconstriction following use of salmeterol xinafoate via the metered-dose inhaler in adult asthmatics, Am. Rev. Respir. Dis. 147 (1993) A61.
[20] D.J. Clark, B.J. Lipworth, Dose-response of inhaled drugs in asthma, an update, Clin. Pharmacokinet. 32 (1997) 58–74.