

RECOMMENDATIONS ON THE POTENCY LABELLING OF FACTOR VIII AND FACTOR IX CONCENTRATES

SSC/ISTH Factor VIII / Factor IX Sub-committee Project on the Potency of Clotting Factor Concentrates

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Introduction

This document addresses two main objectives of product labelling – the first being to define the quantity of the active substance in the vial for manufacturing and marketing purposes, and the second to guide physicians on the dose to be used for treatment that would correlate with recovery data measured in clinical laboratories. For the latter to be effective, the labelling of potency needs to correlate with methods that are predominantly used in hospital laboratories. These correlations may be difficult to establish for individual products and should be resolved at the level of the manufacturers and regulators. This document primarily relates to the potency labelling of new factor VIII (FVIII) and factor IX (FIX) concentrate products. The following recommendations are made in recognition that the potency measurement of some new products might be highly dependent on the choice of assay methods and reagents.

1 Manufacturer's characterisation of new product potency:

1.1 All new products should be tested against the current WHO International Standards (WHO IS) for FVIII or FIX Concentrate to establish if statistically valid estimates are possible.

1.2 FVIII and FIX assays should be performed using both 1-stage clotting and chromogenic methods following the SSC recommendations and relevant monograph methods where applicable, e.g. pre-dilution in appropriate factor-deficient plasma; albumin in dilution buffers; specified activation times. Best practice for testing includes multiple dilutions (at least three) of standard and product samples to enable assessment of linearity and parallelism of the dose-response relationships. Potency estimates based on single dilutions of test samples should be avoided and are not acceptable for product labelling. (Chromogenic assays for FIX should be included for information even though the method has only recently become available).

1.3 Evaluation by 1-stage clotting method should be performed using different APTT reagents, e.g. silica-based and ellagic acid. It is anticipated that the potency of modified products by the 1-stage clotting method may be highly dependent on the choice of APTT reagent in some cases.

1.4 In addition to potency assessment against the WHO IS Concentrate, assays should also be conducted using a plasma reference. This information may not be used in connection with product potency assignment but could be useful when considering the use of a plasma reference to monitor the recovery of new products in clinical laboratories. Data from other assay systems may provide further supportive information.

1.5 Where only one method for FVIII potency provides valid tests relative to the WHO IS Concentrate (e.g. 1-stage clotting or chromogenic) this could be used for labelling. However, if both methods provide valid tests and there is a significant potency discrepancy then agreement between regulators and manufacturers, on a single method for labelling, will be necessary. This decision may be guided by the in vitro characteristics of the product including the activation kinetics. A large variability in potency estimates when different APTT reagents (1-stage clotting method) or incubation times (chromogenic method) are used could exclude the use of one method. Additionally, data on in vivo efficacy may indicate increased clinical relevance for one of the assay methods. Where both methods are associated with large variability among reagents or kits it may be necessary to agree on a specific procedure for potency labelling of the product, in IU, relative to the WHO IS. Where

assays against the WHO IS are invalid the introduction of a product reference labelled in arbitrary “product-specific units” should be considered. An illustration of the decision process relevant to the potency labelling of new FVIII products is shown in Figure 1. (FIX potency labelling currently relies solely on the 1-stage clotting method and the relevance of potencies by the chromogenic method should be evaluated for each individual product).

2 Calibration of manufacturer’s product reference:

Manufacturer’s product reference preparations should be calibrated in IU, wherever possible, depending on valid assays relative to the WHO IS Concentrate as described in section 1. Where assays against the WHO IS are invalid then it may be necessary to assign a potency value in arbitrary "product-specific units".

3 Manufacturer’s pharmacokinetic studies:

3.1 Pharmacokinetic (PK) studies should be conducted according to current internationally recognized guidelines and approved protocols with sampling strategies relevant to the product characteristics.

3.2 The plasma samples collected in the PK studies should be measured using at a minimum the chromogenic and 1-stage clotting assays against the product reference as well as a plasma reference following the principles of best practice in section 1.2. If the activity of the product is sensitive to assay reagents (e.g. as described in section 1.3) additional assays should be performed to produce results for comparison among reagents.

3.3 The study should establish the relationship between the dose based on the labelled potency and the expected FVIII/FIX recovery in the patient. This relationship may be assay method and/or reagent dependent. The strategy and rationale used to derive a dosing guideline for the product should be described and justified in the marketing authorisation dossier or the summary basis of regulatory action. The dosing guideline should be included in the package insert or other readily available source, e.g. web posting. With this information, the clinician should be able to

determine an appropriate dose for the patient, and monitor FVIII/FIX recovery by correlating results generated from the local laboratory with those in the package insert.

4 Post-infusion testing in clinical laboratories:

4.1 The optimal approach to quantification involves testing against a product reference composed of the same material as that which is infused. However, this may be difficult to implement in the routine laboratory.

4.2 Routine in-house assays can be used for post-infusion testing provided the local assay system (method and reference) is included in the manufacturer's guidance as described in section 3.3. Robust assay designs of post-infusion samples should be used. Estimates based on a single dilution are not best practice. The use of a product reference may be indicated by the manufacturer's dosage guideline when valid assays are not possible using conventional/local standards.

NOTE

These recommendations are made on behalf of the SSC/ISTH Sub-committee on Factor VIII and Factor IX and must not be construed as the formal policy of regulatory agencies.

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FIGURE 1 DECISION TREE FOR NEW FACTOR VIII PRODUCTS

