



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## **Q&A on the revision of the guidelines on clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 Rev. 2) and FIX products (EMA/CHMP/BPWP/144552/2009 Rev. 2)**

### **What are the changes?**

Inhibitor development, associated with a reduction in efficacy of the haemostatic effect of Factor VIII and occurring very commonly during the first fifty days of treatment with Factor VIII products in Previously Untreated Patients (PUPs), is one of the most serious complications in the management of severe haemophilia A. To a lesser degree this also applies to Factor IX in haemophilia B.

The former guidelines and core SmPCs were previously revised following the EMA haemophilia registry workshop held in July 1-2, 2015; these Guidelines requested the inclusion of PUPs in clinical trials. In due course, however, certain developments led to reconsider this requirement and led to a concept paper on the FVIII guideline and core SmPC which was published in 2016. These developments encompassed the publication of three large cohort studies in PUPs (including inhibitor development), the fact that therapy options were dramatically expanding, and in general that recruitment of PUPs due to the relatively small numbers is increasingly difficult.

Therefore, the aim of the current revision was to remove the obligation to perform clinical trials in previously untreated patients and instead to request post-authorisation studies based on a set of core data elements to be collected in haemophilia registries.

A workshop on haemophilia registries was held on 8 June 2018 which aimed at ensuring the practical implementation of using existing registries to support post-authorisation studies of haemophilia products. Following the agreement reached by all stakeholders at the workshop, the revised FVIII guideline and core SmPC was published in July 2018. The revised FIX guideline and core SmPC have also been finalised and published in November 2018.

### **How this will impact the marketing authorisation?**

As a consequence to the changes in the revised guidelines for FVIII and FIX medicines, when submitting PSURs/PSUSAs, MAHs will change their post-marketing requirement as follows:

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30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555

Send a question via our website [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact)

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- For new recombinant and human plasma-derived factor product developments, the obligation in the PIP to conduct a clinical trial in PUPs will no longer be required; this will be replaced by the provision of PUPs data coming from post-authorisation measure based on registries' data.

- For products where a clinical trial in PUPs is ongoing (in the case when interim results are available) or completed, the results of the study should be provided in PSUR/PSUSA submissions. Provision of PUPs data coming from post-authorisation measure based on registries' data will also be required.

**How will this impact the Paediatric Investigation Plan?**

Ongoing or planned clinical trials in PUPs are part of agreed Paediatric Investigation Plans (PIP). For any changes requested for an agreed PIP, the MAHs would need to submit a PIP modification to the PDCO in order to propose changes e.g. with respect to removing a requirement to conduct a PUP study.