EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on revision of Guidelines on the clinical investigation and core SmPC of recombinant and human plasma-derived factor VIII products

Agreed by Blood Working Party	June 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	1 August 2016
End of consultation (deadline for comments)	30 September 2016

The proposed guideline will replace 'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products' (EMA/CHMP/BPWP/144533/2009 rev. 1)

Comments should be provided using this template. The completed comments form should be sent to BPWPSecretariat@ema.europa.eu.

Keywords	**clinical investigation, efficacy, safety, immunogenicity, inhibitor, recombinant Factor VIII, plasma-derived Factor VIII**

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1. Introduction

The current “Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products” (EMA/CHMP/BPWP/144533/2009 rev. 1, adopted January 2016) are in operation since May 2016. The last update of the clinical guideline and the corresponding core SmPC (EMA/CHMP/BPWP/1619/1999 rev. 2) has been performed to align the document with necessary formal modifications according to regulatory decisions e.g. potency labelling and monitoring of patient plasma samples.

In the light of increasing scientific knowledge [1,2,3,4] and taken into account the unique situation that many factor concentrates are available, just entering the market or are in the pipeline and other non-replacement therapy options are currently in development for treatment of haemophilia a revision of the guideline(s) is regarded necessary.

2. Problem statement

The last basic revision of the concerned guidelines coming into operation in 2012 requires a minimum clinical data package of 100 Patients (PTP) to be presented at the time of marketing authorisation and with the obligation to present post-authorisation data from at least 200 patients (PTP) within a certain time frame. Additionally, for novel products clinical trials in 100 PUPs have been required. The development of new therapy options in Haemophilia is increasing dramatically. Currently, a variety of new factor concentrates have been developed or are still under development for prolonged half-live properties, which are expected to reduce the frequency of prophylactic therapy and thus enhance patient’s convenience. Because Haemophilia A is a rare disease, the recruitment of suitable clinical trial patients might be a bottleneck.

The most serious problem in hemophilia A is the development of neutralizing antibodies (inhibitors). Usually, inhibitor development occurs in the initial phase of Factor VIII exposure (i.e. in young children basically previously untreated patients -PUP). The publication of three large cohort studies (Rodin, UK Haemophilia Centre Doctors Organisation – UKHCDO and FranceCoag study groups) performed in PUPs lead to the consideration how to get the best capture of data from patients suffering from a rare disease and as such evaluating also the possibilities of haemophilia registries for regulatory purposes.

A workshop to discuss the landscape and options of hemophilia registries was organized at EMA with relevant stakeholders in July 2015 and resulted in consensus statements published on EMA website [5]. These consensus points included the recommendation to

a) establish a minimum core parameter set of data to be collected in registries to address regulatory expectations, but also

b) Reconsideration of the clinical trial requirements for PUP studies.

In addition, general reflections based on the results of the cohort studies and also the information coming from a recent published randomised clinical trial comparing plasma-derived and recombinant Factor concentrates needs to be taken into account [1,2,3,4].

Further aspects to be considered for the revision of both documents are based on the non-replacement therapy products being developed for Hemophilia treatment such as monoclonal antibodies, small peptides and gene therapy products.

3. Discussion (on the problem statement)

The historically unique situation of a rapid and broad development of haemophilia therapeutic products needs to be reflected in the clinical guideline and core SmPC for FVIII.
Hereby, focus will be given on the reflection of the clinical trial concept and specifically on the requirements regarding clinical trials in PUPs. Furthermore, to complement current knowledge regulatory standards for registry data collection will be explored and defined. However, in light of the recently published information on inhibitor development in PUPs [1,2,3,4] the reconsideration of the PUP clinical trial concept needs to be aligned with the approval of a minimum core data set of parameters to be collected in registries as well as basic quality standards for running registries in haemophilia addressing regulatory purposes. In addition, clarification on applicability of the requirements of the GL and core SmPC for non-replacement products needs to be provided.

4. Recommendation

The BPWP recommends revising the clinical Guideline on FVIII as well as the corresponding core SmPC for FVIII taking into account recent regulatory decisions (e.g. ABR) but basically regarding the following aspects:

- Reconsidering the clinical trial requirements in PUPs (e.g. applicability, concept, patient numbers, exposure days, statistics, consequences…)
- Establishing a minimum core parameter set on data collection in haemophilia disease registries addressing specifically safety aspects e.g. inhibitor detection
- Addressing non-replacement therapies in Haemophilia

5. Proposed timetable

Q2/2016-Discussion of the concept paper in BPWP/adoption CHMP for public consultation

Q3/2016-Q4/2016-Revision of the Guideline and coreSmPC/discussion BPWP and relevant WP/committees

Q1/2017- release for public consultation for 3 months

Due to the rapid development in hemophilia the revised guidelines should come immediately in operation once adopted. The relevant guidelines for FIX will be revised subsequently.

6. Resource requirements for preparation

The revision of these documents will be discussed during the meetings of the BPWP. External Parties do have the opportunity to comment during the public consultation phase.

7. Impact assessment (anticipated)

The rapidity of progress and changes in haemophilia treatment reflected by the fact that many factor concentrates are available now, so called long acting products are entering the market and other non-replacement therapy options are in development makes it inevitable to reconsider the current requirements of the clinical trial concept taking into account the limits in availability of suitable patients but exploring also other data collection systems like registries. Modification of the clinical concept for factor V III might have an impact on paediatric investigation plans but also on RMP requirements.

Beneficial for all stakeholders (patients, doctors, industry and regulators) would be to adapt the clinical trial requirements in combination with harmonized standards for haemophilia registries to strengthen and bundle efforts to get the best capture of information. The revised guidelines will better reflect the current medical knowledge, clinical practice and therapeutic product development in haemophilia.

The resource implications for the revision might include a stakeholder meeting.

8. Interested parties

Internal parties: PDCO and PRAC will be involved before CHMP discussion/adoption

External parties: Patient organisation, Academia, Industry will comment during public consultation

9. References to literature, guidelines, etc.

1 Gouw S et al.; Factor VIII Products and Inhibitor Development in Severe Hemophilia A; N Engl J Med 2013

2 Calvez T et al.; Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A; Blood 2014

3 Collins P et al.; Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011; Blood 2014

4 Peyvandi F et al.; A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A; NEJM Med 2016

5 Consensus Points – Workshop on Haemophilia Registries EMA/CHMP/BPWP/380896/2015