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Reflection paper on the dissolution specification for generic oral immediate release products

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Reflection paper on the dissolution specification for generic oral immediate release products

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Introduction

During the last few years the suitability of dissolution specifications has been discussed in marketing authorisation procedures. Some referrals concerning this topic have been raised through the CMD(h).

A decision tree is proposed to make the evaluation process more transparent. However there may be some drugs with very narrow therapeutic ranges or products where there is prior knowledge of critical dissolution behaviour (e.g. sublingual or orodispersible tablets with some buccal absorption), which still have to be evaluated on a case by case basis.

Scope

In the context of this reflection paper immediate release is identified as at least 75% of the active substance is dissolved within 45 minutes. This derives from the Ph. Eur. (5.17.1) recommendation for conventional release dosage forms.

This paper discusses the suitability of the dissolution method and the specifications for *in vitro* dissolution of orally administered generic drug products with immediate release characteristics. Where applicable, this reflection paper should be read in connection with the principles of relevant guidelines listed as references.

The dissolution specification should ensure batch to batch consistency and, ideally, signal potential problems with *in vivo* bioavailability.

This reflection paper does not discuss the dissolution tests in three different buffers required as complementary to bioequivalence studies, those tests required in support of biowaiver of strengths or BCS biowaiver as defined in 4.2.1 and 4.2.2 and Appendix III respectively of the (human) Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**) or in the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).

Definitions

Dissolution specification

The dissolution specification is expressed in terms of the quantity (*Q*) of active substance dissolved in a specified time, expressed as a percentage of the content stated on the product label.

Discriminatory Power

The discriminatory power is the ability of a test procedure to discriminate between batches with respect to critical process parameters and /or critical material attributes which may have an impact on the bioavailability. Ideally all non-bioequivalent batches should be detected by the *in vitro* dissolution test results.

Biobatch

Biobatch is a batch used in a bioavailability/bioequivalence study or in clinical testing. In the context of this Reflection Paper the biobatch is the batch of the applied product, which has been shown to be bioequivalent in a bioequivalence study of a generic vs. a reference drug product.

Discussion

1. Test method

1.1. Development of dissolution method

A dissolution procedure intended to be used as a routine control test for immediate release drug products should be robust, reproducible and discriminatory in order to assure a consistent product quality and to detect altered product quality attributes, which may affect the *in vivo* performance. For the development of such a dissolution procedure, the following aspects in particular should be considered:

- Selection of a suitable dissolution medium should be based on the physico-chemical characteristics of the active substance(s) and the intended dose range of the drug product to be tested. It should be ensured that sink conditions are met.
- In general, an aqueous medium should be used and the pH should first be evaluated in the physiological pH range. The addition of surfactants should be avoided. When surfactants are used, for instance to achieve sink conditions for poorly aqueous-soluble active substances, the type of surfactant should be justified. The concentration of the surfactant should be as low as possible and be justified by relevant solubility and dissolution data and an accompanying scientific discussion.
- The development of methods using the paddle apparatus should start with a stirring speed of 50 rpm. Higher stirring speeds may be applied with an appropriate justification. A higher stirring speed may be justified by high variability of the results (e.g. > 20% RSD at time-points ≤ 10 minutes, > 10% RSD in the later phase for a sample size of 12) observed at lower speed rates due to hydrodynamic effects (e.g. coning) or other factors (e.g. tablet sticking). However, it is known that methods with increased stirring speeds may be less discriminatory. Increasing the stirring speed at the expense of the discriminatory power simply to reduce variability of the results or to obtain complete dissolution in a shorter time should be avoided. An increase of the stirring speed may be considered in case of over-discriminatory conditions towards *in vivo* performance. However, in all cases the dissolution profiles at increased stirring speeds should have sufficient discriminatory power for drug product quality control.
- During development, the contribution of method parameters to the variability of the results should be investigated and reduced to a minimum.
- The discriminatory power should be discussed (see also section 1.2).

Further procedural recommendations on dissolution testing are provided in the European Pharmacopoeia.

1.2. Test conditions and discriminatory power

To allow extrapolation of the results of a bioequivalence study from the biobatch to commercial batches, it is necessary to have a suitable specification of the amount of active substance released at a specified time-point. The test conditions should be chosen to allow discrimination between batches with different *in vitro* release characteristics. In an optimal case the *in vitro* results can mimic the *in vivo* situation; the next best approach is to reproduce the rank order between batches and discrimination of batches with different quality attributes without knowing about the *in vivo* relevance of these differences. Both approaches may be used for routine batch control.

The suitability of the test conditions for routine batch testing should be demonstrated using batches with different quality attributes. To achieve this, batches with meaningful changes compared to the applied finished product should be manufactured. Such changes may relate to the quantitative formulation, input parameters and/or using slightly modified process parameters. Current knowledge of both the characteristics derived from the Biopharmaceutics Classification System (BCS) and the finished product must be taken into account when choosing the quality attributes to change. For instance, for a finished product where the *in vivo* absorption (rate and/or extent) is expected to be limited by solubility / intrinsic dissolution of the active substance, i.e. BCS 2 and 4, suitable quality attributes may be particle size of the active substance or other attributes that would have an impact on the *in vivo* dissolution. For a finished product where the *in vivo* absorption is expected to be limited by gastric emptying or intestinal permeability, i.e. containing BCS 1 or 3 class active substance with rapid or very rapid dissolution (refer to BE Guideline), suitable quality attributes may be factors in the formulation and/or manufacturing process that will have an impact on the disintegration of the finished product and significantly affect the rate of *in vitro* dissolution.

Changes to the composition of the drug product to create a “bad batch” should be covered by the proposed qualitative batch formula and only the proportions of the employed excipients might be changed. The complete omission of one or more specific excipients from the formulation (e.g. binder, disintegrant) is not supported. The dissolution test conditions should be able to detect these changes by setting a suitable specification.

However, for drug products containing a BCS class 1 or class 3 active substances with very high solubility over the physiological pH range, it may not always be possible to detect any differences in dissolution behaviour after meaningful changes in relevant formulation and/or manufacturing parameters have been made.

1.2.1. Batches with different in vivo behaviour included in pharmaceutical development

In cases where several batches of the drug product have been tested during development *in vivo* leading to batches with acceptable pharmacokinetic parameters and those with non-acceptable pharmacokinetic parameters, dissolution test conditions should be chosen which allow discrimination between acceptable and non-acceptable batches by setting a suitable specification.

1.2.2. Only batches with acceptable in vivo behaviour included in pharmaceutical development

Batches representing different *in vitro* dissolution profiles, derived from the defined manufacturing process by setting process parameters within the range of maximum variability expected from process validation studies, are so-called “side-batches”. The dissolution profiles of the side-batches can be used to set a suitable dissolution specification, when bioequivalence with the reference product is demonstrated. If the batches with the extreme range of *in vitro* dissolution profiles (i.e., fastest and slowest) are found to be bioequivalent to the reference product, then future batches with dissolution profiles within this range are also expected to be bioequivalent (when using the same manufacturing process). Thus, a suitable specification may be set based on the *in vitro* dissolution profile of the side batch with the slowest dissolution, using the methodology described in section 2.

For a marketing authorisation application for a generic medicinal product, a bioequivalence study between a representative batch of the generic product (test) series versus the originator product on the market (reference) has to be performed. The acceptance criteria for bioequivalence are set for the

pharmacokinetic parameters AUC and C_{max}. The latter is a measure of dissolution speed *in vivo*; in case of the same AUC, a larger C_{max} indicates faster *in vivo* dissolution. In a bioequivalence study design a comparison of the dissolution profiles (n=12) of test and reference products is required using the proposed test conditions of the generic drug product.

To estimate the discriminatory power of the dissolution test it may be helpful to look at the *in vivo* data (point estimates and the respective confidence intervals) of the bioequivalence study. Due to the acceptance criteria for bioequivalence the point estimates for C_{max} plus the respective 90% confidence interval of the generic product have to be between 80% and 125% of the C_{max} of the reference product. According to the equivalence rules (opposite to a superiority test with the objective of detect statistical significant differences) small differences without clinical relevance will be accepted as long the 90% confidence interval fulfils these criteria.

In such a case the rank order of the *in vivo* and *in vitro* results should be compared. If a test product with significantly larger C_{max} shows faster *in vitro* dissolution than the reference product, this may be used as an indicator for suitability of the chosen test conditions. The larger the difference of the *in vivo* point estimates is, the greater the chance that this difference may also be reflected *in vitro*. In case of an opposite rank order, i.e. a test product with significantly larger C_{max} shows slower *in vitro* dissolution behaviour or vice versa, the test conditions should be further optimised in order to reflect the *in vivo* trend.

1.2.3. No batches with in vivo behaviour included in pharmaceutical development

In certain instances the need for a bioequivalence study is waived based on fulfilling the criteria of the so called BCS-biowaiver. In such instances there is no batch used in a bioavailability/bioequivalence study or in clinical testing (biobatch) and by analogy, the batch that has been shown to be equivalent with a reference product based on satisfactory *in vitro* discriminatory dissolution data in at least three different pH media is considered to be the test batch.

For more information see Appendix III in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**) and /or Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).

2. Setting Specifications

When the dissolution test conditions have been chosen a suitable dissolution specification should be set. The dissolution specification is defined by a *Q* value, i.e. mean value, at a given time point, which allows discrimination between acceptable and non-acceptable batches. Batch results showing compliance with stage S_1, S_2 and S_3 (Ph. Eur. 2.9.3.) are acceptable. The specification should be set in such a way so that during routine manufacture and testing it would be expected that compliance with S_2 is attained.

Before setting the *Q* value, the time range allowing discrimination should be considered from the dissolution profile of the biobatch. Sampling time points should be sufficient to obtain a meaningful dissolution profile (c.f. human BE guideline, Appendix I).

To ensure that the results of the bioequivalence study may be extrapolated to the drug product administered to the patient, all commercial batches should show similar behaviour compared to the biobatch. The dissolution profile of the biobatch, using test conditions providing discriminatory power should be used to set a suitable specification. Similar dissolution of two batches may be assumed in

case of differences of less than 10% in their mean results. Therefore, the *Q* value is recommended to be set on the basis of the biobatch dissolution result (mean value) minus 10%.

The acceptance criteria the *Q* value is usually set in the range between 75-85% (5% intervals) to demonstrate discriminatory power and satisfactory dissolution. It is not considered relevant to have a limit of more than 85%. Usually the time points 15, 30 or 45 minutes would be sufficient, but other time points may be used if justified. It is not considered relevant to choose a time point before 15 minutes.

The recommendations in Annex 1 are meant as guidance for setting the specification. The discriminatory power is closely linked to the time point and *Q* value chosen. If time points/*Q* values other than proposed in the decision tree would lead to discriminatory power, this is also acceptable.

How to read the recommendations in Annex 1:

- If the dissolution of the biobatch is larger than or equal to 95% in 15 minutes, the specification may be set to *Q*=85% after 15 minutes[1];
- If the dissolution of the biobatch is less than 95% but larger than or equal to 85% in 15 minutes, the specification (*Q*) may be set to 75%, 80% or 85% whichever is closer to *Q*=biobatch result -10 % at 15 minutes[1];
- If dissolution of the biobatch is larger than or equal to 85% after 30 minutes, the specification (*Q*) may be set to 75%, 80% or 85% whichever is closer to *Q*=biobatch result -10 % at 30 minutes;
- If dissolution is larger than or equal to 85% after 45 minutes, the specification may be set to 75%, 80% or 85% after 45 minutes.

In case dissolution of the biobatch is less than or equal to 85% after 45 minutes, a minimum of 75% after 45 minutes should be specified if possible. Otherwise, if the dissolution specification (*Q*) is less than 75% after 45 minutes, the drug product is not inside the recommendation of the Ph. Eur. of an immediate release dosage form (see Annex 1: Decision tree for the principles for setting specifications). Therefore, the dissolution specification should be based on more than one time point.

In case there is no biobatch (e.g. BCS biowaiver), the specification limit with a fixed Q value within 15 min (for BCS class I and III) or 30 minutes (applicable only for human BCS class I products) can be established. This Q value should be 80% using discriminatory test conditions, irrespective of the dissolution results of the test batch observed in the study used to claim the BCS biowaiver. The conditions for the dissolution test in the specification should be chosen as the most discriminatory between those used in the comparative dissolution study.

Conclusion

This refection paper should facilitate congruent decisions on setting specifications for *in vitro* dissolution of generic drug products with immediate release characteristics. The principle is to derive the specification of the drug product on the basis of the quality characteristics of the biobatch. Similar principles may be considered for deriving the specification for innovator products.

[1] Both these bullet points are captured in the first decision box in the decision tree in Annex 1.

References

European Pharmacopoeia (Ph. Eur.), 5.17.1, Recommendations on Dissolution Testing ;

Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **);

Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2);

European Pharmacopoeia (Ph. Eur.) 8th edition, 2.9.3, Dissolution Test for Solid Dosage Forms;

Guideline on quality of oral modified release products (EMA/CHMP/QWP/428693/2013);

ICH guideline Q8 (R2) on pharmaceutical development (EMA/CHMP/ICH/167068/2004);

Note for Guidance Specifications: Test Procedures and Acceptance Criteria for new Drug Substances and new Drug Products – Chemical Substances (CPMP/ICH/367/96);

VICH GL52 on Bioequivalence: blood level bioequivalence study (EMA/CVMP/VICH/751935/2013 – Corr.1).

Annex 1: Decision tree for the principles for setting specifications based on the dissolution results of the biobatch