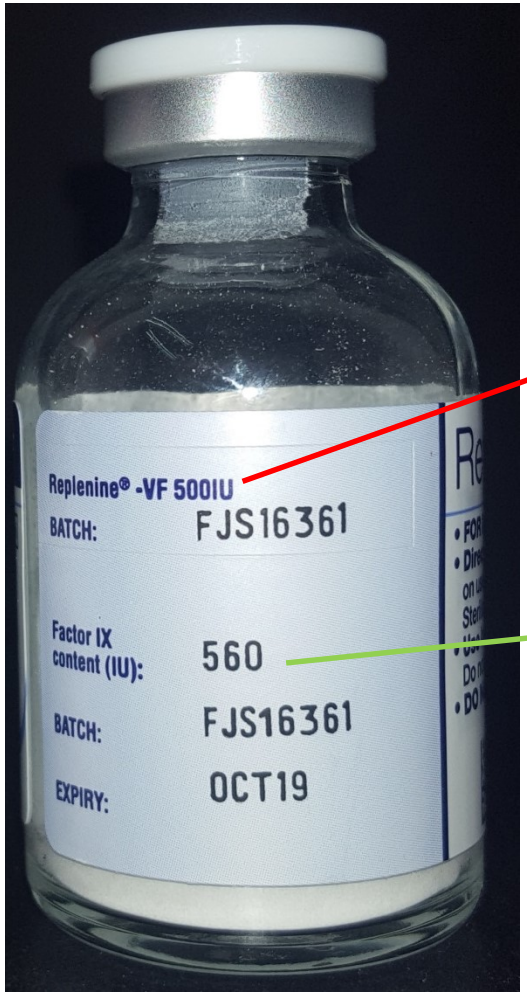
Potency labelling of extended half-life FVIII and FIX products

Elaine Gray

Medicines and Healthcare Products Regulatory Agency

ECAT, Leiden; 7 November 2018

Potency Labelling



Stated Potency
500 IU per vial

Estimated Potency
560 IU per vial

SUMMARY OF PRODUCT CHARACTERISTICS (SPC) -Alprolix

Posology

Dose and duration of the substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of recombinant factor IX Fc administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma).

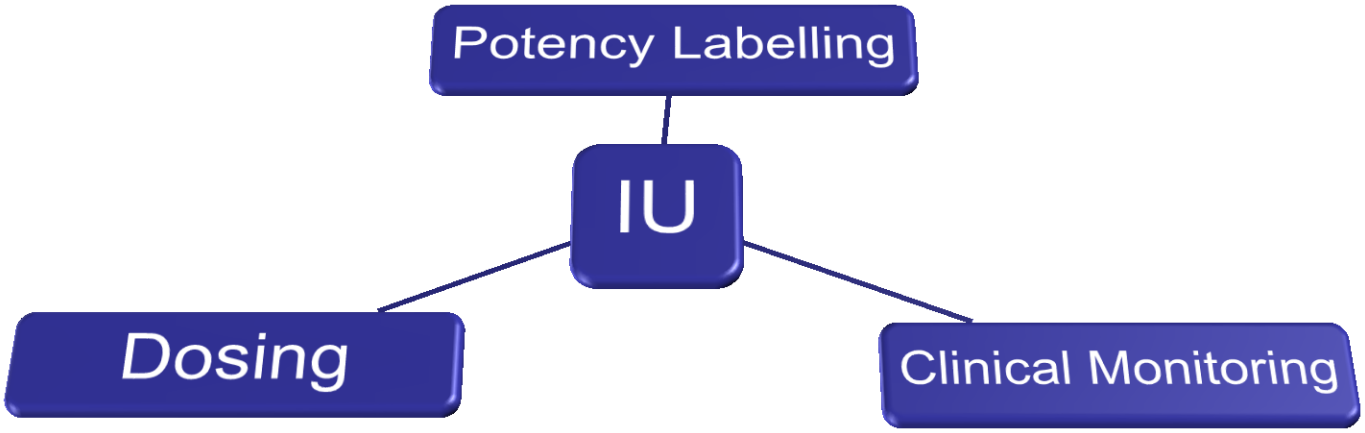
One International Unit (IU) of recombinant factor IX Fc activity is equivalent to that quantity of factor IX in one mL of normal human plasma.

On demand treatment

The calculation of the required dose of recombinant factor IX Fc is based on the empirical finding that 1 International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by 1% of normal activity (IU/dL). The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) (IU/dL) x {reciprocal of observed recovery (IU/kg per IU/dL)}

Role of International Unit (IU)



Potency labelling - in International Unit (IU) is important as dosing is in International Units

For FIX: based on 1 IU of product per kg body weight to raise activity by 1 IU/dL

Advantages of International Unit (IU)

- 1 IU = activity found in 1 ml of normal plasma

1 IU/ml = 100 IU/dl = 100% normal

- While activity of local normal pool can change and that normal pool from different labs are “not the same”, once the IU is defined for the first standard then it is fixed for subsequent replacement preparations
- Local pools should be calibrated against the International Standard (IS) or other reference preparations traceable to the IS

Facilitate agreement of level of “activity” between labs

- Labelled potency of products in IU are linked to the Plasma IU

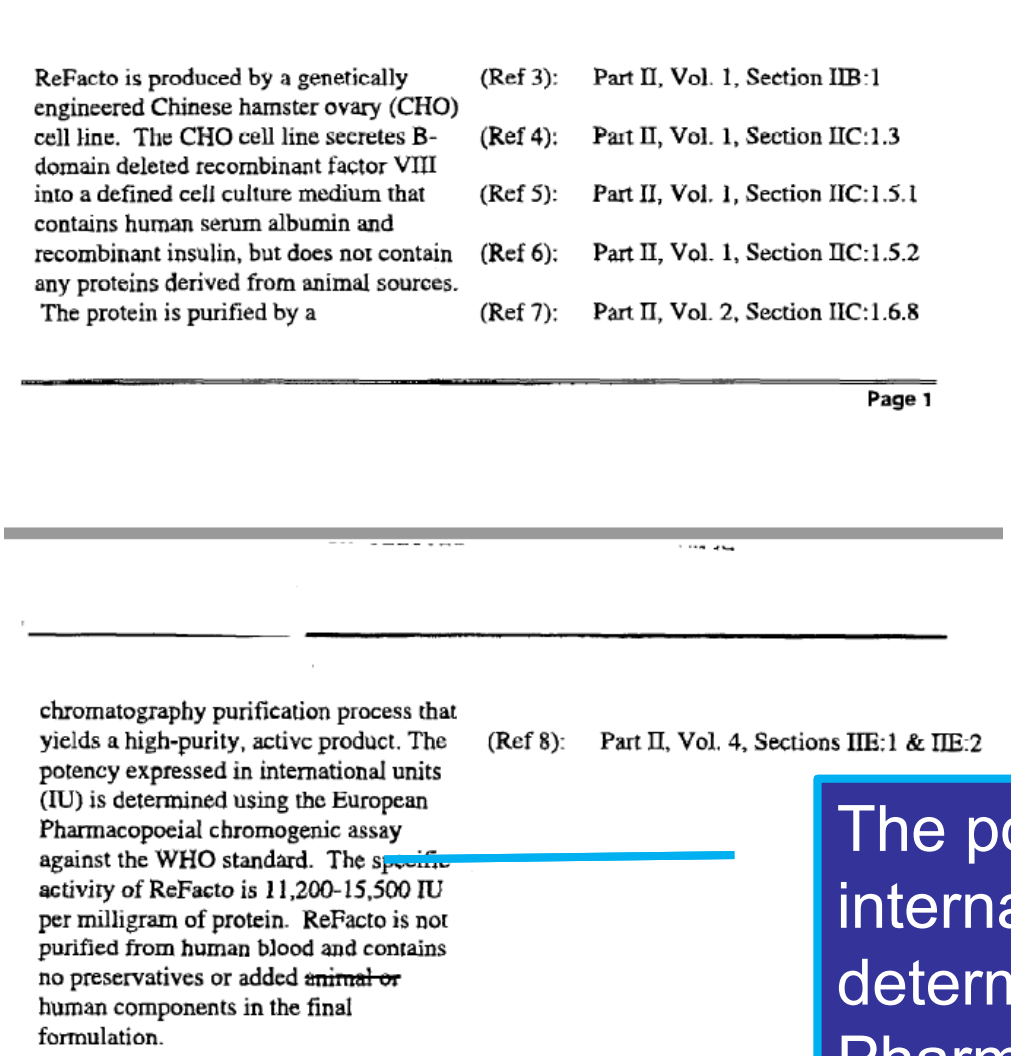
Enable the understanding of normal and deficient levels and aids the calculation of target levels for therapy.

Potency labelling

- Agree between local regulator and manufacturer as part of marketing authorisation (MA)
  - Global: issues by individual country e.g. US FDA
  - In EU: issued by Member State (National or mutual recognition) or Centrally by the European Medicines Agency (EMA) representing the European community
    - Centralised route of MA
      - All Member States: **Compulsory route** for certain product types and therapeutic areas e.g. recombinant products

Can lead to global disharmonisation

Refacto – B domain deleted recombinant FVIII Licensed in Europe and US in 2000



ReFacto is produced by a genetically engineered Chinese hamster ovary (CHO) cell line. The CHO cell line secretes B-domain deleted recombinant factor VIII into a defined cell culture medium that contains human serum albumin and recombinant insulin, but does not contain any proteins derived from animal sources. The protein is purified by a

(Ref 3): Part II, Vol. 1, Section IIB:1
(Ref 4): Part II, Vol. 1, Section IIC:1.3
(Ref 5): Part II, Vol. 1, Section IIC:1.5.1
(Ref 6): Part II, Vol. 1, Section IIC:1.5.2
(Ref 7): Part II, Vol. 2, Section IIC:1.6.8

Page 1

chromatography purification process that yields a high-purity, active product. The potency expressed in international units (IU) is determined using the European Pharmacopoeial chromogenic assay against the WHO standard. The specific activity of ReFacto is 11,200-15,500 IU per milligram of protein. ReFacto is not purified from human blood and contains no preservatives or added ~~animal or~~ human components in the final formulation.

(Ref 8): Part II, Vol. 4, Sections IIE:1 & IIE:2

Package insert 2000 for US market

- Despite clotting and chromogenic assay discrepancy, potency labelling in EU and US harmonised
- Patients across the continents received same amount of product

The potency expressed in international units (IU) is determined using the European Pharmacopoeial chromogenic assay against the WHO standard.

Second generation B-domain deleted FVIII: Assay Discrepancy lead to global potency disparity

Potency labelled against Plasma derived International Standard

-licensed as "Xyntha" in USA (2008) - labelled by clotting assay
-licensed as "ReFacto AF" in Europe (2009) - 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)

i.e. Clotting : chromogenic ratio approximately 1.38

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

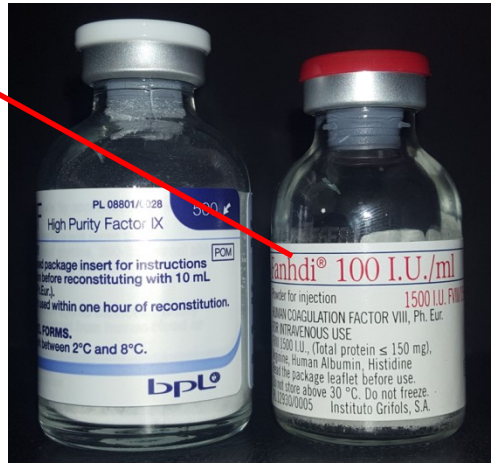
Market Authorisation (MA)

European Pharmacopoeia, Ph. Eur.

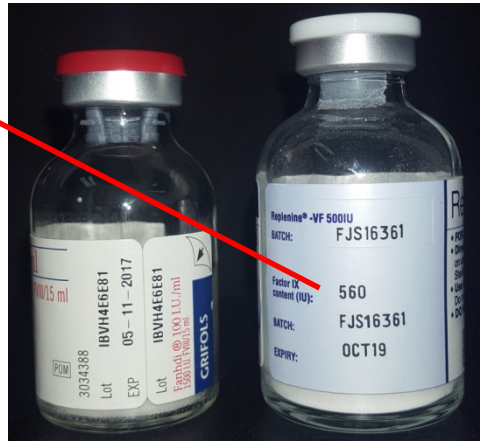
- Mandatory in European MA dossiers in 36 Member States (Ph.Eur.Convention)
- Recognised as the only official Pharmacopoeia in Europe, to be used for international trade

edqm
European Directorate for the Quality of Medicines & HealthCare

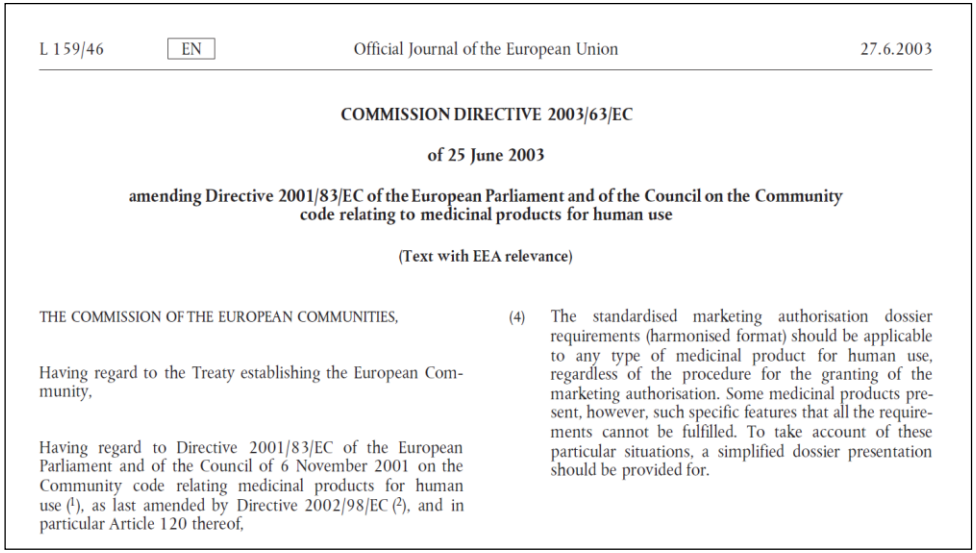
Nominal/stated potency



Estimated/actual potency



Legal Status of European Pharmacopoeia



L 159/46 EN Official Journal of the European Union 27.6.2003

COMMISSION DIRECTIVE 2003/63/EC

of 25 June 2003

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating medicinal products for human use (1), as last amended by Directive 2002/98/EC (2), and in particular Article 120 thereof,

(4) The standardised marketing authorisation dossier requirements (harmonised format) should be applicable to any type of medicinal product for human use, regardless of the procedure for the granting of the marketing authorisation. Some medicinal products present, however, such specific features that all the requirements cannot be fulfilled. To take account of these particular situations, a simplified dossier presentation should be provided for.

- Legally binding in the EU
- One single quality standard applied to same type of products aimed for all EU
- Harmonisation of specifications for therapeutics originated from different sources - reducing barrier to trade
- Provides validated analytical methods and lay out minimum requirements and specifications for important quality attributes
- Additional requirements may be requested by the competent authority

'ANNEX I

ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

European Pharmacopoeial Monographs for Factor VIII and factor IX

07/2013:0275

HUMAN COAGULATION FACTOR VIII

Factor VIII coagulationis humanus

DEFINITION

Sterile, freeze-dried preparation of a plasma protein fraction containing the glycoprotein human coagulation factor VIII together with varying amounts of human von Willebrand factor, depending on the method of preparation. It is prepared from human plasma that complies with the monograph on *Human plasma for fractionation (0853)*. The preparation may contain excipients such as stabilisers.

The potency of the preparation, reconstituted as stated on the label, is not less than 20 IU of factor VIII:C per millilitre.

01/2008:1643

HUMAN COAGULATION FACTOR VIII (rDNA)

Factor VIII coagulationis humanus (ADNr)

DEFINITION

Human coagulation factor VIII (rDNA) is a freeze-dried preparation of glycoproteins having the same activity as coagulation factor VIII in human plasma. It acts as a cofactor of the activation of factor X in the presence of factor IXa, phospholipids and calcium ions.

Human coagulation factor VIII circulates in plasma mainly as a two-chain glycosylated protein with 1 heavy (relative molecular mass of about 200 000) and 1 light (relative molecular mass 80 000) chain held together by divalent metal ions. Human coagulation factor VIII (rDNA) is prepared as full-length factor VIII (octocog alfa), or as a shortened two-chain structure (relative molecular mass 90 000 and 80 000), in which the B-domain has been deleted from the heavy chain (moroctocog alfa).

01/2011:0554
corrected 7.6

HUMAN PROTHROMBIN COMPLEX

Prothrombinum multiplex humanum

DEFINITION

Sterile plasma protein fraction containing human coagulation factor IX together with variable amounts of human coagulation factors II, VII and X; the presence and proportion of these additional factors depends on the method of fractionation. It is obtained from human plasma that complies with the monograph on *Human plasma for fractionation (0853)*. The preparation may contain excipients such as stabilisers, heparin and antithrombin.

The potency of the preparation, reconstituted as stated on the label, is not less than 20 IU of human coagulation factor IX per millilitre.

01/2011:1223
corrected 7.6

HUMAN COAGULATION FACTOR IX

Factor IX coagulationis humanus

DEFINITION

Sterile freeze-dried preparation of a plasma protein fraction containing coagulation factor IX. It is obtained from human plasma that complies with the monograph on *Human plasma for fractionation (0853)*, by a method that effectively separates human coagulation factor IX from other prothrombin complex factors (human coagulation factors II, VII and X). The preparation may contain excipients such stabilisers, heparin and antithrombin.

01/2016:2522

HUMAN COAGULATION FACTOR IX (rDNA) CONCENTRATED SOLUTION

Factoris IX coagulationis humani (ADNr) solutio concentrata

YNSGKLEEFV	QGNLERECME	EKCSFEEARE	VFENTERTTE	40
FWKQYVDGDQ	CESNPCLNGG	SCKDDINSYE	CWCPFGFEGK	80
NCELDVTCNI	KNGRCEQFCK	NSADNKVVCS	CTEGYRLAEN	120
QKSCEPAVPF	PCGRVSVSQT	SKLTRAEAVF	PDVDYVNSTE	160
AETILDNITQ	STQSFNDFTR	VVGGEDAKPG	QFPWQVVLNG	200
KVDAFCGGSI	VNEKWIVTAA	HCVETGVKIT	VVAGEHNIEE	240
TEHTEQKRNV	IRIIPHHNYN	AAINKYNHDI	ALLELDEPLV	280
LNSYVTPICI	ADKEYTNIFL	KFGSGYVSGW	GRVFHKGRSA	320
LVLQYLRVPL	VDRATCLRST	KFTIYNNMFC	AGFHEGGRDS	360
CQGDSGGPHV	TEVEGTSFLT	GIISWGEECA	MKGKYGIYTK	400
VSRYVNWIKE	KTKLT			415

Pharmacopoeial Limits for Potencies

Monograph	Limits for estimated potency (% of stated potency)
Human Coagulation Factor VIII 07/2013:0275	80 – 120
Human Coagulation Factor VIII (rDNA) 01/2008:1643	80 – 125
Human Prothrombin Complex 01/2011:0554	80 – 125
Human Coagulation Factor IX 01/2011:1223	80 – 125
Human Coagulation Factor IX (rDNA) Concentrated Solution 01/2016:2522	80 – 125

European Pharmacopoeia Monograph potency assays for FVIII and FIX

- One stage clotting, based on APTT – factor deficient plasma

Test factor dilution/patient plasma
+ factor deficient plasma

APTT reagent (Phospholipid + Activator)

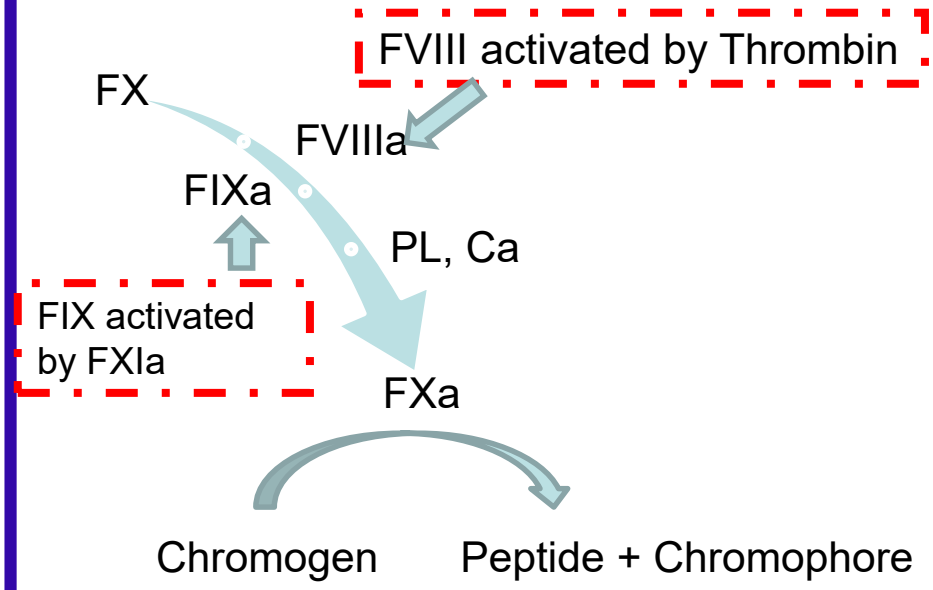
Ca^{2+}

Fibrin clot

Over 60 APTT reagents with different phospholipid compositions and activators

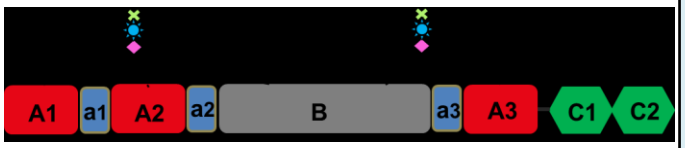
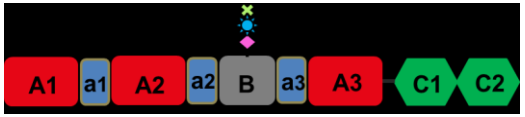
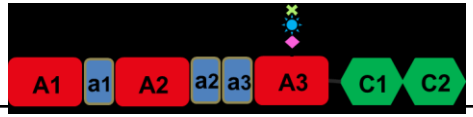
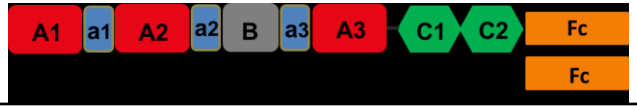
- Chromogenic – purified reagents

Test factor dilution/patient plasma

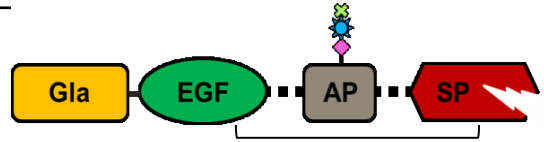
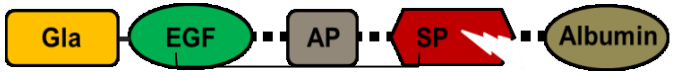


FIX 2 commercial kits
FVIII > 4 commercial kits
Plus in-house methods

Extended half-life FVIII products

Manufacturer	Product	INN	Domain Structure	Description
Shire	Adynovate	Rurioctocog alfa pegol		PEGylated Advate -rFVIII
Novo-Nordisk	N8-GP	Turoctocog alfa pegol		GlycoPEGylated Turoctogog Alfa
Bayer	KG-N BAY949027	Damoctocog alfa pegol		PEGylated B-domain deleted rFVIII
CSL Behring	Afstyla	Lonoctocog alfa		rFVIII-Single chain
Biogen Idec	Eloctate	Efmoroctocog alfa		rFVIII FC fusion protein

Extended half-life FIX products

Manufacturer	Product	INN	Domain Structure	Description
Novo-Nordisk	Refixia	Nonacog beta pegol		GlycoPEGylated rFIX
Biogen Idec	Alprolix	Eftrenonacog alfa		rFIX Fc fusion protein
CSL Behring	Idelvion	Albutrepenonacog alfa		rFIX Albumin fusion protein

Offer better yield, longer acting ……
BUT substantial standardisation challenges

Workshop on "Characterisation of new clotting factor concentrates (FVIII, FIX) with respect to potency assays used for labelling and testing of post infusion samples" ***28-29 November 2013***

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Journal of Thrombosis and Haemostasis, **11**: 988–989 DOI: 10.1111/jth.12167

OFFICIAL COMMUNICATION OF THE SSC

Recommendations on the potency labelling of factor VIII and factor IX concentrates

A. R. HUBBARD,* J. DODT,† T. LEE,‡ K. MERTENS,§ R. SEITZ,† A. SRIVASTAVA,¶ M. WEINSTEIN‡ and ON BEHALF OF THE FACTOR VIII AND FACTOR IX SUBCOMMITTEE OF THE SCIENTIFIC AND STANDARDISATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

**National Institute for Biological Standards and Control, Potters Bar, UK; †Paul-Ehrlich-Institut, Langen, Germany; ‡Center for Biologics Evaluation and Research/Food and Drug Administration, Rockville, MD, USA; §Sanquin Blood Supply Foundation, Amsterdam, the Netherlands; and ¶Christian Medical College, Vellore, India*

Journal of Thrombosis and Haemostasis, **11**: 988–989 DOI: 10.1111/jth.12167

NIBSC

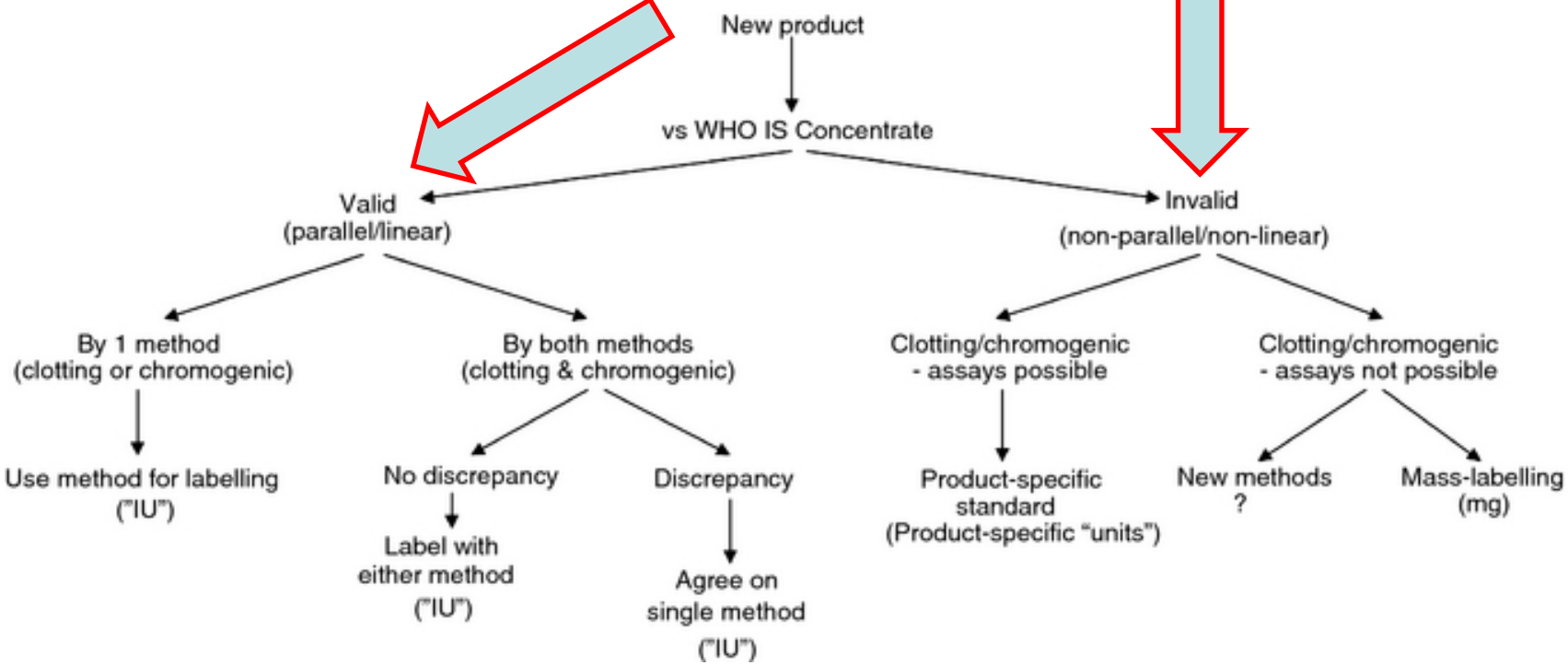
OFFICIAL COMMUNICATION OF THE SSC

Recommendations on the potency labelling of factor VIII and factor IX concentrates

A. R. HUBBARD,* J. DODT,† T. LEE,‡ K. MERTENS,§ R. SEITZ,† A. SRIVASTAVA,¶ M. WEINSTEIN‡ and ON BEHALF OF THE FACTOR VIII AND FACTOR IX SUBCOMMITTEE OF THE SCIENTIFIC AND STANDARDISATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

**National Institute for Biological Standards and Control, Potters Bar, UK; †Paul-Ehrlich-Institut, Langen, Germany; ‡Center for Biologics Evaluation and Research/Food and Drug Administration, Rockville, MD, USA; §Sanquin Blood Supply Foundation, Amsterdam, the Netherlands; and ¶Christian Medical College, Vellore, India*

Statistical Assessment



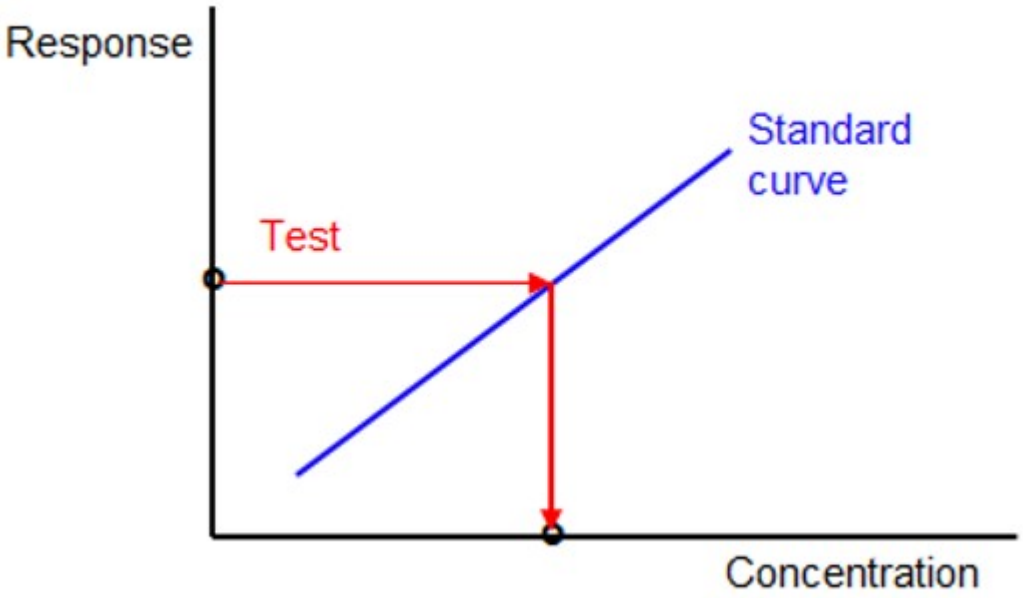
Possibility that potency labelling method is not the monograph method

Essentials of Bioassays

- Require a standard preparation to measure activity of test sample
- The standard and test material must be assayed under identical conditions to allow a valid relative potency estimation
    - *same incubation time*
    - *same dilution buffer*
    - *same reagents*
    - *same procedure*
    - *same instrument*
- The test dilutions in effect behave as if they are dilutions of the standard preparation

Estimation of Activity/Potency: single point estimation for test

Test concentration interpolated from a single point on the standard curve:

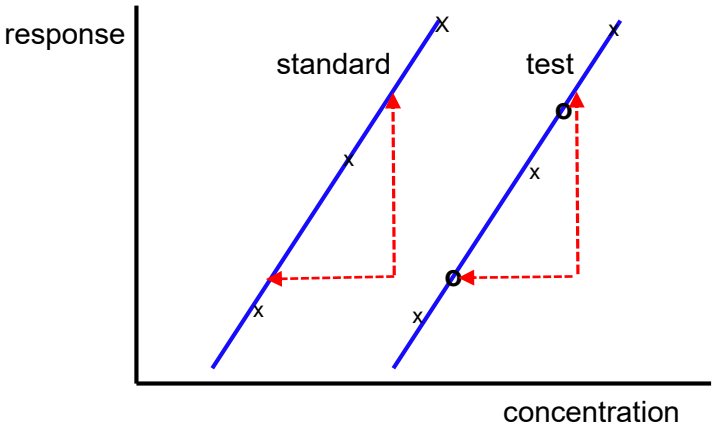


Common practice in clinical labs

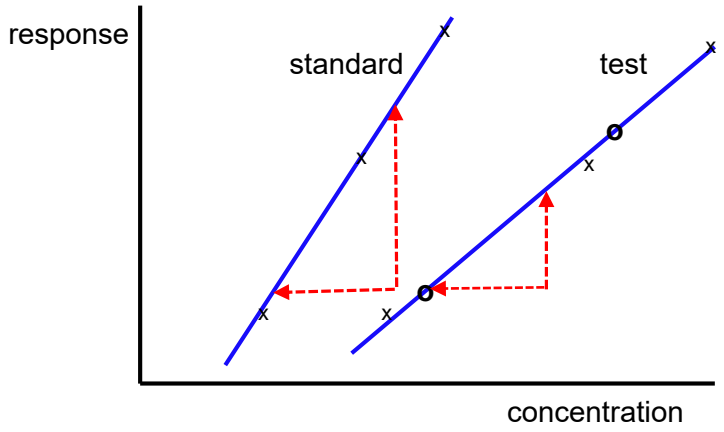
Estimation of Activity/Potency: Multiple dose response for test

Single point estimates for potency can be misleading when the dose-response relationships of standard and test are not parallel.

Standard Slope = Test Slope
Standard Slope/Test slope = 1

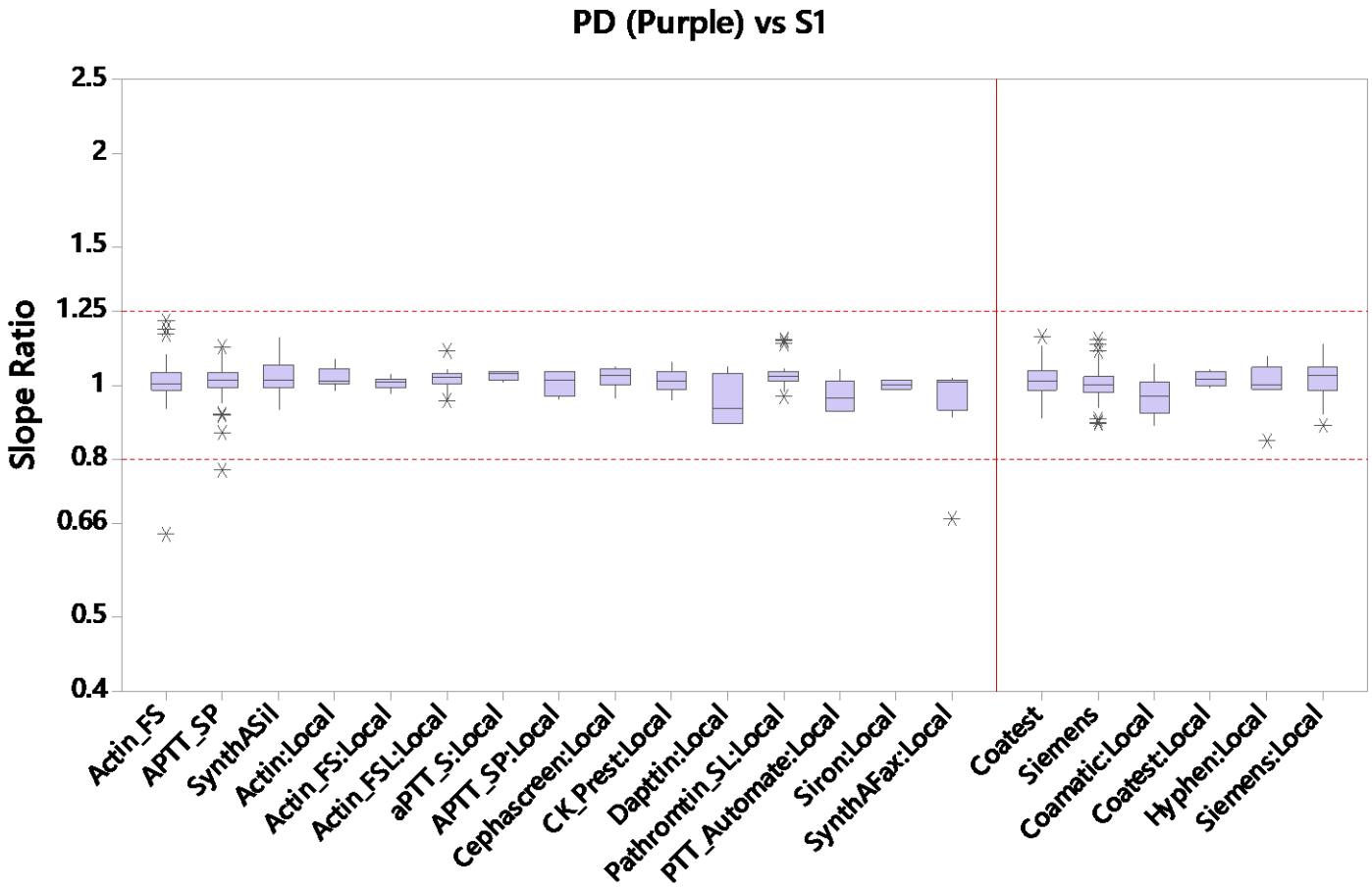


Standard Slope < Test Slope
Standard Slope/Test slope < 1



- Multiple dilutions of both test and standard to obtain best fitted lines for assessment of linearity and parallelism
- In an ideal situation, the ratio of the slopes for standard and test should be 1

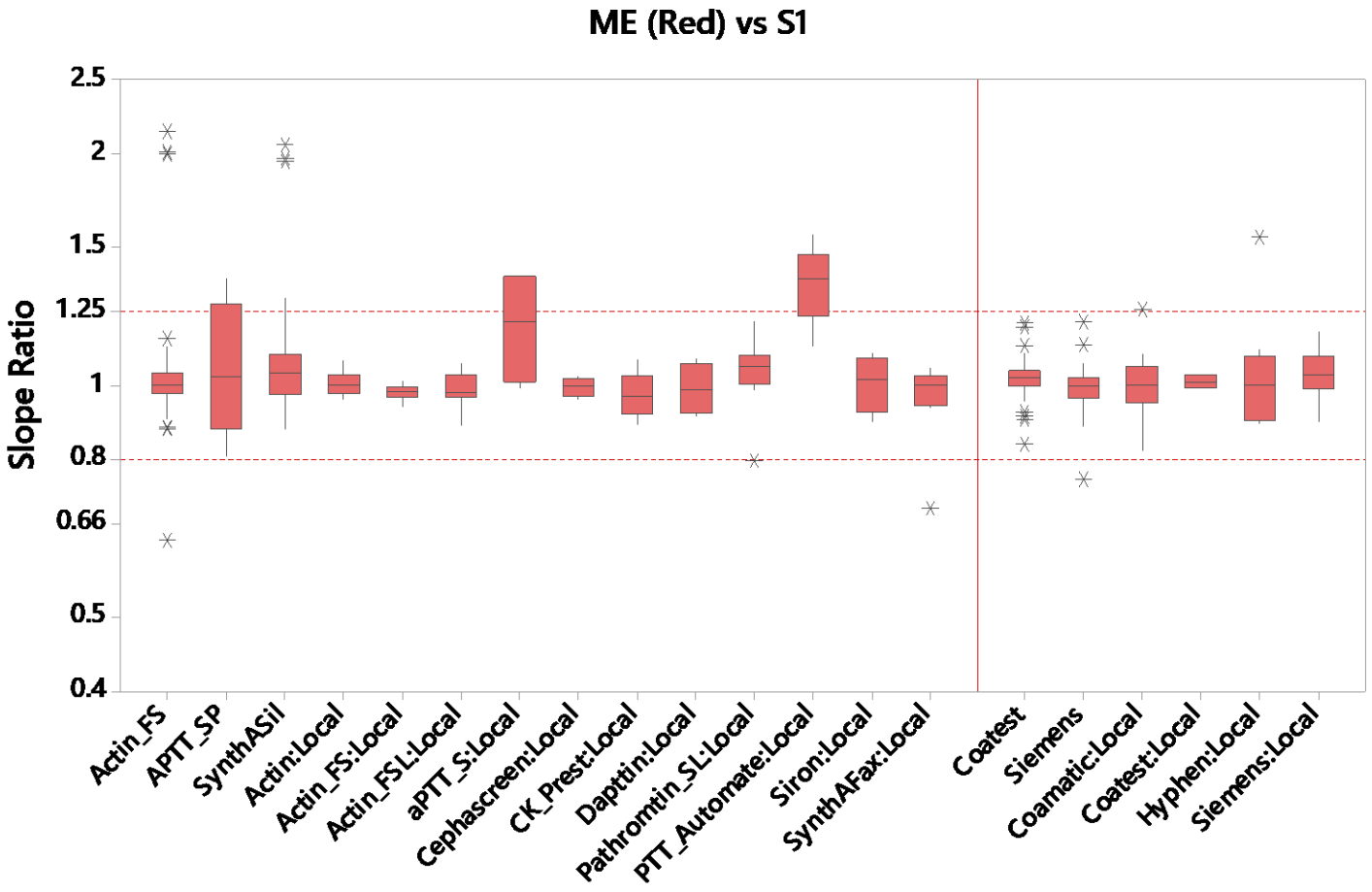
Plasma derived FVIII against Plasma derived FVIII Concentrate IS



- Majority of ratios of slopes close to 1 and within 75% interquartile range
- Only 3 assays gave ratios outside 0.8 – 1.25 acceptance criterion

NIBSC EHL-FVIII collaborative study, 2018

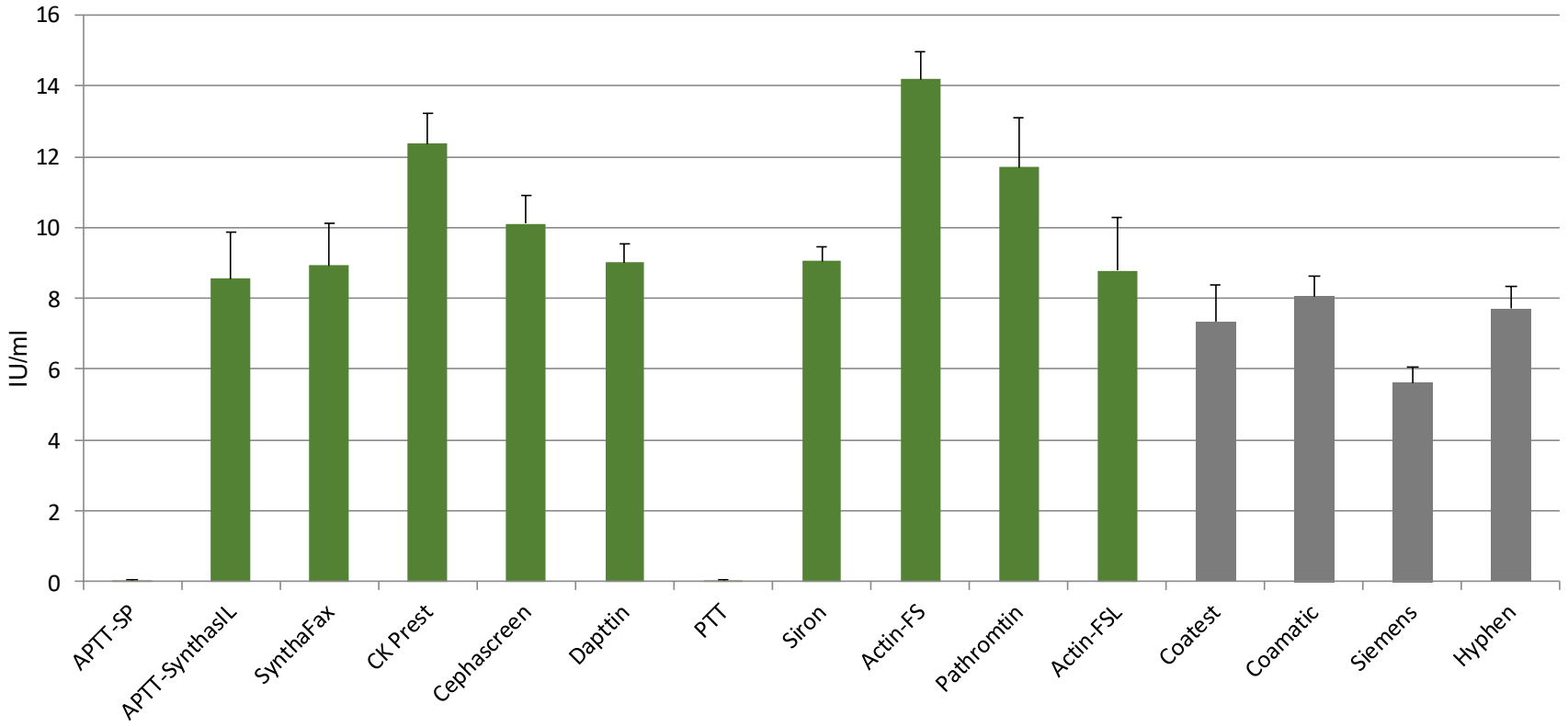
EHL FVIII against Plasma derived FVIII Concentrate IS



- With some exceptions, majority of reagents gave ratios of slopes close to 1 and within 75% interquartile range
- 10 assays gave ratios outside 0.8 – 1.25 acceptance criterion

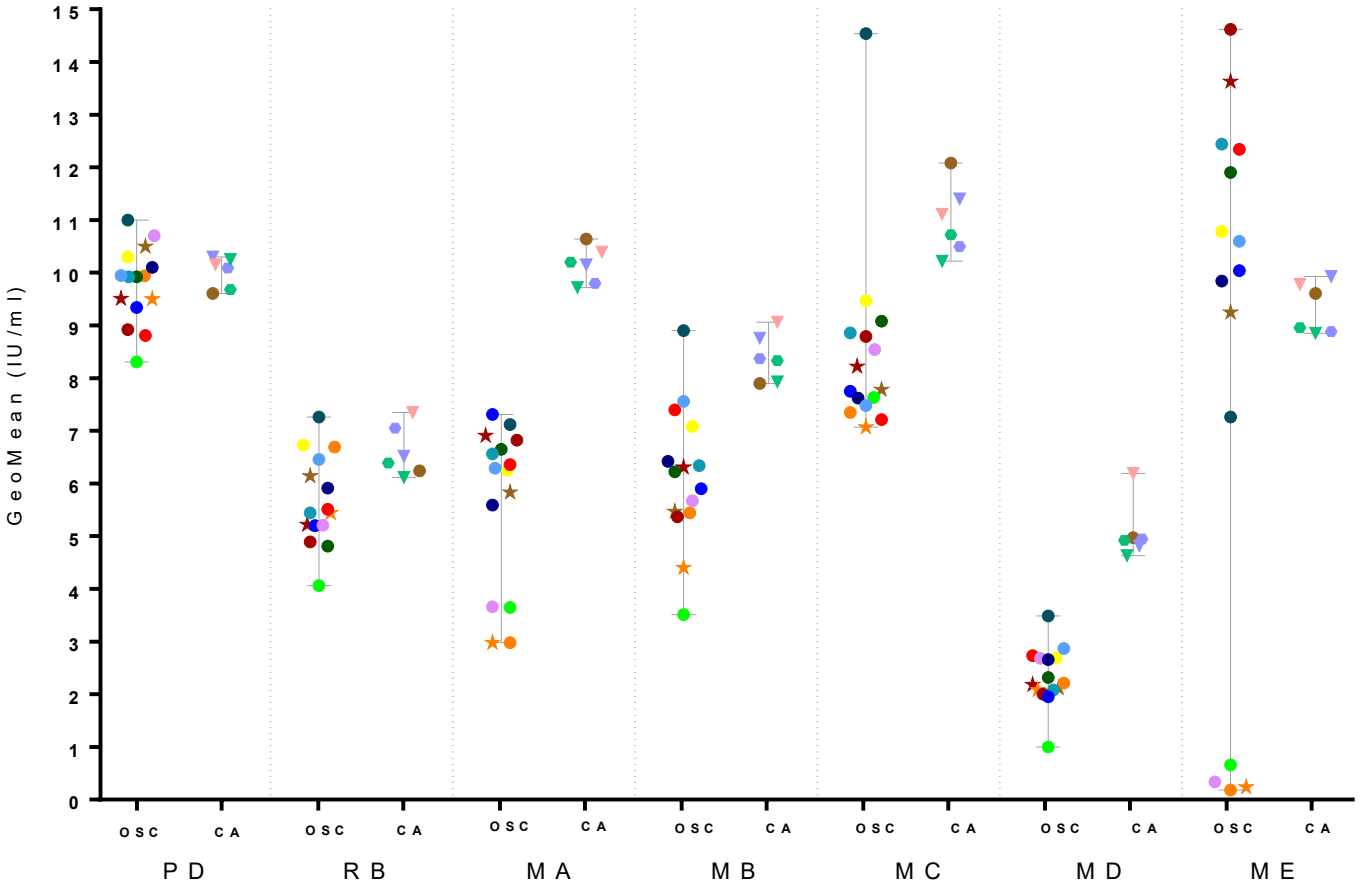
NIBSC EHL-FVIII collaborative study, 2018

Extended half-life FVIII: Potencies relative to 6th IS for FVIII Concentrate (07/352) – NIBSC 2015 in-house study



	One-Stage Clotting	One stage clotting without results from APTT-SP or PTT	Chromogenic	All assay methods	Exc APTT-SP and PTT
GM (IU/ml)	3.7	10.1	7.1	4.4	9.1
%GCV	829.3	20.0	17.7	574.3	27.2

Extended half-life FVIII products: Ranges of Geometric Mean Potencies relative to 6th IS for FVIII Plasma



OSC Reagents:

- Actin-FS
- APTT-SP
- SynthASil
- Actin-FS:Local
- APTT-SP:Local
- Actin-FSL:Local
- Actin:Local
- aPTT-S:Local
- Cephascreen:Local
- CK-Prest:Local
- Dapttin:Local
- Pathromtin-SL:Local
- PTT-Automate:Local
- Siron:Local
- SynthAFax:Local

CA Kits:

- Coatest
- Siemens
- Coatest:Local
- Siemens:Local
- Coamatic:Local
- Hyphen:Local

NIBSC EHL-FVIII collaborative study, 2018

ADYNOVI – Rurioctocog alfa pegol Licensed in US (2016); in EU (2018)

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dose

- Each vial label of ADYNOVATE states factor VIII potency in international units. This may be more or less than the nominal potency/content. One international unit corresponds to the activity of factor VIII in one milliliter of normal human plasma.
- Dosage and duration of treatment depend on the severity of factor VIII deficiency, the location and extent of the bleeding, and the patient's clinical condition. Careful monitoring of replacement therapy is necessary in cases of serious or life-threatening bleeding episodes.
- Potency assignment is determined using a one-stage clotting assay. Plasma factor VIII levels can be monitored clinically using a one-stage clotting assay.
- Calculate the dose of ADYNOVATE based on the empirical finding that one international unit of ADYNOVATE per kg body weight increases the plasma factor VIII level by 2 IU per dL of plasma. Use the following formula to estimate the expected *in vivo* peak increase in factor VIII level expressed as IU per dL (or % of normal) and the dose to achieve a desired *in vivo* peak increase in factor VIII level:

US

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADYNOVI 250 IU / 5 ml powder and solvent for solution for injection
Each vial contains nominally 250 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 50 IU/ml after reconstitution with 5 ml solvent.

ADYNOVI 500 IU / 5 ml powder and solvent for solution for injection
Each vial contains nominally 500 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 100 IU/ml after reconstitution with 5 ml solvent.

ADYNOVI 1000 IU / 5 ml powder and solvent for solution for injection
Each vial contains nominally 1000 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 200 IU/ml after reconstitution with 5 ml solvent.

ADYNOVI 2000 IU / 5 ml powder and solvent for solution for injection
Each vial contains nominally 2000 IU human coagulation factor VIII (rDNA), rurioctocog alfa pegol, corresponding to a concentration of 400 IU/ml after reconstitution with 5 ml solvent.

The potency (International Units) is determined using the chromogenic assay. The specific activity of ADYNOVI is approximately 4000-6500 IU/mg protein.

The active substance rurioctocog alfa pegol is a covalent conjugate of the protein octocog alfa* with a 20 kDa polyethylene glycol (PEG).

EU

US: Potency assignment is determined using a one-stage clotting assay
EU: The potency (International Units) is determined using the chromogenic assay

Potency labelling for EHL products

- For all EHL products, statistically valid assays against the International Standards (Concentrate), justifying potency labelling in International Unit (IU)

- Assay discrepancies exist within and between method type(s)

- Current EU licensed EHL products labelled by European Pharmacopoeia Monograph methods: chromogenic assays for FVIII, OSC for FIX

- Other EHL products in pipeline following the same route?????

- Manufacturers are managing assay discrepancy for potency labelling by establishment of in-house product specific standard using specific reagent/kit traceable to the IS

Acknowledgements

- NIBSC
  - Anthony Hubbard
  - Peter Rigsby
  - Thomas Dougall
  - Helen Wilmot
  - John Hogwood
  - Sarah Daniels
  - Stella Williams

- UKNEQAS/Royal Hallamshire Hospital
  - Steve Kitchen

NIBSC
Confidence in Biological Medicines

Thank you for your attention

Questions???

Medicines and Healthcare Products Regulatory Agency