

## Data from patient registries to replace clinical trials in previously untreated haemophilia patients

**November 30, 2018** – EMA has published revised guidelines on the tests and studies needed to support marketing authorisation applications for certain haemophilia medicines. The revised guideline for haemophilia medicines for factor VIII deficiency was published in July 2018 and the revised guideline addressing medicines for factor IX deficiency was published today.

The revision introduces an important change in relation to the investigation of recombinant and human plasma-derived factor VIII and factor IX haemophilia medicines in previously untreated patients: for this very small subset of haemophilia patient data should be collected from patient registries rather than from small clinical trials, that may not be fully representative of how the medicine is used day-to-day once it is on the market.

This new approach relies on data from registries as a source of high-quality, real-world data to support regulatory decision-making. It reflects that in this subset of patients, clinical data are difficult to obtain as the subset is highly selected and the numbers available for trials are very small.

The updated guidelines aim to optimise and facilitate the use of these registries and provide parameters for core data sets that should be collected. The new approach described in the haemophilia guidelines waiving the requirement for a clinical trial in previously untreated patients was discussed at an EMA workshop on haemophilia registries in July 2015. Following a public consultation in 2017, a second workshop on haemophilia registries was held on June 8, 2018, which aimed at defining the requirements for practical implementation using existing registries to support post-authorisation observational studies of haemophilia medicines. The workshop discussed recommendations on important aspects such as appropriate governance of registries, patient consent, data collection, data quality and data sharing, and interoperability between different registries.

More information on the practical implementation of the guideline is available in a questions-and-answers document. EMA's initiative on patient registries is supported by a task force comprising representatives from its scientific committees and working parties, representatives from the European Commission and experts from national competent authorities.

# Regulatory Matters

## Biowaiver: The magic wand to reduce time and cost

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The concept of a biowaiver is likened to the use of a magic wand to wave away the requirements for expensive *in vivo* testing. Biowaivers eliminate unnecessary human testing while providing a fast track for drug development. Cost savings from avoiding expensive clinical trials is possible with biowaivers, and this ideally would translate to more affordable medicines for patients worldwide to achieve universal accessibility to quality medicines.

The key for regulatory medical writers is to use the right “spell” in different situations to increase the chance of successful wand use, i.e., provide proper documentation to fulfil set requirements. Although biowaivers are more commonly applicable for generic drugs, they can also apply to new drugs or line extensions (e.g., new strength, new formulation) when certain criteria are met.

Some common biowaiver mechanisms include:

- Biowaiver for additional strength(s)
- Biowaiver for specific dosage forms
- Biopharmaceutics Classification System (BCS)-based biowaiver

### Biowaiver for additional strength(s)

This type of biowaiver is applicable to all types of marketing authorisation applications (new medicinal products, generic products, hybrid, etc.). Bioequivalence (BE) testing is generally performed on the higher strength, while it is waived for the lower strength if the *in vitro* pharmacokinetics are proven to be equivalent. Pharmacokinetic linearity of the active substance is a prerequisite for the application of an additional strength biowaiver. The strength(s) to be chosen for the BE study are determined by critically reviewed data on pharmacokinetics linearity. Similarity of *in vitro* dissolution between additional strength(s) and the strength used for

BE testing are demonstrated using the similarity factor ( $f_2$ ) test or other justified methods.<sup>1,2</sup>

In general, all the strengths should have the same manufacturing process, same qualitative composition, and the same ratio between the amounts of each excipient to the amount of active substance(s) for all strengths. If there is deviation from the quantitatively proportional composition of the strengths, biowaivers may still be considered if certain conditions regarding the amount of active substance(s), core excipients, and fillers are met.<sup>1,2</sup>

### Biowaiver for specific dosage forms

This type of biowaiver may apply to formulations such as aqueous oral solutions, parenteral solutions, locally acting, locally applied products (e.g., eye drops, nasal sprays, or cutaneous solutions), and gas for inhalation.<sup>2</sup> Certain pharmaceutical dosage forms are exempted from the provision of equivalence data due to their inherent characteristics. A prerequisite is that the test product should not contain a different salt (unless similar properties), ester, ether, isomer, mixture of isomers, complex, or derivative of an active substance than the reference medicinal product. In addition, the excipients should not influence the bioavailability of the active drug substance.<sup>1</sup>

### BCS-based biowaiver

The application for a BCS-based biowaiver is restricted to highly soluble immediate-release (IR) solid oral dosage forms or suspensions with systemic action, i.e., either Class I or Class III (see Table 1).<sup>1,3</sup> Modified-release products are not accepted for BCS-based biowaivers. Pharmaceutical alternatives (e.g., tablet versus capsule) and fixed-dose combinations may be considered if all the drug substances are BCS Class I or Class III. Importantly, drug substance(s) should not have a narrow therapeutic index. *In vitro* dissolution testing is used in lieu of a surrogate test to evaluate the bioequivalence of a test and reference product.<sup>1,3</sup> Table 1

The BCS-based biowaiver criteria is judged based on solubility, permeability, dissolution, and

quantitative and qualitative composition of test product versus reference medicinal product. For the comparison of dissolution profiles, the similarity factor ( $f_2$ ) is estimated. Two dissolution profiles are considered similar when the  $f_2$  value is between 50 and 100. However, in the case of very rapid solubility ( $\leq 15$  minutes) of both test and reference products, the dissolution profiles are considered similar and  $f_2$  testing is unnecessary.<sup>3</sup>

In certain cases, BCS-based biowaiver might not be feasible due to product-specific characteristics despite the drug substance being BCS Class I or Class III; for example, the *in vitro* dissolution being less than 85% within 15 minutes (BCS Class III) or 30 minutes (BCS Class I), either for test or reference, or unacceptable differences in the excipient composition.<sup>1,3</sup>

For products with multiple strengths, the criteria for BCS-based biowaiver must be applied for each strength, i.e., dissolution profiles of test and reference product should be compared at each strength.<sup>1,3</sup>

It is interesting to note that the BCS classification of a drug substance may differ in different jurisdictions (EMA, USFDA, PMDA, etc.).<sup>4,5</sup> Provisional BCS classification may be



searched via online databases such as that of the Drug Delivery Foundation,<sup>6</sup> while there is no official list for drugs with narrow therapeutic index. These aspects are reviewed by regulatory authorities on a case-by-case basis.

In conclusion, biowaivers are important mechanisms for new and generic drug development to bring essential medicines to those who need them most. It is important to be informed of the rationale for the choice of biowaiver and the necessary conditions to be fulfilled to provide effective documentation.

**Table 1: Biopharmaceutics Classification System (BCS) Classes for Drug Substances**

<p><b>Class I</b>  <b>High solubility, high permeability</b>            Compounds are well absorbed, and their absorption rate is usually higher than excretion rate  <b>Examples:</b> Metoprolol, propranolol, captopril</p>	<p><b>Class III</b>  <b>High solubility, low permeability</b>            Absorption is limited by the permeation rate, but the compound is solvated very rapidly  <b>Examples:</b> Ranitidine, cimetidine, atenolol</p>
<p><b>Class II</b>  <b>Low solubility, high permeability</b>            The bioavailability of the compounds is limited by their solvation rate  <b>Examples:</b> Naproxen, diclofenac, carbamazepine</p>	<p><b>Class IV</b>  <b>Low solubility, low permeability</b>            Usually not well absorbed over the intestinal mucosa, and a high variability is expected  <b>Examples:</b> Furosemide, hydrochlorothiazide</p>

## References

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