Potency Assignment of Clotting Factor Concentrates

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On behalf of the FVIII/IX sub-committee SSC-ISTH project group
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Potency assignment of FVIII and FIX Concentrates

-Since establishment of the WHO 1st ISs for Factor VIII (1970) and Factor IX (1976) all therapeutic concentrates have been labelled using the same International Units
  - this has many advantages:
    • confidence in equivalent clinical efficacy
    • ease of product comparison
    • facilitates calculation of dosage (1 IU = 1 ml normal plasma)

-Units assigned by a clotting (APTT) or chromogenic assay

-Chromogenic method recommended by SSC/ISTH (1993)

-EMA requirement for labelling by chromogenic and FDA requirement for labelling by clotting

Courtesy: A Hubbard, NIBSC
"Albumin-free" B-domain-deleted Factor VIII

Licensed as new product in USA (2008) "Xyntha"
- labelled by clotting assay
Licensed as variation in Europe (2009) "ReFacto AF"
- labelled by chromogenic assay

"1 IU of the Xyntha product is approximately equivalent to 1.38 IU of the ReFacto AF product" (ReFacto AF product insert)

1000 IU vial of USA product contains approx 30% more Factor VIII protein than 1000 IU vial of European product

Courtesy: A Hubbard, NIBSC
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Other issues with current practice

1. Most service laboratories use APTT based assays for assessing recovery after infusion – Can be difficult for them to correlate with products labelled by chromogenic method

2. Issues with assay discrepancies with specific products often not adequately addressed or left to be resolved at the level of service labs

3. Challenge of designing assays for novel structure / function modified FVIII and FIX products
Project group of FVIII/IX subcommittee on Potency Assignment of Clotting Factor Concentrates

Aim:

"The mandate of this working party will be to find ways to harmonize the recommendations for the methods to be used for assigning potency of clotting factor concentrates. This will also include recommendations for assay of post-infusion samples to assess recovery."

Members:

A Hubbard (NIBSC, UK - Chair)
J Dodt (EMA/PEI, Germany)
R Seitz (EMA/PEI, Germany)
T Lee (FDA/CBER, USA)
M Weinstein (FDA/CBER, USA)
K Mertens (Sanquin, Netherlands)*
A Srivastava (CMC, Vellore, India)

* Courtesy: A Hubbard, NIBSC
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Issues to be addressed

1. Potency assignment of existing products that have dual labeling

2. Potency assignment of new ‘biosimilar’ products – function / structure not intentionally modified from native FVIII / IX molecule (except deletion of B domain)

3. Potency assignment of novel FVIII / IX products
Potency Assignment of CFC

Guiding principles

1. Define the quantity of the drug in the vial for manufacturing and marketing purposes

2. Guide physicians on the dose to be used for treatment that would correlate with recovery data measured in clinical laboratories

Therefore, new recommendations for potency assignment should attempt to resolve assay issues at the level of the manufacturers and regulators & provide clinical laboratories clear guidelines on methodology, reagents and calculation strategies for recovery assays
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_Draft recommendations_

I. Manufacturer’s responsibilities:

1. **New products should be tested against the current WHO International Standards (FVIII or FIX) Concentrate to establish if valid estimates are possible.**

   *Factor VIII assays should be performed using both 1-stage clotting and chromogenic methods following the SSC recommendations and relevant monograph methods (eg. pre-dilution in FVIII-deficient plasma containing normal VWF; albumin in dilution buffers; specified activation times).*

   *Evaluation by 1-stage clotting method should be performed using different APTTT reagents, eg. 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 APTTT reagent in some cases.*
Potency Assignment of CFC

*Draft recommendations*

I. Manufacturer’s responsibilities (contd.):

*In addition to potency assessment against an appropriate concentrate reference, FVIII assays should also be conducted using a plasma reference standard. This information should not be used in connection with product potency labeling but could be useful when considering the use of a plasma reference standard to monitor the factor VIII recovery of new products.*

2. Where only one method provides valid tests this could be used for labeling. If there is a potency discrepancy between methods (e.g. 1-stage clotting vs chromogenic) then agreement between regulators and manufacturers, on a single method, will be necessary.
Potency Assignment of CFC

Draft recommendations

II. Potency assignment of manufacturers' product standards:

Whenever possible, in-house product standards should be labeled in IU depending on valid assays relative to the WHO Concentrate IS established in section 1.

Where assays against the WHO IS are invalid then it may be necessary to label in arbitrary "product-specific units".
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**Draft recommendations**

III. Manufacturer’s pharmaco-kinetic studies:

*Pharmaco-kinetic studies should be performed according to the currently existing guidelines (in case of long-acting products this may require longer sample interval times). In vivo recovery should be based on the label potency, and on post-infusion assays against the product standard (current SSC recommendation).

*These assays should be performed using multiple assay systems: both chromogenic and 1-stage clotting and, if applicable, with multiple reagents. This stage should also include a plasma standard to see whether or not valid estimates of circulating FVIII or IX are possible.
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*Draft recommendations*

III. Manufacturer’s pharmaco-kinetic studies (contd.):

*These studies should establish the relationship between dosage, in terms of IU (or arbitrary units), and the expected FVIII/IX rise in the patient.

This relationship/dosage key may be assay dependent and should be described in the registration dossier and also in the package insert or other readily available sources in order to inform the clinician of the predicted recovery for specific assay systems.

This information may need to relate to specific 1-stage assay reagents in use in different parts of the world.
Conclusions:

1. Measurement of Bay 94-9027 (PEG-rFVIII activity by chromogenic assay yielded expected results

2. Measurement by aPTT based assays produced varied results –
   * Silica activators may give <10% of expected values
   * Ellagic acid gives expected or higher than expected values.

3. Analyzers using optical detection yielded expected values (100±20%) where as analyzers using mechanical clot detection consistently overestimated aPTT based activities.

The chromogenic assay is proposed to be the assay of choice for monitoring of PEG-rFVIII therapy in plasma.
Potency Assignment of CFC

Draft recommendations

IV. Post-infusion assays in clinical laboratories:

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

*Routine in-house assays can be used for post-infusion testing providing the local assay system (method and reference standard) is included in the manufacturer’s dosage key as described in section 3. Robust assay designs incorporating multiple dilutions of post-infusion plasma should be followed.

The use of a product standard may be indicated by the manufacturer’s dosage key when valid assays are not possible using conventional/local standards.
Post-infusion testing – What is current practice?

Do most laboratories use clotting assay vs plasma standard?
Experience with product-specific standards?

- Questionnaire despatched to 25 expert clinical laboratories – 6 responses:

Methods: 4/6 1-stage clotting, 1/6 2-stage clotting, 1/6 chromogenic

Standards: all used plasma standards for majority of products

Product-specific standards: 3/6 have used ReFacto Standard; 3/6 thought this approach logistically difficult

Courtesy: A Hubbard, NIBSC
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Special issues

*What is 1 iu of a modified FVIII or IX – Does the definition of iu apply to such products?

*Clinical correlates of recovered factor levels?

*Units for bypassing agents? Role of global assays in assessing hemostasis response with such drugs?
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Questions & Comments