

10 September 2013
EMA/439957/2013
Human Medicines Development and Evaluation

Workshop on “Characterisation of new clotting factor concentrates (FVIII, FIX) with respect to potency assays used for labelling and testing of post infusion samples”

1. Introduction

Group 6B (Blood Products) of the European Pharmacopoeia started a review of the FVIII potency assays in October 2010. The current Ph. Eur. assay of FVIII (2.7.4) was introduced in 1995 based on recommendations of the ISTH SSC FVIII/FIX. In the Ph. Eur. the chromogenic FVIII assay is described whereas in clinical laboratories and regulatory areas outside of Europe predominantly the one-stage clotting assay is used.

In the EU the labelled potency of ReFacto AF, a BDD-rFVIII, is based on the European Pharmacopoeia chromogenic substrate assay, in which the manufacturing potency standard has been calibrated to the WHO International Standard using the chromogenic substrate assay. The same product (XYNTHA) approved for use outside Europe has a different potency assigned using a manufacturing potency standard that has been calibrated to the WHO International Standard using a one-stage clotting assay. Due to the difference in methods used to assign product potency 1 IU of the XYNTHA product (one-stage assay calibrated) is approximately equivalent to 1.38 IU of the ReFacto AF product (chromogenic assay calibrated). This situation has an impact for the safe treatment of patients travelling between regulatory areas. Many experimental details were identified which could contribute to the performance of the respective assays and influence the resulting potency assignment. The complexity of the issue is large and novel recombinant and/or modified products (fusion proteins with albumin, Fc portions, pegylation or sialylation as well as site-directed mutagenesis of clotting factors) may challenge even more the labelling of clotting factor concentrates.

Group 6B, therefore, is concerned about the best way of labelling of potency of factor VIII products (or other clotting factor concentrates). A working group of the ISTH (International Society on Thrombosis and Haemostasis) has recently published “Recommendations on the potency labelling of factor VIII and factor IX concentrates”¹. These included advice for the characterisation of products with respect to

¹ Hubbard AR, Dodt J, Lee T, Mertens K, Seitz R, Srivastava A, Weinstein M, On behalf of the Factor VIII and Factor IX Subcommittee of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Recommendations on the potency labelling of factor VIII and factor IX concentrates. J Thromb Haemost 2013; **11**: 988-9

potency assays, calibration of manufacturers' product reference, pharmacokinetic studies and testing of post-infusion samples.

During their meeting in April 2013 experts of group 6B expressed their strong wish to be informed about the current knowledge of characterisation of new clotting factor concentrates (FVIII, FIX) with respect to potency assays and testing of post infusion material. Therefore it was proposed to find possibilities to have a workshop on "Characterisation of new clotting factor concentrates (FVIII, FIX) with respect to potency assays used for labelling and testing of post infusion samples".

At the EMA, this proposal received positive support from the Blood Product Working Party (BPWP) and Biologics Working Party (BWP). It will be very helpful to have an overview of this topic so that discussion of possible regulatory consequences can be initiated in advance of individual applications for Marketing Authorisation.

2. Purpose of the workshop

The purpose of this workshop is to provide an overview of the current knowledge of the characterisation of new FVIII and FIX concentrates with respect to potency assays and testing of post infusion material. This overview will provide the basis for further consideration of the following related issues:

- Regulatory authorities discussion on the most appropriate potency assay for the individual products
- European Pharmacopoeia Group 6B discussion on whether to propose revision of the European Pharmacopoeia monographs in the light of information on new FVIII and FIX concentrates.

3. Time and location of the workshop

28 November (approx. start time 1pm) to 29 November 2013 (approx. finish time 5pm), Room 4A at the European Medicines Agency

4. Organisation of the meeting

Organised jointly by EMA (with BWP/BPWP support) and EDQM. (Correspondence to BPWPSecretariat@ema.europa.eu)

5. Steering committee

N. Aaby Kruse, BWP

J. Dodt, Chair of Group 6B (blood products) European Pharmacopoeia

A. Hilger, Chair of Blood Products Working Party (BPWP)

A. Hubbard, NIBSC

B. Neugebauer, EMA

G. Silvester, EMA

C. Vielle, EDQM

6. Participants

N. Aaby Kruse: BWP

E. Charton, EDQM (tbc)

J. Dodt, Chair of Group 6B (blood products) European Pharmacopoeia

E. Gray, NIBSC

A. Hilger, Chair of Blood Products Working Party (BPWP)

A. Hubbard, NIBSC

S. Kitchen, UK NEQAS (tbc)

B. Ljungberg, Vice-Chair of BPWP (tbc)

B. Neugebauer, EMA

G. Silvester, EMA

J-H. Trouvin: Chair Biologics Working Party

M. van den Berg, BPWP expert haemophilia (tbc)

C. Vielle, EDQM

S. Wicks, EDQM (tbc)

Representatives from FDA and Health Canada (plus Adobe Connect link for 28 November pm and 29 November pm)

Industry representatives

A representative from the Patients' Association for haemophilia

To be invited

Other BWP, BPWP and Group 6B members

Are welcome to attend, however EMA/EDQM funding for travel and accommodation is not available. An Adobe Connect link to listen to the workshop will also be possible.

7. Structure of workshop

Meeting with Industry followed by closed session (0.5 day) with regulators/OMCLs/EDQM

Closed Session

In the light of the information presented in the workshop, the closed session will discuss the points identified under the purpose of the workshop (point 2 above).

Preliminary agenda outline

Chairperson: J. Dodt

1. Introductory session

Presentation on assay methods and ISTH/SSC recommendations A R Hubbard

Presentation on current Ph. Eur. monographs and on how such monographs are updated EDQM speaker

Current approach on potency assays in US and Canada speakers FDA and Health Canada (tbc)

UK NEQAS studies of UK haemophilia centre assays of FVIII and FIX for clinical monitoring ...S. Kitchen (tbc)

2. Characterisation of new FVIII and FIX concentrates with respect to potency assays and testing of post infusion material

2.1 FVIII products

Refacto AF – Pfizer to briefly present on in-use experience with its product (tbc)

Presentations from manufacturers with new products in development. *Structure of this session will be developed once feedback is available from manufacturers. Specific questions will be taken after individual presentations (5 mins).*

Workshop discussion on FVIII

Discussion will focus on key issues arising from the presentations and identify where the new products fall in the flow diagram in the ISTH/SSC recommendations.

Will labelling in IU be feasible?

Is there a need for potency labelling of any of the new products using a one-stage clotting assay for FVIII?

Causes of variability in assay results (e.g. reagents) and whether there is a need for further standardisation.

2.2 FIX products

Summary of outcome of NIBSC collaborative study on FIX potency in preparation for the replacement of the international standard (including October 2012 meeting) -E. Gray

Presentations on assays of clinical samples from manufacturers with new products in development

Workshop discussion on FIX

Discussion will focus on key issues arising from the presentations and identify where the new products fall in the flow diagram in the ISTH/SSC recommendations.

Will labelling in IU be feasible?

Causes of variability in assay results (e.g. reagents) and whether there is a need for further standardisation.

3. Summary and close of open session.....Chairperson