



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Points to consider for assessors

New factor VIII and factor IX products: potency determination for labelling and assays for testing post-infusion samples

Background

Effective dosage and monitoring of replacement therapy for haemophilia A and haemophilia B requires reconciliation of the clotting factor potency applied to the finished product with that recovered from post-infusion patient plasma samples. A variety of assay systems for factor VIII (FVIII) and factor IX (FIX) potency measurement are available and difficulties can arise when significantly different product potencies are obtained with the different methods. These method-related potency discrepancies can impact both the finished product potency labelling and also the clinical monitoring post-infusion. The situation could become even more complicated where potency labelling depends on reagents used with a specific method. Such observations were noted with novel recombinant and/or modified FVIII and FIX products (e.g. fusion proteins, proteins modified by pegylation, sialylation or amino acid exchanges) but may also apply to any FVIII and FIX product. E.g. in a NIBSC collaborative study the mean potency of one modified rFIX product varied by 15-fold when different APTT reagents were used in the one-stage clotting assay (NIBSC Report to the Participants, October 2013). This raised concerns regarding the clinical monitoring and dosing of patients post-authorisation as the one-stage clotting assay is used in clinical practice. Thus, the assignment of potency is a complex issue interlinking quality, clinical, SmPC and RMP aspects and needs careful multidisciplinary evaluation.

Scope

This document has three objectives:

- The description of the product potency characteristics which should be provided by the manufacturer in support of the chosen method for final product potency labelling,
- The identification of key points which should be addressed to ensure a robust system for potency determination in the final product and in patient plasma post-infusion,
- To advise assessors (quality, clinical and RMP) to liaise for multidisciplinary evaluation of potency determination for labelling and testing of post-infusion samples.

These points apply to all new factor VIII and factor IX products, i.e. products not previously registered in the EU including plasma-derived, recombinant and modified products. The principles may also apply



in other scenarios related to potency determination. This document should be read in conjunction with the referenced documents which provide further information.

Quality

- Comprehensive data on the potency characteristics of new FVIII and FIX products measured relative to the WHO International Standard (IS) Concentrate (FVIII or FIX), as described in the SSC/ISTH recommendations (J Thromb Haemost. 2013; 11:988-9. (DOI: 10.1111/jth.12167), should be provided in the quality part of the dossier (3.2.S.3). This should include data from a variety of potency methods (e.g. the one-stage clotting method using a range of APTT reagents with different composition and the chromogenic method using different kits). Potency data on the product, calculated relative to the WHO IS Plasma (FVIII and FIX) using a variety of methods, should also be available in order to anticipate issues in post-infusion testing where a plasma standard may be used.
- The assay design used for potency characterisation should allow assessment of the statistical validity of testing the product relative to the WHO IS Concentrate (FVIII and FIX) (e.g. parallelism of dose-response relationships). Valid tests of product relative to the WHO IS Concentrate are required to support potency labelling in International Units (IU). Where valid tests are not possible, consideration should be given to labelling in "product-specific units" (EMA/CHMP/BWP/85290/2012).
- Potency values for some products, calculated relative to the WHO IS Concentrate, may differ widely when different assay methods and/or reagents are used but still satisfy the criteria for statistical validity. These assay discrepancies reflect differences between the product and the WHO IS Concentrate. In these situations the manufacturer's internal reference standard is very important to ensure consistency of product potency labelling by restoring a "like vs like" comparison where relative potency estimates should not be affected by different assay reagents or methods. An internal reference standard should be established for product potency labelling and value assigned in IU, relative to the WHO IS Concentrate, using the chosen method. Details of method and reagents used should be provided in the dossier. The stability of the internal reference standard should be monitored and the replacement strategy clearly described.
- If a product shows significant potency discrepancies depending on the assay and reference standards used, it should be demonstrated and justified that the potency chosen for labelling is appropriate.
- When the WHO IS Concentrate is replaced, the continuity of the potency assignment of the internal reference standard should be checked. The manufacturer should outline the procedure in case of a change of the WHO IS in the dossier (3.2.S.5 and/or 3.2.P.6). The manufacturer should be encouraged to collaborate in the development of the replacement WHO IS and to discuss any issues with the competent authorities.

Clinical

- Product potency characterisation in the quality part of the dossier may indicate if significant methods or reagent-based potency discrepancies are likely. However, potency discrepancies may not have been observed in clinical studies because the Applicant/Sponsor/Company has controlled the assays and reagents used for testing patient plasma samples. Potency discrepancies may become apparent with clinical monitoring with wider use after Marketing

Authorisation. In liaison with the quality assessor it should be checked whether the company has investigated the effect of different test methods and reagents on the measurement of representative post-infusion samples. Appropriate measures to be addressed in the SmPC and the risk management plan (RMP) should be considered.

SmPC

- Product information includes high level information to alert users to the issue. The core SmPCs for FVIII and FIX provide guidance for this (EMA/CHMP/BPWP/1625/99 Rev. 2; EMA/CHMP/BPWP/1619/1999 Rev. 2). It should be considered whether the information given in section 4.2 "treatment monitoring" of coreSmPC is applicable.

Risk management plan

- The RMP is the appropriate place to discuss the strategy to inform/train users and clinical laboratories that may be needed to address the risk of discrepant assay results in clinical monitoring, where the quality/clinical documentation has highlighted that significant discrepancies can occur (EMA/CHMP/BPWP/144552/2009 Rev 1; EMA/CHMP/BPWP/144533/2009 Rev.1). If applicable the RMP should consider:
 - Information on suitable and unsuitable methods and reagents for post-infusion testing
 - Availability of a product-specific laboratory reference material where the use of a local reference material is not advised
 - Information on correction factors to adjust measured potency

General aspects

- Manufacturers could be encouraged to initiate collaboration with Proficiency Testing Schemes in the evaluation of product / post-infusion sample testing in the wider community following marketing authorisation.

References

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. (DOI: 10.1111/jth.12167).

Dodt J, Hubbard AR, Wicks SJ, Gray E, Neugebauer B, Charton E, Silvester G. Potency determination of factor VIII and factor IX for new product labelling and postinfusion testing: challenges for caregivers and regulators. *Haemophilia* 2015; 1 - 7 (DOI: 10.1111/hae.12634)

Workshop report: Characterisation of new clotting factor concentrates (FVIII, FIX) with respect to 587 potency assays used for labelling and testing of post infusion samples, 28-29 November 2013 588 (EMA/135928/2014)

Guideline on core SmPC for human plasma derived and recombinant coagulation factor IX products (EMA/CHMP/BPWP/1625/99 Rev. 2)

Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products (EMA/CHMP/BPWP/1619/1999 Rev. 2)

Guideline on clinical investigation of recombinant and plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009 Rev 1)

Guideline on clinical investigation of recombinant and plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 Rev.1)

Guideline on the declaration of the quantitative composition / potency labelling of biological medicinal products that contain modified proteins as active substance (EMA/CHMP/BWP/85290/2012)

H. Wilmot, T. Dougall, P. Rigsby, E. Gray; Collaborative Study to Investigate the Comparability of Recombinant and new Generation Factor IX products with WHO International Standard for FIX Concentrate: Report to the Participants, October 2013