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Commentary

Medicinal products with pH-dependent solubility - a problem for BA/BE assessment?

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ABSTRACT

The ICH M13A draft bioequivalence guideline allows the exclusion of very low plasma profiles from the statistical evaluation in exceptional cases, i.e., if such phenomenon occurs due to non-compliance of subjects (not swallowing the product). Moreover, the draft ICH guideline requests additional bioequivalence studies for medicinal products with pH-dependent solubility after concomitant administration of gastric pH modifying preparations, e.g., proton pump inhibitors. Both regulations are scientifically sound, however, would need further specification. Main problem in this context is that compounds with very low solubility and slow intrinsic dissolution in the intestinal environment will cause significant bioavailability problems if their solid oral dosage forms are emptied from the stomach undisintegrated. Also very low plasma profiles may result under these circumstances. Such cases can occur accidentally and are not resultant of non-compliance. Thus, limitation for one case per study only as suggested in the guideline is not justified.

KEY WORDS: ICH M13A draft guideline; bioequivalence; exclusion of very low profiles, pH-dependent solubility, rapid gastric emptying

In the draft ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) M13A bioequivalence (BE) guideline [1] some new regulations are suggested which may need further scientific consideration. This commentary aims to draw the attention especially on two aspects and stimulate the discussion on these:

- Drug product solubility dependent on pH
- Removal of data due to low exposure

Under certain circumstances both issues are closely related. Such relationship is not mentioned in the draft guideline and, thus, should be highlighted in the following with the example of dasatinib immediate release solid oral dosage forms.

Drug product solubility dependent on pH

The ICH M13A draft BE guideline considers medicinal products with pH-dependent solubility as "critical" for bioavailability and bioequivalence. This applies in particular to those medicinal products for which pharmaceutical formulations have specifically been developed by adding certain excipients in order to reduce or completely avoid pH-dependency of drug dissolution/release.

There should be no doubt that products with pH-dependent dissolution of the active ingredient are sensitive to any pH-change in the stomach. This may be due to the concomitant intake of a meal which may increase gastric pH over certain period of time, but occurs especially in combination with other medications that cause a significant rise in pH, such as proton pump inhibitors.

For such problematic products (the guideline refers to them as "high-risk" medicines), additional confirmation of bioequivalence will be required in the future, thus, under the influence of a combination with stomach-pH modifying products. Through such additional studies the bioequivalence conclusion should be extended also to other therapeutic situations that may be highly relevant in practice.

The dependence of the solubility of active substances on pH can develop in two different directions. Compounds that are poorly soluble in acidic media (e.g. in the stomach under fasting conditions) but easily soluble in a neutral environment (i.e., in the intestine) should generally be less problematic. Examples of this category are the non-steroidal anti-inflammatory drugs, such as diclofenac or ibuprofen. There is no need in these cases to worry about a significant loss of systemic exposure due to changes in gastric pH. Total exposure (AUC) remains unaffected in most cases, while peak exposure (C_{max}) often does.

The situation is, however, quite different with immediate release preparations of drug substances that are soluble in acidic media, but poorly soluble or almost insoluble in a neutral environment. Such products should dissolve quickly and to a large extent in the fasted stomach, but their solubility largely collapses after arrival in the intestine. It will, therefore, be very important that these products disintegrate very rapidly during gastric residence to give the active ingredient the chance to dissolve in the acidic gastric environment. There may be certain (re)precipitation under the intestinal pH conditions, resulting in some delay in absorption which, however, should not collapse completely.

Gastric residence time in fasted state and impact on drug absorption

Thus, the time needed for disintegration as well as the gastric residence time can be determining factors for the bioavailability of such preparations.

Gastric emptying of non-disintegrated monolithic products after fasted administration is highly variable, with a median gastric residence time of approximately 20 minutes [2]. Studies using imaging techniques (e.g., Magnetic Marker Monitoring [2] or Magnetic Resonance Imaging [3]) have also shown that under fasting conditions gastric emptying of tablets and capsules can sometimes occur very early, before they (completely) disintegrate. For example, in a recent study with ten administrations of HPMC-based hard capsules under fasting intake conditions disintegration took place in the small intestine in three cases due to early gastric emptying [3]. Our evaluation of more than 100 gastro-intestinal transits visualised by Magnetic Marker Monitoring technique indicated that after fasted intake of monolithic products about 25 % of the dosage forms left the stomach within 10 minutes after swallowing and few already within seconds [unpublished].

Accordingly, preparations with disintegration times of 10 minutes or longerwill, thus, have the chance to be emptied from the stomach before being completely disintegrated. In such cases dissolution will be impaired if the active ingredient has poor solubility in the intestinal environment. As a consequence, drug absorption will be delayed in these cases and systemic exposure considerably reduced.

Very low plasma profiles after fasted administration of dasatinib tablets

A well-established example in this context is dasatinib, a poorly soluble compound in neutral media. The innovator brand product contains dasatinib as monohydrate which, moreover, shows slow intrinsic dissolution at pH 4.5 [5]. If a solid oral dosage form with such properties is emptied from the stomach into the small intestine before its complete disintegration, serious problems in drug dissolution, intestinal absorption and bioavailability should be expected. In individual subjects aberrant and very low plasma concentrations might result as consequence.

Such observation was first published by a Canadian CRO [4] presenting data from six BE studies, three of those with full-replicate design. Very low plasma profiles (<10% of geometric means) were observed in more than 5 % of subjects after receiving the reference product's tablets. The following graph extracted from the poster presented at the AAPS (American Association for Pharmaceutical Scientists) annual conference 2017 [4] confirms this very clearly. The authors concluded "that a significant portion of subjects express abnormally low AUCt of the RDL (Reference Listed Drug), which is the innovator brand product.

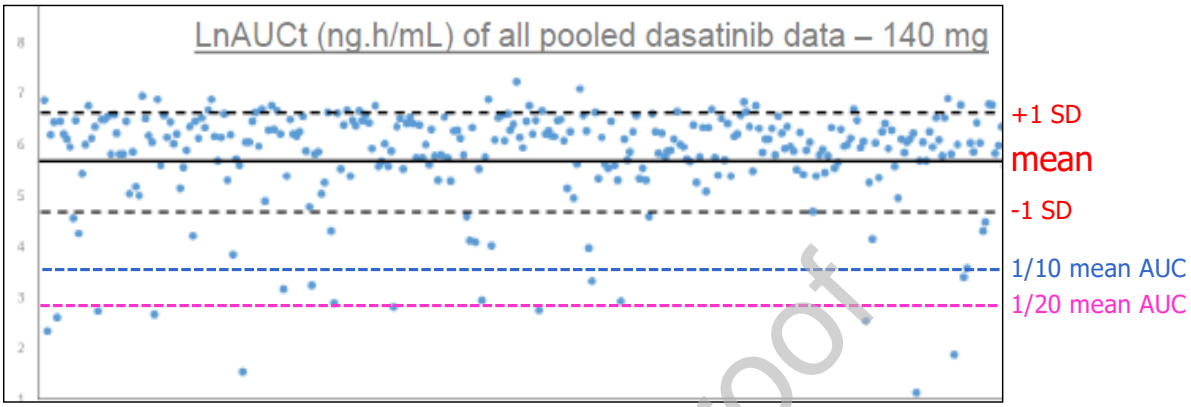

Figure 1: Scatter plots of individual LnAUC$_t$-values of individual subjects dosed with dasatinib RLD [4]

Similar observations were made in another full-replicate design (test and reference product given twice) BE study with aberrantly low profiles, all determined after intake of the reference product [5]. As examples individual profiles observed in two subjects with normo-chlorhydria in this trial are shown in Figure 2 [6]:

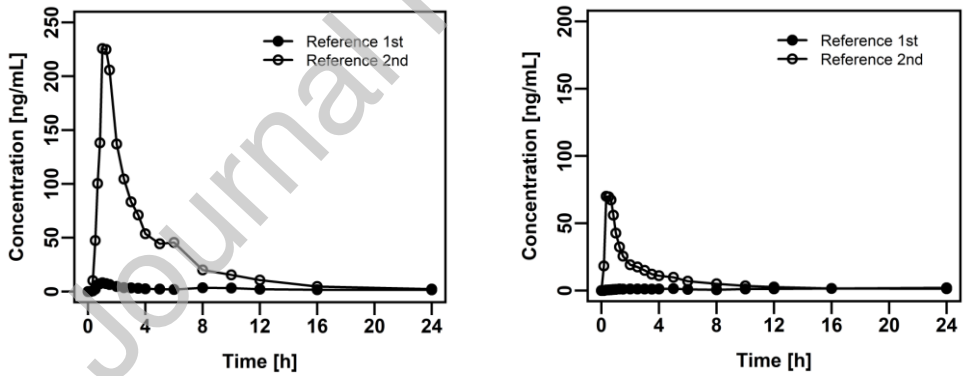

Figure 2: Individual plasma profiles of two subjects after replicate administration of the approved reference product

Such observations require comprehensive root-cause analysis.

- It is interesting to note that the low or almost non-existing profiles occurred only after one intake of the product while "normal" exposure was observed after the other administration to the same subject(s). Thus, it can be excluded that (partial) achlohydria could be causative for this observation.
- Non-compliance of the subjects with very low profiles – i.e., due to not swallowing the tablets, as considered as reason for such observations in the draft ICH M13A guideline [1] – was also excluded in all individual cases (mouth check).

- Moreover, indications for pharmaceutical quality problems of single tablets were also not found for the biobatches used in this study. Indications for such quality issues should be easily detectable by means of *in-vitro* tests.

A more likely explanation may be derived from the product and compound properties described above: given the properties of dasatinib monohydrate with high solubility in acidic media and very low solubility under intestinal conditions and, in particular, very slow intrinsic dissolution [5], lack of drug release/dissolution and impaired intestinal absorption must be expected if tablets are emptied rapidly and undisintegrated from the stomach. Moreover, also the frequency of occurrence of such phenomenon in the cited studies is in line with the above described gastric residence time distribution after fasted administration.

Such observations are not only critical in case of bioequivalence studies since the statistical evaluation is significantly impacted, but, even more important, will also affect the consistent treatment of patients. The situation would be comparable to a scenario where the intake of a tablet has been missed.

In this context it should be mentioned that attempts have been made to overcome these problems with alternative dasatinib preparations. Successful developments have been described in the literature based on an amorphous solid dispersion of dasatinib [7] or the use of anhydrous dasatinib instead of its monohydrate (contained in the innovator product) [5]. In the latter case especially the intrinsic dissolution of the anhydrate at pH 4.5 occurred significantly faster than that of the monohydrate.

With both generic alternatives considerable improvement of bioavailability could be achieved with the consequence that bioequivalence in comparison with the innovator reference product could be confirmed with an almost 30 % lower dose. In case of the anhydrous compound this could be explained by its significantly improved intrinsic dissolution.

Conclusion, suggestion

What should be concluded from these examples and considerations for the BE requirements recommended by the ICH M13A guideline? An understanding of “very low concentrations … as result of subject non-compliance” as stated in the guideline is a too limited perspective. Such reason needs to be excluded by proper monitoring of the study subjects. As other reasons seem more realistic and can occur more frequently, the intended limitation to “exceptional cases” (in general not more than one subject per study) cannot be supported.

Medicinal products with pH-dependent dissolution are problematic, especially those containing compounds with low solubility in the intestinal environment. To request additional BE confirmation after concomitant administration e.g., of PPI (proton pump inhibitors) is scientifically sound and should be supported (see [8]). However, the problem of very rapid gastric emptying of undisintegrated solid oral dosage forms cannot be adequately addressed by these additional studies.

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Graphical Abstract