A clinically relevant approach to assess *in vitro* bioequivalence for regulatory approval of DPIs: A case study

A comparison of three tiotropium DPIs using a mouth/throat model and a range of realistic inhalation profiles

Dennis Sandell, PhD;[a] Peter Elfman, MSc[b] and Mårten Svensson, PhD[b]
[a]S5 Consulting
[b]Emmace Consulting AB

Caution: *This article is being published for purposes of education and discussion. The approach for IVBE comparability assessment applied here challenges the current standards in several ways and should not be used as a regulatory tool unless agreed upon with the regulator.*

Introduction

In 2016, a clinically more relevant approach for comparing the aerodynamic particle size distribution (APSD) of a generic dry powder inhaler (DPI) to that of an originator was proposed by Sandell.[1] Briefly, products are compared using anatomically correct mouth/throat (MT) models and a range of realistic patient- and product-specific inhalation profiles (IPs), and parameters described by Delvadia, et al[2] with characteristics defined by peak inspiratory flow rate (PIFR), acceleration (time to PIFR, T_{PIFR}) and inhalation time (T), varied according to a reduced factorial designed experiment (DOE) to cover the full range of profiles found in the relevant patient population. Moreover, it was shown[1] how the PIFR percentiles could be determined based on device resistance and published data for different relevant patient populations,[3] thereby avoiding the need to determine these experimentally in patients for every new DPI.

It was argued[1] that using the proposed approach is a clinically more relevant means to assess APSD *in vitro* bioequivalence (IVBE) between a generic and an originator DPI that potentially can replace the EU standard to separately compare at three constant flows, corresponding to 10%, 50% and 90% PIFRs of the relevant patient population. The proposed approach should be more relevant, not only since it uses a test method better mimicking the way a patient uses the product, but also because products are compared based on a mix of data obtained under different realistic conditions. This approach therefore follows the general philosophy for comparing treatments used in standard clinical testing. A further advantage with the DOE approach[1] is that the potential effects by PIFR, T_{PIFR} and T can be individually estimated, thus allowing deeper understanding of device and formulation characteristics for both products studied.

This article describes the results of a study that follows these principles for APSD IVBE assessment of three tiotropium DPIs: the Spiriva® Handihaler® (innovator product, Boehringer Ingelheim), the Tiova® Rotacaps®

Table 1

A reduced 3^{3-1} factorial design: Percentiles (%) for PIFR, T_{PIFR} and T for defining inhalation profiles for comparison of products

IP No.	PIFR	T_{PIFR}	T
1	10	10	10
2	10	50	90
3	10	90	50
4	50	10	90
5	50	50	50
6	50	90	10
7	90	10	50
8	90	50	10
9	90	90	90

IP No. = inhalation profile number
PIFR = peak inspiratory flow rate
T_{PIFR} = acceleration (time to PIFR)
T = inhalation time

Revolizer® (Cipla) and a tiotropium blister DPI (in development, Celon). Note that the Celon DPI never could be considered for an "*in vitro* only" approval with the Spiriva HandiHaler as a reference; this is because the formulations are not the same and the two devices operate in very different ways.

Each product was tested with nine IPs, modeled with characteristics defined by device resistance and 10%, 50% and 90% percentiles for PIFR, T_{PIFR} and T, to represent the full range of patients with chronic obstructive pulmonary disease (COPD), based on prior results from Sandell[1] and data from Azouz.[3] The medium Oropharyngeal Consortium MT model (OPC)[4] model was used for all testing. The Celon blister DPI was also tested with the small and large OPC throats, as well as with the United States Pharmacopeia (USP) inlet,[5] for one inhalation profile.

Material and methods

Spiriva batches 507942 and 506306 and Tiova Rotacaps batch BA61365 were tested together with three technical batches of Celon's tiotropium DPI (differing only in the percentage of lactose fines: 1%, 3% or 5%). The Next Generation Impactor (NGI; USP <601> Apparatus 5),[5] in combination with small, medium and large OPC anatomical throat models[4] applying mixing inlet methodology,[6] was utilized. A breathing profile generator, F-SIG 6300 (Lung simulator; AB Fia, Södra Sandby, Sweden), was used to create the patient-realistic inhalation profiles. The flow through the NGI was PIFR + 10 L/min for the various inhalation profiles.

The NGI cups were coated with a solution consisting of 40 g glycerol and 10 mL of a mix of 15 g Brij35 in 100 mL 96% ethanol. The anatomical throat model was covered with a 50%/50% ethanol/Brij35-glycerol solution to prevent bouncing. Six doses were collected per impactor test. The amounts of drug deposited in throat, inhaler adapter, pre-separator, stage 1 to stage 7, and the MOC and filter were extracted with internal standard solution (metagin in acetonitrile and 10 mM ammonium phosphate buffer). The amount of tiotropium was quantified by reversed phase high performance liquid chromatography (HPLC).

Inhalation profiles of the form proposed by Delvadia, et al[2] were used to describe how the flow rate (FR) changes with time (t):

$$FR(t)=PIFR\ sin\left(\frac{\pi}{2}\frac{t}{T_{PIFR}}\right)\ 0 \le t < T_{PIFR}$$

$$FR(t)=PIFR\ cos\left(\frac{\pi}{2}\frac{(t-T_{PIFR})}{(T-T_{PIFR})}\right)\ T_{PIFR} \le t \le T \qquad [1]$$

In formula 1, PIFR is the peak inspiratory flow rate, T denotes the total inhalation time and T_{PIFR} the time to PIFR; i.e., the acceleration. A designed experiment as suggested in Sandell[1] was performed for each of the three DPIs; Table 1 shows the design.

The values corresponding to different percentiles (P; unit: %) were for PIFR calculated from the devices' resistance (R; unit: $kPa^{0.5}\ L^{-1}min$) using formula 2 provided for COPD patients in Sandell.[1]

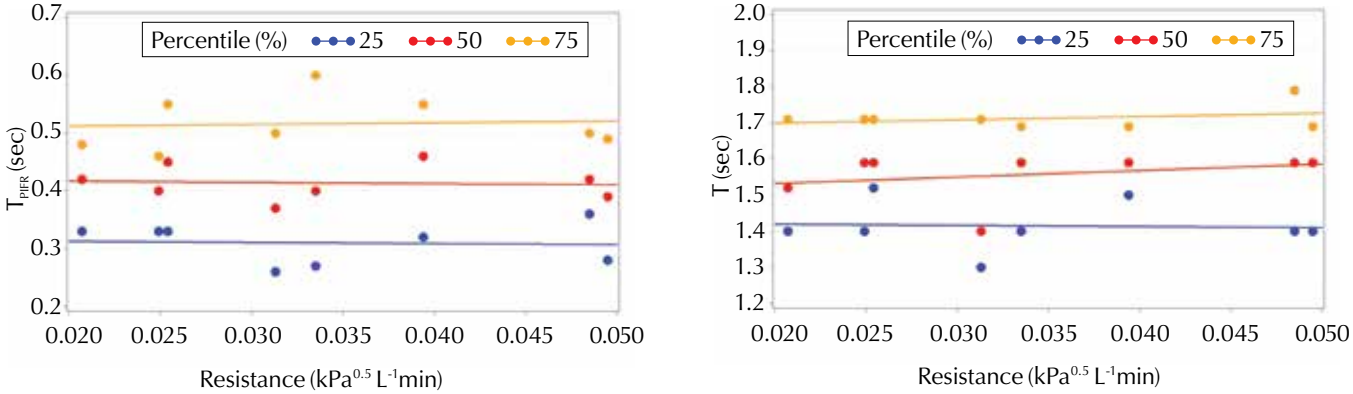
$$PIFR(P, R) = (-0.0247 + 0.0025P)/R^{1.4962} + 39.1927 \qquad [2]$$

Percentiles for T_{PIFR} and T were determined using data for COPD patients in Azouz[3] and following the approach for PIFR in Sandell.[1]

For each product and each of the nine IPs in Table 1, three APSDs were collected using the medium OPC MT model. For the Celon DPI and IP No. 3, three additional APSDs were collected using the USP inlet as well as the small and large OPC throats. For each test, the deposition on the adapter, in the throat, in the pre-separator, on Stages 1 to 7, and in the MOC and terminal filter were collected. Based on these raw data, the drug amount in the size ranges < 1 µm, < 3 µm and < 5 µm, as well as mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated.

Figure 1

Effect of device resistance ($kPa^{0.5}\ L^{-1}min$) on 25%, 50% and 75% percentiles for acceleration and inhalation time. Left: T_{PIFR} (acceleration, sec). Right: T (inhalation time, sec). Data from reference 3.



The primary statistical evaluation is assessing equivalence between the test products (Revolizer DPI and Celon DPI) and the reference product (Spiriva HandiHaler) by comparing a 90% confidence interval (CI) for the mean T/R ratio to the standard 85.00 - 117.65% *in vitro* bioequivalence acceptance interval (AI). Equivalence is concluded if the CI is completely contained in the AI. The 90% CI is constructed using a traditional log-transformation approach. The effect of IP design factors on fine particle dose (FPD) < 5 was studied using analysis of variance (ANOVA) and the main effects were estimated using the least square means. The difference between OPC MT models and the USP inlet was assessed visually and by descriptive statistics.

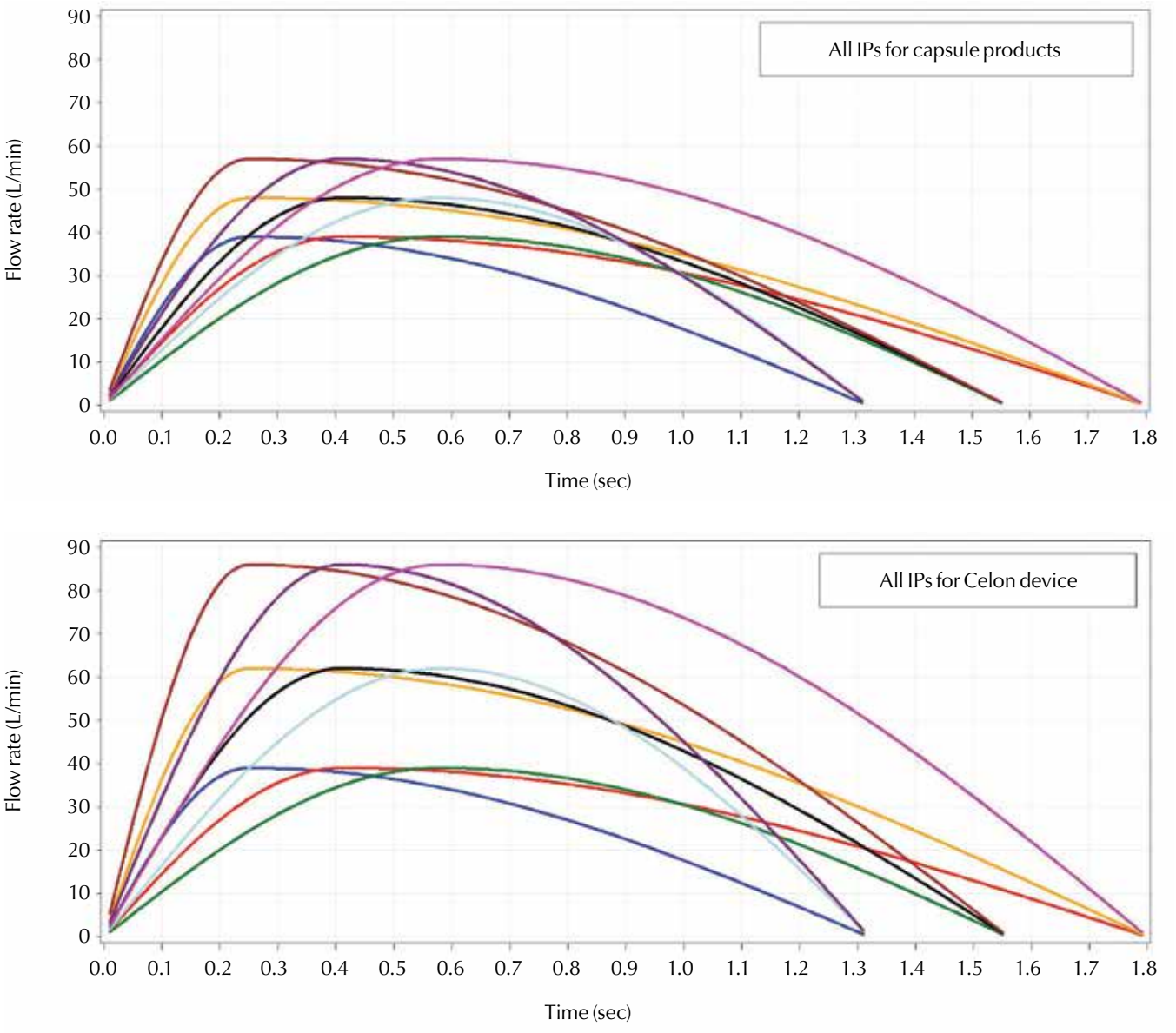
Results

The resistance for both the Handihaler and the Revolizer was 0.0433 $kPa^{0.5}$ L^{-1}min, while for the Celon DPI it was 0.0250 $kPa^{0.5}$ L^{-1}min. Using formula 1, it is found that the 10%, 50% and 90% percentiles correspond to PIFRs of 39, 48 and 57 L/min for both capsule DPIs, and to 39, 62 and 86 L/min for the blister DPI. The result in which the 10% percentiles agree for all three devices—despite differences in resistance—might at first seem surprising but it is due to the flow being unaffected by resistance for percentiles approaching zero. Based on data for eight different products tested by COPD patients,[3] the relation between T_{PIFR} and T (25%, 50% and 75% percentiles) and resistance was studied, following the approach used for PIFR in Sandell[1] (Figure 1).

The results shown in Figure 1 strongly suggests that for COPD patients both the acceleration and inhalation time are independent of device resistance, for all percentiles. This is in agreement with the findings in Delvadia, et al.[2] We therefore assume a linear relation $X = a + b \cdot P$ and estimate a and b from the data shown

Figure 2

Inhalation profiles used when assessing products. Top: capsule products. Bottom: Celon DPI.



in Figure 1 using standard regression analysis. The results are:

$$T_{PIFR}(P) = 0.207 + 0.0041 \times P \qquad [3]$$

$$T(P) = 1.26 + 0.0060 \times P \qquad [4]$$

The models explained 85% (T_{PIFR}) and 83% (T) of the total variation. Based on formulas 2 and 3, the 10%, 50% and 90% percentiles for all three products are given by 0.25, 0.41 and 0.58 sec (T_{PIFR}) and by 1.32, 1.56 and 1.80 sec (T); this completes the determination of the study design. The obtained IPs are shown in Figure 2.

The NGI delivered doses (DDs) for each of the 3 x 9 x 3 = 81 individual tests are presented in Figure 3. This shows that the results are much higher for the Revolizer DPI (average 15.7 µg) and the Celon DPI (15.9 µg) than for the Spiriva HandiHaler DPI (10.4 µg). Due to the apparent difference in NGI delivered doses, it is obvious that neither the Cipla product, nor the Celon DPI, are *in vitro* bioequivalent to the Spiriva HandiHaler. Despite this, we present in Table 2 the formal product comparisons for NGI DDs and FPDs in the intervals < 1, 1-3, 3-5 and < 5 µm together with the coarse particle dose > 5 µm (CPD > 5).

Table 2 shows that the delivered dose measured by the NGI (NGI DD) is about 50% higher for both test products and, as a consequence, most other parameters are also higher than those of the reference product. The only exceptions are for extra fines for the Celon DPI, although only the FPD 1-3 meet the standard EU IVBE acceptance criteria. Based on this clinically more relevant comparison, it can therefore be concluded that neither of the test products are IVBE to the Spiriva HandiHaler. However, note that Cipla's product was not developed with this intent and that Celon's DPI is still in development.

For a company developing a new product, a natural question to ask in this situation is whether their product would meet IVBE criteria if the delivered dose first was corrected to match. This can be investigated by first normalizing endpoints to the NGI DD before the *in vitro* equivalence assessment, thereby studying the dose fractions instead. This analysis then answers the question if two products are IVBE after the T product has been modified to provide the appropriate delivered dose. The fine particle fractions (FPFs) in the intervals <1, 1-3, 3-5 and < 5 µm, together with the coarse particle fraction > 5 µm (CPF > 5) were assessed (Table 3).

The results show that neither of the "DD corrected" test products are fully IVBE to the Spiriva HandiHaler. For particles > 3 µm, a good match is achieved for both alternative products, while for extra fines a clear mismatch is seen: the Revolizer shows more extra fines than the Spiriva HandiHaler while the Celon DPI delivers less.

Figure 3

Delivered dose, as measured by the NGI, for Spiriva (left panel), Revolizer (middle panel) and Celon DPI (right panel)

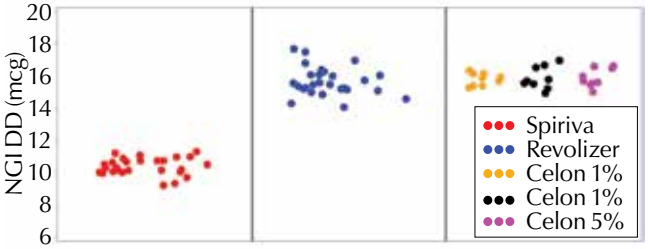


Table 2

Equivalence assessment comparing key APSD endpoints between test products (Revolizer DPI and Celon DPI) and the reference product (Spiriva HandiHaler): geometric mean ratio (GMR) and associated 90% confidence interval

Endpoint	Revolizer DPI		Celon DPI	
	GMR	90% CI	GMR	90% CI
NGI DD	150.3	146.7-154.0	152.3	149.3-155.4
CPD > 5	138.1	134.1-142.3	157.0	153.5-160.5
FPD < 5	211.5	202.5-220.9	128.2	120.3-136.6
FPD 3-5	166.6	159.9-173.6	171.6	162.8-180.9
FPD 1-3	241.3	228.0-255.4	96.3	88.2-105.1
FPD < 1	287.8	207.9-398.5	114.2	64.7-201.7

GMR = geometric mean ratio
CI = confidence interval
NGI DD = delivered dose measured by the NGI
CPD = coarse particle dose
FPD = fine particle dose

Table 3

Equivalence assessment comparing relative APSD endpoints between test products (Revolizer and Celon DPI) and the reference product (Spiriva HandiHaler): geometric mean ratio (GMR) and associated 90% confidence interval

Endpoint	Revolizer		Celon DPI	
	GMR	90% CI	GMR	90% CI
CPF > 5	91.9	90.95-92.85	103.1	101.96-104.16
FPF < 5	140.7	134.6-147.0	84.2	79.2-89.4
FPF 3-5	110.8	105.69-116.23	112.7	106.69-118.96
FPF 1-3	160.5	151.99-169.54	63.2	58.17-68.71
FPF < 1	191.5	137.98-265.68	75.0	42.36-132.74

GMR = geometric mean ratio
CI = confidence interval
CPF = coarse particle fraction
FPF = fine particle fraction

Figure 4

Average FPD < 5 by inhalation profile for Spiriva (red), Revolizer (blue) and Celon DPI (orange)

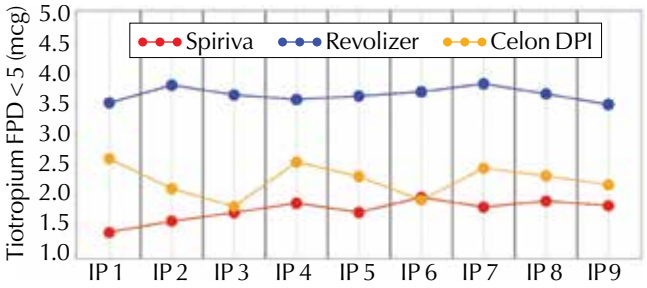


Table 4

Results from ANOVA (p-values) assessing the effect of design factors for Spiriva, Revolizer and Celon DPIs

Product	PIFR	T_{PIFR}	T
Spiriva	0.0008	0.0570	0.9511
Revolizer	0.9735	0.7785	0.9749
Celon DPI	0.2907	0.0002	0.9651

PIFR = peak inspiratory flow rate
T_{PIFR} = acceleration (time to PIFR)
T = inhalation time

An added benefit of using a DOE approach when comparing product performance is that the effects from the various design factors can be separated and are not mixed, as when using recorded "real" inhalation profiles. This means, for example, that one can study the effect of the acceleration T_{PIFR} without this being disturbed by the (possible) effects of PIFR and T.

In Figure 4, the average FPD < 5 is shown for each IP and product. Apart from the obvious observation that FPD < 5 is higher for the Revolizer, it is noted that FPD < 5 varies most between IPs for the Celon DPI. The highest FPD < 5 results are seen for IPs 1, 4 and 7. Interestingly, these are *not* those with highest PIFR but those with fastest acceleration (10% percentiles for T_{PIFR}).

The possible effects of the design factors on FPD < 5 were assessed using a fixed effects ANOVA for each product. The results of this analysis (p-values) are shown in Table 4. The results show that PIFR affected FPD < 5 only for Spiriva and that FPD < 5 is independent of inhalation time for all three products. The acceleration, however, had a strong effect on the FPD < 5 for the Celon DPI and a borderline statistically significant effect for Spiriva. The FPD < 5 least square means (pure PIFR effects adjusted for effect by the two other factors) for the three PIFR percentile levels are shown for each product in Table 5A, together with the difference in FPD < 5 between 90% and 10% percentiles, in percent of the median; this "change index" is a measure of the effect by a factor, inspired by the Q index introduced by Weers, et al.[7] Table 5B shows the corresponding for T_{PIFR}.[7]

Table 5A shows that, as expected, FPD < 5, increases with PIFR for Spiriva. Note, however, that there is no change in FPD < 5 from the 50% to 90% percentiles (i.e., from 48 to 57 L/min). The Revolizer DPI and the Celon DPI are flow-independent within the ranges studied. Table 5B shows that FPD < 5 decreases with T_{PIFR} for the Celon DPI, from 2.53 µg at 0.28 sec (10% percentile) to 1.96 µg at 0.58 sec (90% percentile). It is interesting that the borderline significant change in FPD < 5 for Spiriva is in the opposite direction with a higher FPD < 5 for a slower acceleration. The Revolizer, which is a capsule DPI, is clearly independent of T_{PIFR}. It is reasonable to believe that capsule-based products are less sensitive to variations in the acceleration in general since the powder aerosolization process is longer compared to that of a dose loaded in a cavity pocket.

The APSD of the Celon DPI (batch with 1% fines) was also determined for IP No. 3 (PIFR = 10%; 39 L/min, T_{PIFR} = 90%; 0.58 sec, T = 50%; 1.56 sec) using the USP inlet as well as the small (S), medium (M) and large (L) OPC MT models. This profile was selected because it was expected to show the lowest FPD < 5 and, therefore, the highest mouth/throat (MT) deposition. The average NGI DD for the four throats were similar: 14.1 µg (USP), 15.9 µg (S), 15.1 µg (M) and 16.0 µg (L), while the average throat depositions differed significantly between the USP inlet (2.62 µg) and OPC MT mod-

Table 5

A

FPD < 5 (µg): Flow index and least square means for 10%, 50% and 90% PIFR percentiles for Spiriva, Revolizer and Celon DPIs

Product	10%	50%	90%	Flow Index
Spiriva	1.55	1.84	1.83	15.2
Revolizer	3.67	3.64	3.67	0.0
Celon DPI	2.17	2.25	2.30	5.7

B

FPD < 5 (µg): Acceleration index and least square means for 10%, 50% and 90% T_{PIFR} percentiles for Spiriva, Revolizer and Celon DPIs

Product	10%	50%	90%	Acceleration Index
Spiriva	1.67	1.72	1.82	8.2
Revolizer	3.65	3.71	3.62	-0.8
Celon DPI	2.53	2.24	1.96	-22.5

els (13.8 µg, 11.6 µg and 12.3 µg for S, M and L OPCs, respectively). In Figure 5, the average results for the pre-separator, Stages 1 to 4, and Stage 5 to the filter are shown for the four throats. It is seen that pre-separator deposition is much higher when using the USP inlet, a natural consequence of the low filtering capacity of this inlet. However, it is seen also that for later stages, the deposition is higher when using the USP inlet; the results are between 1.6-3.1 times higher than the average OPC deposition. The results for Stages 1 to 3 differ clearly between OPC models, with lowest depositions for the small model.

Discussion

It is acknowledged that the approach for IVBE comparability assessment applied here challenges the current standards in several ways. The proposal is presented for discussion and should not be used as a regulatory tool unless agreed upon with the regulator.

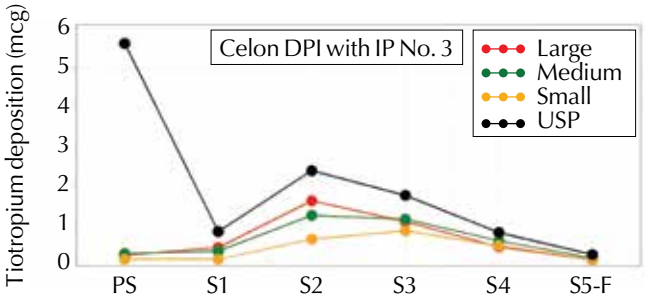
The approach in Sandell[1] was developed to improve the relevance of collected data and, therefore, of generic/innovator product comparison. The price for this is more complicated testing, but that is, to some extent, balanced because the total amount of testing is reduced up to a third and increased understanding of the effect of inhalation factors on outcomes can be obtained. Moreover, the data collected has the potential to be particularly useful for correlating with *in vivo* data to better understand the outcomes of pharmacokinetic studies.

A case study was presented to illustrate the steps in the proposed approach: (i) use published data to determine the inspiratory characteristics of the target population when using the investigated devices, (ii) select a suitable range of realistic inhalation profiles from models based on these data, (iii) design the experimental plan for testing, (iv) select suitable endpoints and (v) statistical evaluation of product equivalence. Application of the proposal for Cipla's Revolizer and Celon's blister DPI showed that neither was IVBE to the reference product, Spiriva Handihaler. This is not surprising as Cipla's product is not intended as a generic and Celon's DPI is still in early development. However, both cases serve well as illustrations of the suggested approach.

We believe the approach presented could be further improved in several ways. First, as suggested in Sandell,[1] several batches of each product should be included in the study. Further, all testing in the main study was performed using the medium OPC MT model. To better represent the full range of possible mouth/throat geometries represented by patients, it would be beneficial to include several different anatomical throats. Data for the comparison of OPC throats when testing the Celon DPI shows that differences in APSD are seen for different models and this should be advantageous to include for improved relevance of the product comparison.

Figure 5

Average tiotropium deposition on pre-separator, Stages 1 to 4 and the grouping of Stages 5 to 7, MOC and filter: Celon DPI (1% fines) tested with inhalation profile No. 3 and four different throats



The factorial design has the advantage of allowing estimation of the pure effect of a factor without that being disturbed by possible effects of other factors. However, collecting the same number of replicates for each of the IPs is probably not the optimal approach to represent the range in characteristics of the target patient population. For example, IP No. 5 (50-50-50 percentiles) obviously mimics the inhalation performance of many more patients than does IP No. 1 (10-10-10 percentiles). Therefore, it seems appropriate to collect more replicates for IP No. 5 than for IP No. 1, if the intention were to collect a data set that together represents the intended patient population. Exactly how this should best be done, the percentiles to use, the profiles to select and the proportion of the total sample that should be allocated to each profile are difficult questions that need to be discussed.

Considering one parameter only, for instance PIFR, it obvious to allocate 10% of the total sample for testing profiles with 10% percentile PIFR. But how should the number of tests be determined when the profile depends on three parameters? A three-dimensional percentile is not well defined; or putting it differently—how should a 10% percentile *profile* look? How should the three parameters be selected? A first proposal for how the number of tests (N) per inhalation profile should relate to the percentiles is presented for discussion in Table 6. This is based on the model

$$N(P, Q, R) = c \times [(50-|P-50|) + (50-|Q-50|) + (50-|R-50|)] \quad [5]$$

where P, Q and R are the percentiles for PIFR, T_{PIFR} and T, and c is a constant determined so the total number of profiles equals the desired number.

If the desired total number of profiles is 27, Table 6 shows that one test for profile 1 and one for profile 9 (since 27 x 4.8/100 = 1.3) would be appropriate, as well as 6 tests for profile 5 (since 27 x 23.8/100 = 6.4) and 3 tests for each of the remaining profiles (since 27 x 11.1/100 = 3.0). This, however, sums to 26 so one

further replicate may be added to profile 5. A disadvantage of using this unbalanced design is that more rare profiles cannot be tested with all three batches and all three OPC throats (unless the total sample size is very large).

The approach to mimic the patient population could be applied to the standard DPI IVBE studies where one study is performed at each of the 10%, 50% and 90% PIFR percentiles, each typically involving 30 tests for each product (10 units from each of three batches). It appears more logical to perform three tests per product at the 10% percentile (one per batch), 24 tests per product at the 50% percentile, and 3 tests per product at the 90% percentile, and then pool all data for a given product for the final IVBE assessment.

The perhaps ideal, but most complex, approach following this aim to collect *in vitro* data that best represents the intended patient population is to first do a study in M patients and collect the full inspiratory profile for each when they inhale via the test and reference devices. The APSD data should then be determined in the lab for each of the recorded M tests and M reference profiles, and finally compared using standard equivalence testing for the suitable parameters. To the authors, this seems to be to an excellent approach for IVBE assessment of two products.

Finally, one experience learned from the present study is that using an NGI flow of PIFR + 10 L/min is not optimal if a comparison of individual stages is desired. For this purpose, it would be better to collect APSDs for all IPs using a common NGI flow above that of the highest PIFR for any profile studied. Some work is, however, required to confirm that no bias is introduced when the PIFR and NGI flows differ significantly.

The approach proposed in Sandell[1] that combines established test methodology with a factorial design for inhalation patterns to obtain clinically more relevant *in vitro* bioequivalence assessment of the APSDs of two orally inhaled products has been applied for two tiotropium DPIs (the Cipla Revolizer and the Celon DPI) compared to the Spiriva Handihaler. Products were tested with the medium OPC mouth/throat model and nine different inhalations profiles, selected to represent the full COPD patient population.

Results assessed by the NGI showed that the delivered dose (NGI DD) was 50% higher for both alternative products, and the fine particle dose < 5 µm (FPD < 5) and most other mass endpoints deviated significantly more than 15% from those of the reference product. Therefore, the APSDs of both the Revolizer DPI and the Celon DPI were not bioequivalent to that of the Spiriva HandiHaler. After normalizing data to the delivered dose, the coarse particle fraction > 5 µm (CPF > 5) and the mass fraction 3-5 µm (FPD 3-5) were equivalent to Spiriva for both test products, while the amount of extra fines < 3 µm (FPD < 3) was higher for the Revolizer DPI and lower for the Celon blister DPI. This indicates that correction of delivered dose alone is not sufficient to achieve IVBE.

Assessment of the effects on FPD < 5 by parameters determining the shape of inhalation profiles showed that PIFR only affected Spiriva, while the acceleration (time to PIFR) affected both the Celon DPI and the Spiriva DPI, although in different directions: with slower acceleration, the FPD < 5 decreased 22% for the Celon DPI, while for Spiriva FPD < 5 increased—although only about 8%. Inhalation time did not affect FPD < 5 for any of the three products.

Testing of the Celon DPI with both the USP throat and the small, medium and large OPC mouth/throat models showed OPC depositions in the range 11.6-13.8 µg and USP throat deposition about 20% of this. The majority of the drug escaping the USP inlet was found in the pre-separator, but deposition in all stages of the NGI was significantly higher than that seen when using the OPC throats.

To further improve the clinical relevance of the proposed *in vitro* bioequivalence assessment, it is suggested to use more batches and additional MT models, and to select the number of replicates for each inhalation profile according to the proportion of patients expected to produce these results. A simple formula to calculate these number of replicates is proposed.

Remarks

The Celon tiotropium blister DPI is currently in development. The authors are grateful for the samples provided by Celon. The Cipla Rotacaps batch BA61365 tested with the Revolizer capsule DPI is, according to the authors' understanding, not intended to be equivalent to the Spiriva Handihaler.

Table 6

Test plan with number of tests per inhalation profile proportional to the expected number of patients having each profile, according to equation [5]

IP No.	PIFR	T_{PIFR}	T	N (%)
1	10	10	10	4.8
2	10	50	90	11.1
3	10	90	50	11.1
4	50	10	90	11.1
5	50	50	50	23.8
6	50	90	10	11.1
7	90	10	50	11.1
8	90	50	10	11.1
9	90	90	90	4.8

IP No. = inhalation profile number
PIFR = peak inspiratory flow rate
T_{PIFR} = acceleration (time to PIFR)
T = inhalation time
N = proportion of tests per inhalation profile

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Dennis Sandell, PhD, (corresponding author) is Director, S5 Consulting, Ekvägen 8, S-275 62 Blentarp, Sweden, +46 416 13510, dennis@s5consulting.com, www.s5consulting.com. Peter Elfman, MSc, is a Laboratory Manager and Mårten Svensson, PhD, is CEO at Emmace Consulting AB, Lund, Sweden, www.emmace.se.

Dennis Sandell, Bo Olsson and Lars Borgström have also published "PK bioequivalence testing when between-batch variability is high: A multiple-batch proposal" in *Inhalation*. Read the article in *Inhalation's* free archive.