PK bioequivalence testing when between-batch variability is high: A multiple-batch proposal

A proposal that reduces the risk of false failures to show PK BE, with no serious drawbacks and without increasing the risk of wrongly concluding BE

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Introduction

For the registration of a generic orally inhaled product (OIP), the establishment of bioequivalence (BE) by a pharmacokinetic (PK) study between the test and the reference products is a key element in both the United States and European Union. For the latter, the option of registration based on *in vitro* data only is also a possible, but challenging, route for approval. The typical design of a pivotal PK BE study is to compare inhalers from one batch of the reference product to inhalers from one batch of the test product using a two-way cross-over design. Experiences from such studies during the last five to ten years have shown that it may be challenging to establish PK BE between two OIPs, probably due to high between-batch variability for the reference and/or the test product. Several means to circumvent the variability problem have been proposed,[1-8] but, in our opinion, none fully addresses the fundamental problem: when between-batch variation is high, a single randomly selected batch may not represent the product well.

The consequences of high between-batch variability has recently been elegantly illustrated in a series of papers by Getz, et al.,[9-11] who in two separate PK studies showed that all different batches of the same product, low strength Advair Diskus (100 µg fluticasone propionate and 50 µg salmeterol xinafoate) (GlaxoSmithKline, Brentford, UK) failed the BE requirements when compared pair-wise. To our knowledge, this is the first time such data has been published and the studies confirm the assumption that high between-batch variability may be a key cause for the difficulty in showing PK BE between a generic and an originator product.

The consequences are far-reaching because they put the current paradigm for the way in which to show PK equivalence between two *products* into question. Clearly, in the presence of high between-batch variability, the standard two-way cross-over design comparing inhalers from two *batches* is not surely a scientifically valid approach to compare two *products*. Failure to show BE for the two *batches* is no proof that the *products* are non-equivalent, and neither is demonstration of BE for the two *batches* sufficient evidence that the *products* are BE. Consequently, there is an urgent need for a fair and scientifically more robust approach as a basis for making regulatory decisions.

Due to the need for an alternative PK design approach suited for cases with high between-batch variability, a method called the "Multiple-Batch Approach" is proposed here. This was originally presented at the Management Forum "Inhaled Drug Delivery" Conference in London in 2015[1] and is expanded in this paper to share the proposal with the wider scientific community.

The fundamental idea is simply to create a "composite reference batch" by evenly mixing inhalers from several reference product batches. By doing so, we create a composite of inhalers from different batches, which on average represents the reference (R) product better than a randomly selected single reference product batch. This composite is compared to the test (T) product batch (which may also need to be a composite of test batches, depending on the between-batch variability for the test product) using the standard two-way cross-over design. Subjects are to be dosed from randomly selected inhalers from the reference composite "batch" or from the test batch (possibly also a composite) according to the assigned sequence of treatments (TR or RT) as usual. The statistical evaluation should also be performed according to established methodology, to assess effects by sequence, period and treatment (= product), disregarding batch identity in the analysis.

How large an issue is using the classical approach in the presence of large between-batch variability?

If the T and R products are truly BE, the risk to wrongly fail PK BE when using the traditional approach, comparing inhalers from one reference batch to inhalers from one test batch, clearly increases when the between-batch variability increases. To illustrate how the risk grows with the variability, a simulation study was performed. The following approach was taken:

[1] It was assumed that the area under the curve (AUC) is proportional to the fine particle dose (FPD); AUC = p·FPD, where p is a constant. We do not claim that *in vivo/in vitro* correlation (IVIVC) is this simple but a model to connect an *in vitro* parameter (for which between-batch variability is well understood) to an *in vivo* parameter (where such data is hard to find) is needed. It was expected that this simple model was sufficient to study how variability in an *in vitro* parameter translates to risk to fail in a standard PK study.

[2] A hierarchical model was used, where the FPD varies between batches (relative standard deviation; RSD_B) and within batch (RSD_W) around the overall mean, m.

[3] Two reference batches were randomly selected; one was denoted R1 and the other R2. Because they came from the same product, they are BE on average but, due to the between-batch variability, their characteristics may differ.

[4] For each of the N subjects, one FPD value was randomly selected from each of the FPD distributions for batches R1 and R2.

[5] The associated AUCs were calculated according to the relation described in step (1), adding some pure, within-subject variability (RSD_{SW}).

[6] Based on the thus generated data for the N subjects, the 90% confidence interval (CI) for the mean AUC_{R1}/AUC_{R2} ratio was determined to conclude whether R1 and R2 are BE or not.

[7] Steps (3) through (6) were repeated for 10,000 PK studies and the frequency of studies passing BE was finally calculated.

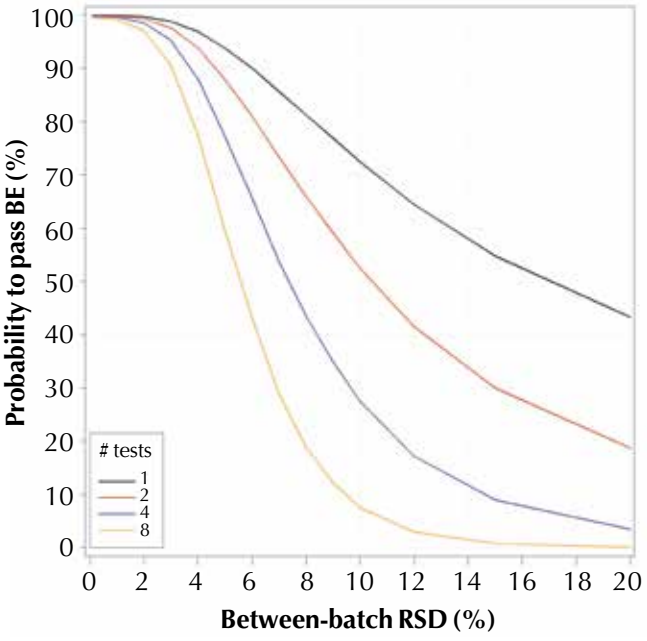
To obtain reliable simulation results, realistic values for the model parameters p, m, RSD_B, RSD_W and RSD_{SW} are required. Unfortunately, this type of data is seldom published but an exception is found in a paper by Lähelmä, et al.[12] where both PK and FPD data for a comparison of budesonide/formoterol EasyHaler® (Orion Pharma, Espoo, Finland) to Symbicort® Turbuhaler® (AstraZeneca, Cambridge, UK) are provided. The publication covers four PK studies and FPD results for 28 Symbicort Turbuhaler high strength (320 µg budesonide and 9 µg formoterol) batches. Based on the budesonide FPD and AUC results for Symbicort Turbuhaler, it was found that p = 29.84, m = 140 µg, and RSD_B = 9% (the formoterol between-batch RSD was also 9%).

No published data for within-batch RSD in FPD has been found. Based on our experiences, an RSD in the 5-20% range is expected, depending on the number of dose withdrawals to the impactor. In the simulations presented, an RSD of 10% was used. Together with an assumed pure within-subject RSD_{SW} of 17%, the total within-subject RSD is 20%.

The initial simulations showed that when T/R = 1 and RSD_B = 9% for both T and R products, the risk to fail one BE test is 23% in a PK study with 72 subjects and a total within-subject RSD of 20%. The situation is, however, more complex since C_{max} must also be compared in order to demonstrate BE. In addition, for inhaled medications, both local exposure (with oral charcoal) and systemic exposure (without oral charcoal) must be shown to be similar. That means the product must pass four BE tests, all of which carry a risk to wrongly fail, and thus contributes to an increasing overall risk to fail at least once. If it is assumed that tests are independent and each has the same risk to fail, the overall risk to fail at least one of the four tests is $1-(1-0.23)^4 = 0.65$; that is, more than half of the studies would wrongly fail. Further, if the registration concerns a combination product, the four tests become eight tests and the overall failure risk grows to 82%, i.e, only an 18% chance to show BE, despite the products being truly equivalent. The probability of passing PK BE for one, two, four or eight tests versus between-batch RSD is shown in Figure 1.

Figure 1

Probability to pass PK BE for two batches of the same product using 72 subjects for one, two, four or eight PKT/R comparisons versus between-batch RSD (%), based on 10,000 simulations



The results in Figure 1 show that when RSD_B grows beyond 3%, the probability to pass quickly decreases. For example, when RSD_B is 9%, the probability to pass all four tests is only 35% and for eight tests is 18%.

The above results and discussion illustrate the significant issue of false failures in showing PK BE and how this risk is influenced by high between-batch variability and the number of tests required. This is, however, only one side of the coin. There is also some risk that high between-batch variability may result in wrongly concluding bioequivalence in cases where the *products* being compared are truly non-equivalent (because the test and reference batches that *happened* to be selected are similar, although the products on average are not). However, considering the number of comparisons required to pass, this risk is much smaller than the risk to wrongly fail BE (assuming the two batches are selected at random and not intentionally chosen to match).

High variability of any type can possibly be countered by increasing the sample size (number of subjects). However, simulation results (not shown) indicate this is not a very efficient tool; increasing from 72 to 144 subjects (when the between-batch RSD is 9%) only increases the chance to pass all of four tests from 35% to 44%.

Another potential option is to reduce the FPD within batch variability RSD_W. A company producing a generic product cannot affect the between-inhaler variability for the reference product but perhaps can improve the variability of its own product. However, simulation results (not shown) indicate that this neither is a very efficient tool; decreasing the RSD_W from 10% to 5% (when the between-batch RSD is 9%) increases the chance to pass all of four tests from 35% to 40%.

The simulation results presented above have all assumed that the two batches being compared come from the same product and therefore, on average, are equivalent; i.e., that the overall T/R geometric mean ratio is 1.00 in the simulations. In practice, however, the test product rarely is perfectly equivalent to the reference product (which is not required for claiming BE). Any deviation from unity of the T/R ratio will, of course, add to the risk of failing PK BE. Figure 2 illustrates how the probability to pass varies with RSD_B for different T/R ratios, again assuming 72 subjects in the study, four tests to pass, an RSD_W of 10% and a within-subject RSD of 20%.

The probability to pass obviously decreases with increasing T/R ratio. If the RSD_B is 10%, the chance to pass decreases from 71% to 46% when the ratio increases from 1 to 1.1.

The above simulation results illuminate why Getz, et al.[9-11] in their PK studies could find that two batches from the same product (Advair Diskus 100/50) were non-BE, and the results clearly show that high between-batch RSD is a problem for registration of generic OIPs. At the heart of the problem is the fundamental inability of a single randomly selected reference *batch* to represent a reference *product* with high between-batch variability. Previously proposed solutions have sought to alleviate the difficulty without addressing the fundamental problem. The consequences of such solutions may be delayed market entries of generic products, thereby upholding higher drug costs for patients and society for an extended time. Therefore, some measure is needed to manage the situation so that fair and rational BE decisions can be made from PK studies.

Previously proposed solutions

As shown above, increasing the number of subjects or reducing within-batch variability is not particularly useful. If the two batches selected for the study happen to be significantly different, (i.e., the geometric T/R mean ratio is truly far away from unity), shortening the confidence interval will not be of much use because it will be wrongly placed. So there remains a bias problem that cannot be resolved only by shortening the CI.

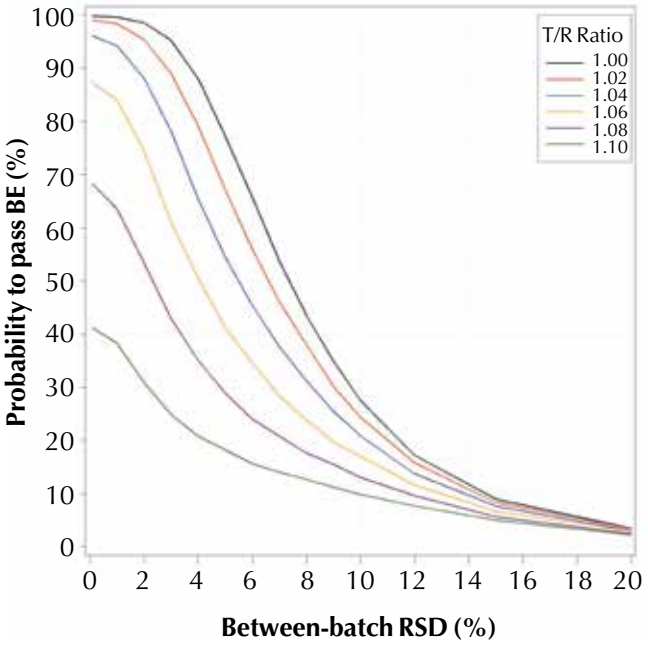
Several other approaches to address the problem of showing PK BE between two OIPs have been suggested. Here we discuss those recommendations and provide some brief comments.

Wider acceptance limits

Introduction of an arbitrary widening of the standard 80-125% PK BE acceptance limits is an obvious solution that surely will reduce the risk to fail showing bioequivalence. Unfortunately, this risk reduction applies also to the case when the products are truly different. In our opinion, this is not an approach that addresses the fundamental problem that batches differ,

Figure 2

Probability to pass four PK BE tests for one batch each of T and R products using 72 subjects versus RSD_B for various T/R ratios, based on 10,000 simulations



but rather avoids it. However, a PK design involving several batches and a statistical evaluation that use these to estimate between-batch variability for the reference product to scale the acceptance criteria accordingly might be possible. This appears to be the line of thinking that Getz, et al.[11] are working along. A key problem with this is likely that the few batches that practically can be included in the study will not provide a reliable estimate of the between-batch variability and therefore such a scaling would be unreliable.

Replicated designs

Some publications indicate that PK designs with several reference batches and possible repetition of one of these would be a way forward. However, they do not provide any details about the way the BE assessments would be performed.[2-5]

Use established methods for "highly variable products"

This approach will not help. These methods[6, 7, 13] were developed for cases where the reference product *within-batch* variability was higher than usual. Although this surely can be the case for OIPs, especially if the training of subjects is inadequate, it does not attack the root of the problem (i.e., the bias).

Use some in-vitro data "correction factor"

This idea was successfully used by Sandoz to obtain approval for the AirFluSal® Forspiro® inhaler (Novartis, Basel, Switzerland).[14] The thinking appears to be as follows, using AUC as an example: If the reference PK batch has an FPD that differs from that of the test PK batch, the AUC T/R confidence interval should be corrected by scaling the lower and upper limits of this with the factor FPD_R/FPD_T, and the corrected AUC interval finally compared to the 80-125% acceptance limits. The argument seems to be "as the test and reference products are equivalent *in vitro* (supposedly shown with data from many batches), the *in vitro* difference present between the two batches used for the *in vivo* study is due to "bad luck" in the batch selection and not representative of the true relationship between products. Therefore, it is appropriate to correct the outcome, according to the mismatch, to obtain results comparable to those that would be found if a representative reference batch had been studied in the PK trial." This is a sophisticated and somewhat questionable way of reasoning but it falls on the debatable assumption that FPD alone can predict PK outcomes for both products. A further assumption is that the test batch is a perfect representative for the test product.

Use a typical reference batch

This appears to be the approach currently recommended by EU regulators[8] and is based on use of the mean unit (or better, the median) as the best choice if a population must be represented with one unit. A typical batch is considered to be one with an FPD within ±15% of the median FPD of the product. The problem with this approach lies in incomplete understanding of IVIVC. What parameter should we use when ranking the available candidate PK batches? FPD is a first choice but there are other candidates. What about FPD < 2 µm? Amount drug dissolved in 30 minutes? Spray angle? Perhaps one should look at several parameters but what if they rank differently? What then? Average rank? Moreover, for a combination product, there is the additional problem that the two APIs might point towards different batches. In summary, the use of a typical reference batch is a good idea but probably hard to use reliably in practice. The approach is also problematic since it sanctions selection bias and "cherry-picking." Using the criterion of ±15% from the median for both the T and R products could lead to falsely concluding PK BE for products that, on the average, have a T/R ratio of 1.35, assuming PK is proportional to FPD.

Design a test batch to match a selected reference batch

This can be considered the hands-on version of the Sandoz "correction factor" approach[14] outlined above. The company selects a reference batch, characterizes this carefully and then uses their best developing skills to manufacture a test batch with matching key performance. Rather than correcting the confidence interval, the company goes back to basics and corrects the batch. This approach also suffers from limited understanding of the *in vitro* characteristics to match. Yet most importantly, a PK study of this type will not compare the two products and successful results thus cannot be taken as any evidence of product BE.

Bracketing design

This approach was put forward in Sandell[1] and is a type of replicated design. The suggestion is to select one "low FPD" (REF_L) and one "high FPD" (REF_H) reference batch, compare these to a single test batch (TEST) in a three-way crossover study and show that the test batch statistically falls between the two reference batches. The statistical principle would be to use two one-sided confidence intervals (CI) and standard acceptance criteria (LL = lower limit, UL = upper limit):

- Make 95% CI for $TEST/REF_L = (LL, \infty)$
- Make 95% CI for $TEST/REF_H = (\infty, UL)$
- Conclude PK BE if $LL \geq 80\%$ and $UL \leq 125\%$.

Similar to the "typical reference batch" approach, the bracketing approach seems to be a sound solution to the problem. Yet it suffers from the same issues: how to define "low" and "high" without fully understanding IVIVC.

Therefore, in our opinion, no fair, practical and scientifically acceptable solution to the high between-batch variability issue has been presented in the literature.

A proposed solution: The multiple-batch approach

The basic problem is: When between-batch variability is high, a randomly selected batch may be a very poor representative of the associated product, and it is not possible—due to incomplete understanding of IVIVC—to reliably select a single batch to represent the product. In the lack of this knowledge, the *only* way to better represent the product is to use a pool of batches. Together (the more, the better), they will provide a more accurate representation of the product, without any need to know how the included batches differ.

Taking this as a starting point, we suggest continued use of the standard two-way crossover design for the PK study, but instead of administering drug to all subjects from the same reference batch, administering drug to the subjects from a random inhaler from a "composite batch," consisting of several reference batches (and similar for the test product if this also has high between-batch variability). For the data evaluation, one disregards batch identity (although one should, of course, keep track of this) and performs the usual statistical analysis with factors product (rather than batch), period and sequence.

A simulation study was performed to assess the effect of this approach. It was again assumed that 72 subjects were included in the PK trial, that data had to pass four tests, and the model assumed RSD_W = 10%, RSD_{SW} = 17% and FPD T/R ratio = 1.00 (i.e., the ratio between the mean FPD for the TEST product divided by the mean FPD for the REF product is 1.00). The only difference from earlier simulations is that the 72 reference units are now selected from the reference composite batch containing samples from a (random) mixture of one, two, three, five or ten batches. Similarly, the 72 test units are drawn at random from a test "batch" composed of one, two, three, five or ten batches.

The results in Figure 3 show that when RSD_B is 9%, increasing the number of batches from one to ten, the probability to pass BE increases from 35% to 90% in this special case. Although this is a significant improvement (without increasing the size of the study), 90% is not 100%. The corresponding simulation with 144 subjects showed that three, five and ten batches were sufficient for a success rate of 83%, 92% and 98%, respectively.

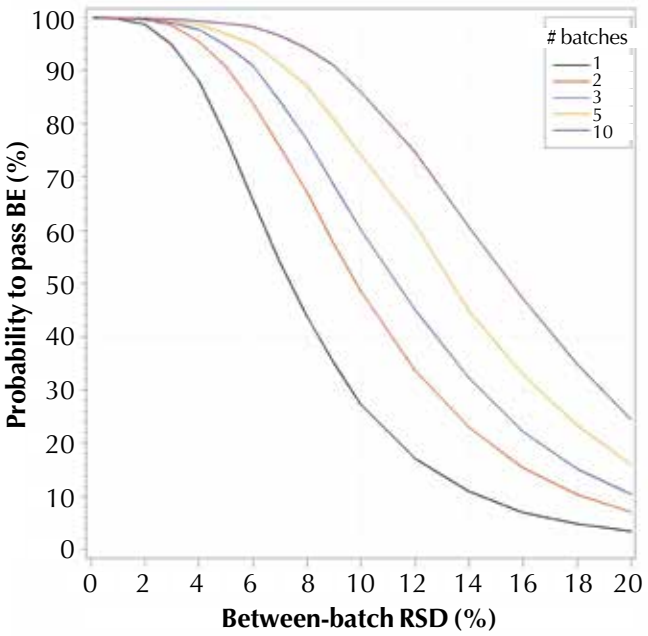
It should be noted that this approach comes without any increased risk of wrongly concluding BE for two truly non-equivalent products. Furthermore, this is a simple solution that fully addresses the problem without any significant practical or theoretical issues involved in the application.

Discussion

Some obvious, initial concerns (shown in italics) to the proposed multiple-batch approach are discussed below.

Figure 3

Probability to pass four PK BE tests in a trial involving batches for both T and R products using 72 subjects versus between-batch RSD (%), assuming a FPD T/R ratio of 1.00, based on 10,000 simulations



If one uses many batches (that are different), the within-subject variability will increase, leading to wider confidence intervals and thus increased risk to fail. It is true that the CIs will be longer, but the increase is expected to be marginal in relation to the dominating biological variation between testing the same subject on separate occasions. Further, if this turns out to be a significant concern, it can—contrary to the bias problem associated with the two-batch approach—be balanced by increasing the number of subjects. It should also be noted that this effect was included in the simulations above.

It will be difficult, or even impossible, to find five to ten different reference product batches on the market at the same time. This is probably correct, so one should start planning early and purchase batches as they turn up on the market. There are no issues (on the contrary) associated with having batches of different ages in the composite batch.

How can one be sure that the collected reference batches reliably represent the product? One can never be 100% sure, but one can probably increase the chances by purchasing reference batches from different markets or different production sites (if applicable) and ensuring that batches from fresh to close-to-expiry are represented. In addition, having more batches rather than fewer is always helpful.

It will be expensive to release all the batches that will be included in the composite batches. Cost is not a valid argument for using a non-scientific approach. Moreover, if cost is an issue, one should be more concerned about using the standard two-batch PK design with the associated considerable risk of needing

to repeat the study several times.

With so many batches, the ability to establish IVIVC is reduced. On the contrary, the ability to assess the way *in vitro* performance affects *in vivo* outcome will be improved (provided realistic *in vitro* data is collected), as data from multiple batches will be available. Consider a standard PK study with two batches in which one wants to investigate whether FPD predicts AUC. With only two points (FPD, AUC), one for the test batch and one for the reference batch, a regression will pass through both; this is true for any combination of *in vitro* and *in vivo* parameters. But with five batches in each composite "batch" (for example), and assuming it was determined which subject was administered drug from a given batch, there are now ten points to fit a model and thus, both a better chance to find a model fitting the data and to compare the fit for different *in vitro* parameters to identify the best of them.

It will be very expensive to manufacture five to ten test batches. In the end, this is probably the only significant objection. However, as noted above, cost is not a valid argument for using a non-scientific approach.

A complete random mixture seems sub-optimal; wouldn't stratified mixing and PK design be better? This is surely the preferred approach, but will impose some restrictions on the number of subjects. However, in most cases, it is still possible to define balanced designs. As an illustration, a full design with six reference (R) batches and three test (T) batches would require 36 subjects but can be reduced to 24 subjects as shown in Table 1.

Conclusion

The consequences of high between-batch variability are far-reaching, as they put in question the current paradigm of the way to show PK BE between two *products*. Comparing two *batches* is not a scientifically valid approach to compare two *products* with high between-batch variability: Failure to show BE for the two *batches* is no proof that the *products* are non-equivalent, and neither is demonstration of BE for the two *batches* sufficient evidence that the *products* are BE.

The issue and consequences of high between-batch variability for several reference OIPs, as well as test OIPs, have been experienced by generic and originator companies for several years and approaches have been proposed to rectify the situation. EU regulators currently recommend the "typical batch approach" but this is associated with some difficult issues due to the limited understanding of IVIVC, namely: In what characteristics should the batch be typical? The US Food and Drug Administration (FDA) seems to move in the direction of replicated designs and scaling acceptance criteria to somehow take between-batch variability into account, but no details have been provided to date. In our minds, both of these approaches fail to address the fundamental problem that no single batch can fully represent a product with high between-batch variability. Both approaches also increase the risk of concluding PK BE for truly non-equivalent products for reasons stated above.

In this paper, a multiple-batch approach has been suggested as a way forward: Instead of comparing two batches, the mixture of several batches (possibly for both test and reference) is compared in a standard two-way cross-over study, which is analyzed in the usual way (disregarding batch identity), thus comparing the products rather than two batches. This is a simple, practical and scientifically sound solution to the problems with false failures to show PK BE, with no serious drawbacks and without increasing the risk of wrongly concluding BE. A simulation study for a special but realistic situation shows that when test and reference products are truly BE, increasing the number of batches from one to ten in a study with 72 subjects may increase the chance to show bioequivalence from 35% to 90%.

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8. Committee for Human Medicinal Products: Questions and answers: Positions on specific questions

Table 1

Example: Design for multiple-batch PK study involving six reference (R) batches and three test (T) batches in 24 subjects

Subject #	1	2	3	4	5	6	7	8	9	10	11	12
Period 1	R1	R1	R2	R2	R3	R3	R4	R4	R5	R5	R6	R6
Period 2	T1	T2	T1	T3	T2	T3	T1	T2	T1	T3	T2	T3
Subject #	13	14	15	16	17	18	19	20	21	22	23	24
Period 1	T1	T1	T1	T1	T2	T2	T2	T2	T3	T3	T3	T3
Period 2	R1	R2	R3	R4	R1	R2	R5	R6	R3	R4	R5	R6

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