U.S. FOOD & DRUG ADMINISTRATION

Coagulation Factor Products: Potency Determination and Related Complications

Mikhail V. Ovanesov, PhD
Research Biologist

Hemostasis Branch
Division of Plasma Protein Therapeutics
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

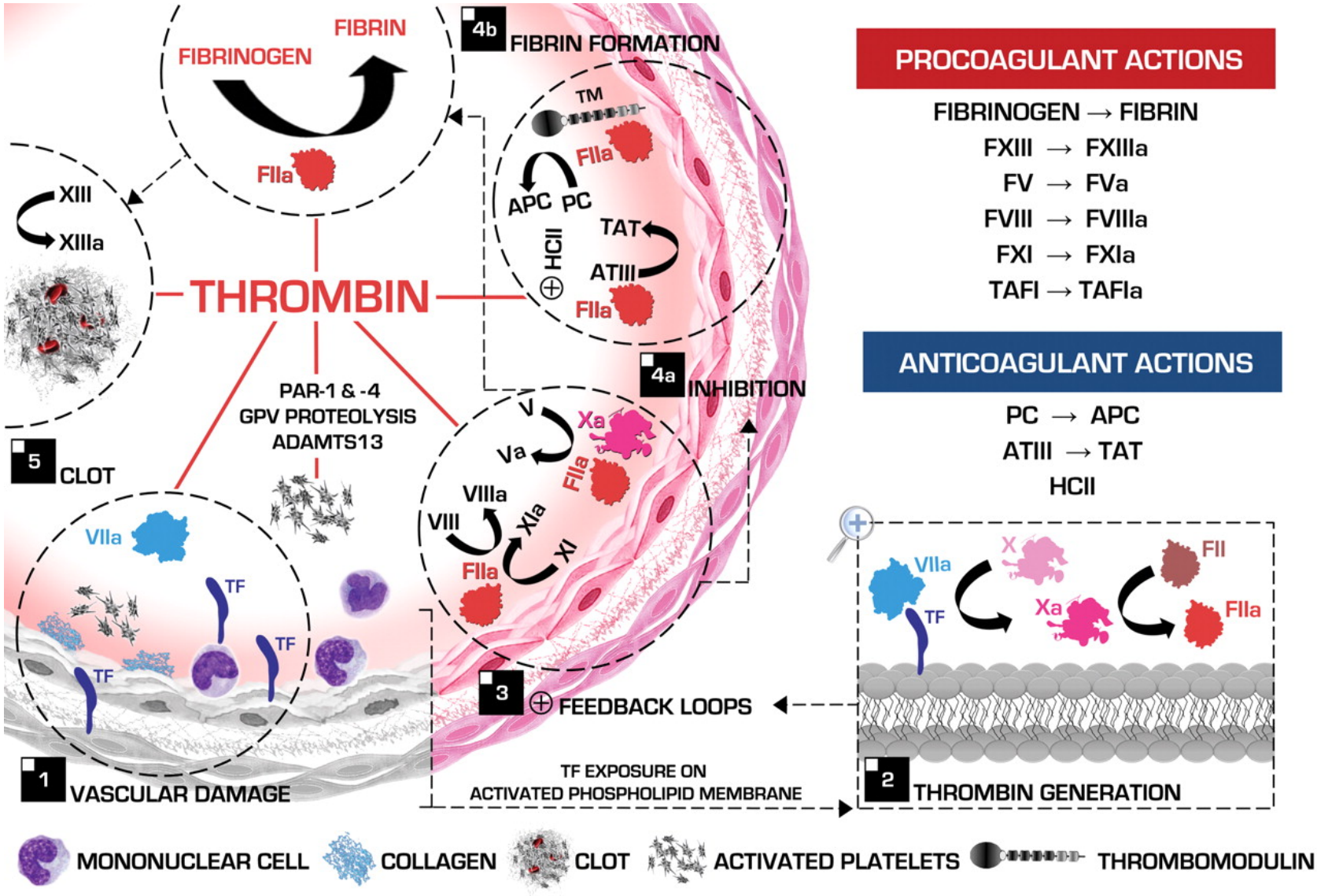
CASSS Bioassays: Regulators: What's On Your Mind?
April 17, 2018
Silver Spring, MD

Disclaimer

- My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.

Background:
International Reference Standards for coagulation factor activity

Haemostasis and coagulation



PROCOAGULANT ACTIONS

FIBRINOGEN → FIBRIN
FXIII → FXIIIa
FV → FVa
FVIII → FVIIIa
FXI → FXIa
TAFI → TAFIa

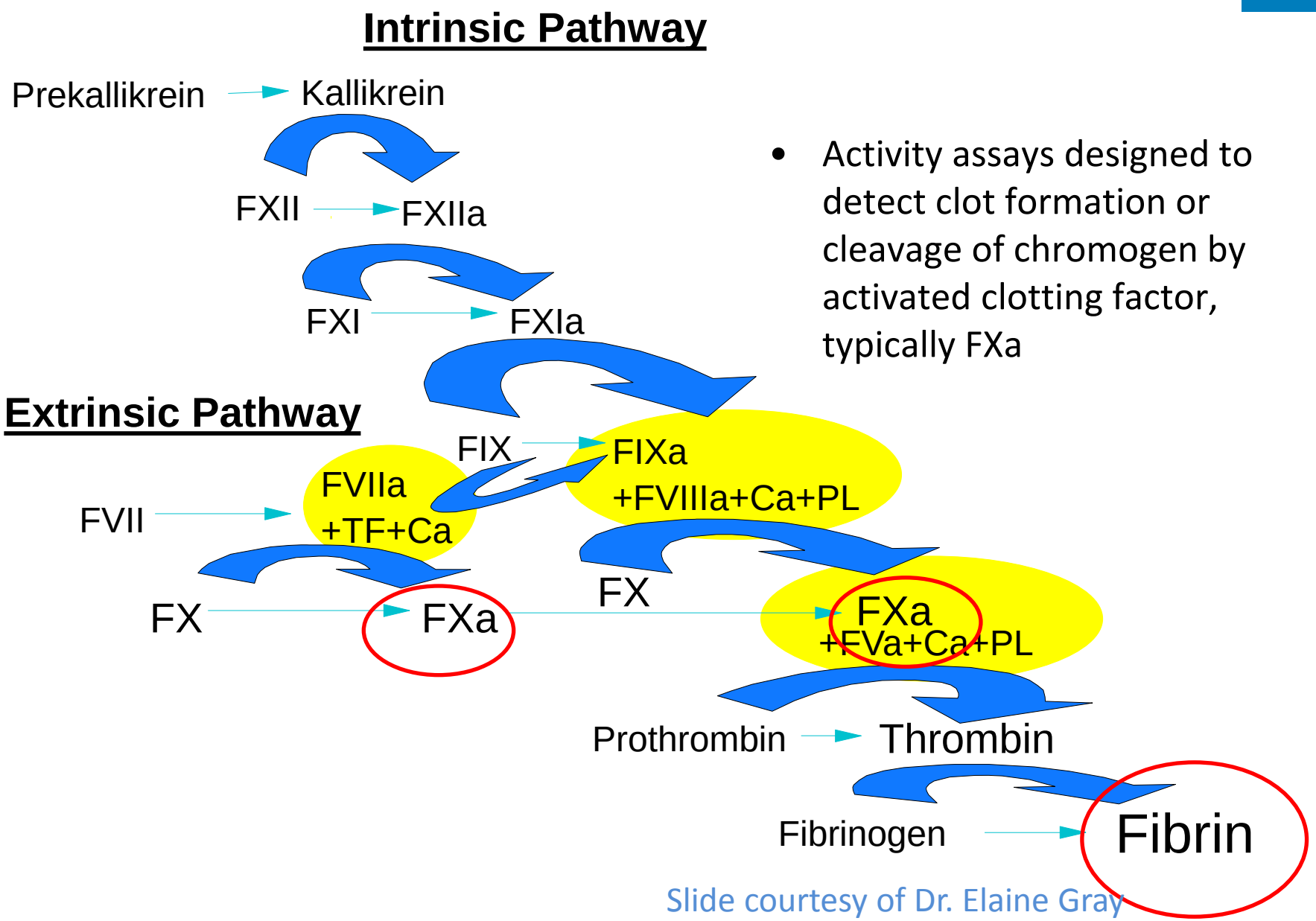
ANTICOAGULANT ACTIONS

PC → APC
ATIII → TAT
HCII

Borissoff et al. Cardiovascular Research (2009) 82, 392–403

Slide courtesy of Dr. Elaine Gray

How do we measure activity of coagulation factors?



- Activity assays designed to detect clot formation or cleavage of chromogen by activated clotting factor, typically FXa

Slide courtesy of Dr. Elaine Gray

Advantages of International Unit (IU)

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

1 IU/ml = 100% normal

- While activity of local normal pool can change and the normal pools 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

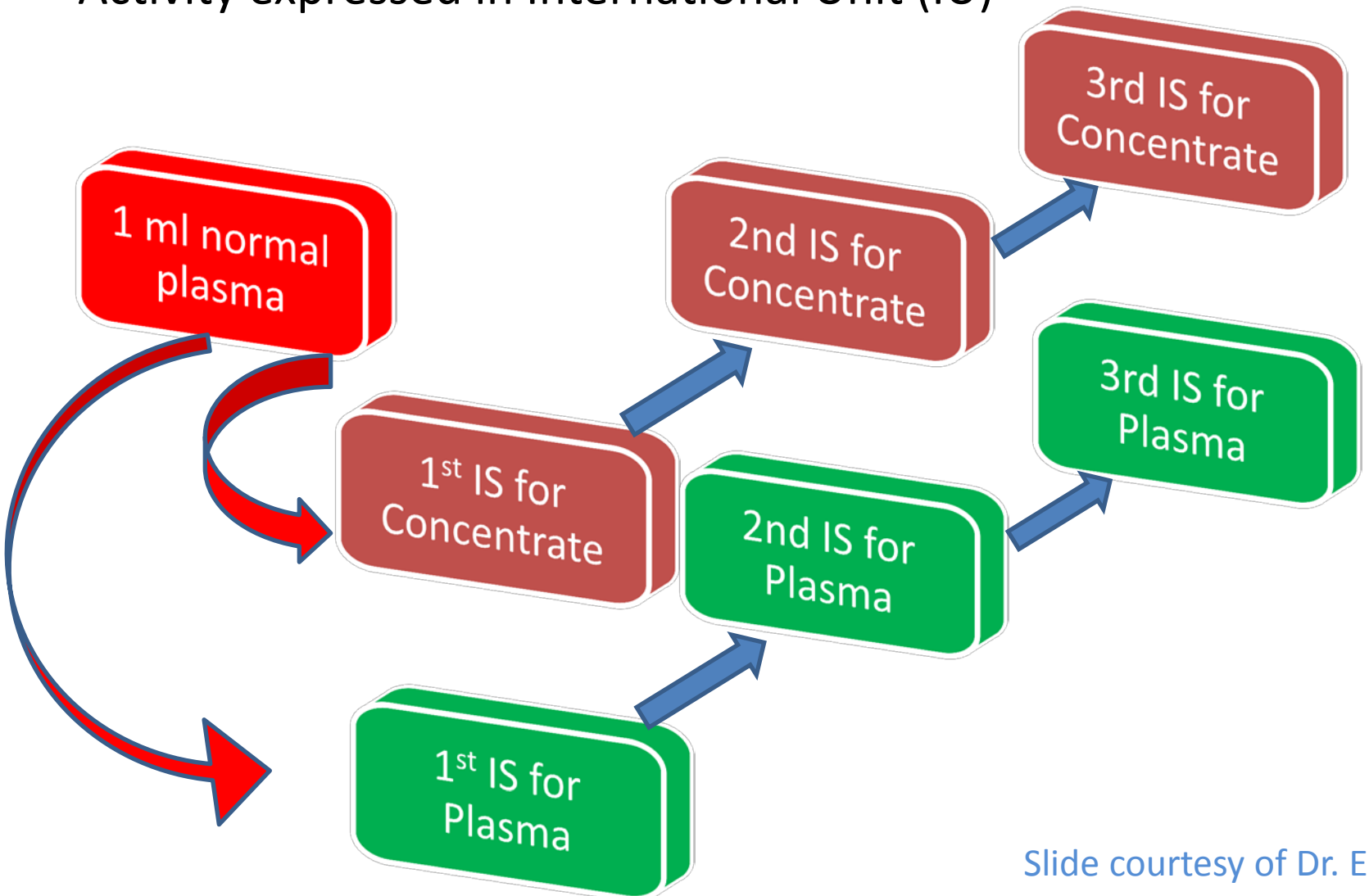
- Labelled potency of products in IU are linked to the Plasma IU

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

Slide courtesy of Dr. Elaine Gray

Unit of activity for therapeutic clotting factors

- Based on biological activity of the coagulation factor
- Activity expressed in International Unit (IU)



Slide courtesy of Dr. Elaine Gray

IUs & the rationale for prophylaxis of bleeding in hemophilia

Haemophilia

Haemophilia (2011), **17**, 849–853 DOI: 10.1111/j.1365-2516.2011.02539.x

ORIGINAL ARTICLE *Clinical haemophilia*

Clinical severity of haemophilia A: does the classification of the 1950s still stand?

I. E. M. DEN UIJL,*† E. P. MAUSER BUNSCHOTEN,* G. ROOSENDAAL,* R. E. G. SCHUTGENS,* D. H. BIESMA,† D. E. GROBBEE† and K. FISCHER*†

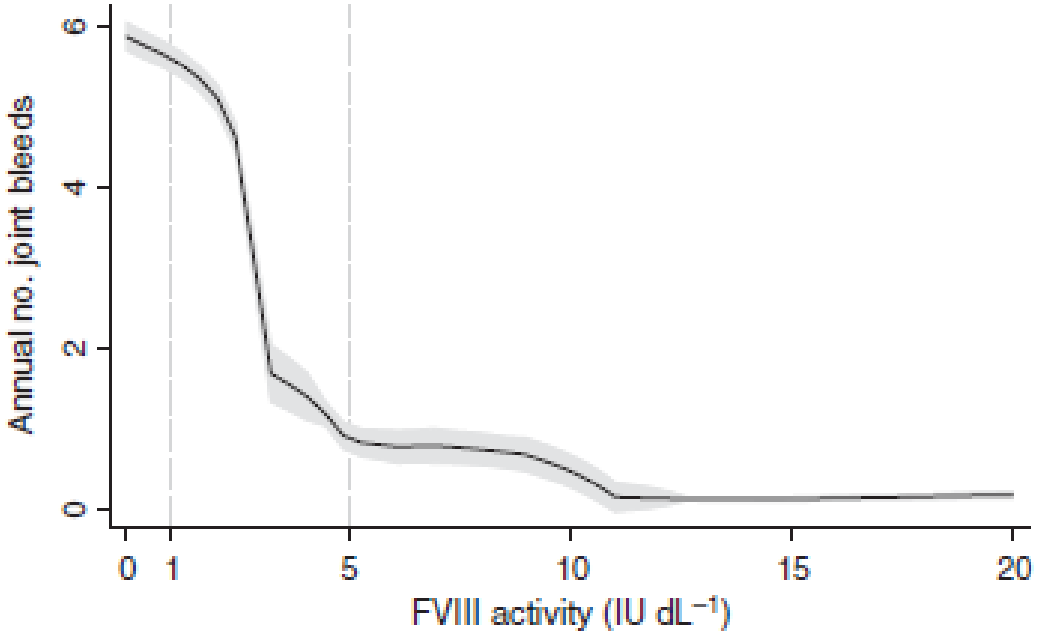


Fig. 2. Annual number of joint bleeds according to FVIII activity. Black lines are medians, shaded areas interquartile ranges.

Presentation outline

1. **Licensed coagulation factor VIII & IX products**
2. Potency assay discrepancy for early recombinant products
3. Choosing the right potency assay for new products

Office of Tissues and Advanced Therapies (OTAT)
Division of Plasma Protein Therapeutics (DPPT)
Hemostasis Branch (HB)

Products regulated by HB: **about 12% of all BLAs in CBER**

- Coagulation Factors
  - **Factors VIII and IX (Human plasma-derived & Recombinant)**
  - **Factor VIII/von Willebrand Factor Complex**
  - **Factor IX and Prothrombin Complex Concentrates**
  - Fibrinogen Concentrate
  - Factor XIII
  - Von Willebrand Factor (Recombinant)
  - Anti-Inhibitor Coagulant Complex (e.g., FEIBA)
  - Recombinant activated Factor VII
- Plasma inhibitors
  - Protein C
  - Antithrombin III (Human plasma-derived & Recombinant)
- Hemostatic Agents
  - Thrombin (Bovine, Human & Recombinant)
  - Fibrin Sealant and Patches
  - CryoSeal FS System

Regulatory Question: potency of FVIII/vWF and FIX products regulated by HB

- **Factor VIII (Anti-Hemophilic Factor)-containing products:**
  1. Advate® **(Shire)**
  2. Adynovate® **(Shire)**
  3. Afstyla® **(CSL Behring)**
  4. *Alphanate®* **(Grifols)**
  5. Eloctate® **(Bioverativ)**
  6. Koate® DVI **(Kedrion)**
  7. Kogenate® FS **(Bayer)**
  8. Kovaltry® **(Bayer)**
  9. Helixate® FS **(CSL Behring)**
  10. Hemofil® M **(Shire)**
  11. *Humate-P®* **(CSL Behring)**
  12. Monoclate-P® **(CSL Behring)**
  13. NovoEight® **(Novo Nordisk)**
  14. Obizur **(Shire)**
  15. Recombinate® **(Shire)**
  16. *Wilate®* **(Octapharma) ***
  17. Xyntha® **(Pfizer)**

  \+ several in the pipeline[1]
- **Factor IX-containing products:**
  1. *Alphanine® SD* **(Grifols)**
  2. Alprolix® **(Bioverativ)**
  3. *Bebulin® VH* **(Shire)**
  4. BeneFix® **(Pfizer)**
  5. Idelvion® **(CSL Behring)**
  6. Ixinity® **(Aptevo)**
  7. *Kcentra®* **(CSL Behring) ***
  8. Mononine® **(CSL Behring)**
  9. *Profilnine® SD* **(Grifols)**
  10. Rebinyn® **(Novo Nordisk)**
  11. Rixubis™ **(Shire)**

*) not FDA licensed for hemophilia treatment

Reference: 1. www.ema.europa.eu “EMA/135928/2014”

Regulatory Question: potency of FVIII/vWF and FIX products regulated by HB

11 new products approved by FDA since 2013

- **Factor VIII (Anti-Hemophilic Factor)-containing products:**
  1. Advate® **(Shire)**
  2. Adynovate® **(Shire)** PEGylated
  3. Afstyla® **(CSL Behring)** single-chain
  4. *Alphanate®* **(Grifols)**
  5. Eloctate® **(Bioverativ)** Fc-fusion
  6. Koate® DVI **(Kedrion)**
  7. Kogenate® FS **(Bayer)**
  8. Kovaltry® **(Bayer)**
  9. Helixate® FS **(CSL Behring)**
  10. Hemofil® M **(Shire)**
  11. *Humate-P®* **(CSL Behring)**
  12. Monoclate-P® **(CSL Behring)**
  13. NovoEight® **(Novo Nordisk)**
  14. Obizur **(Shire)** porcine
  15. Recombinate® **(Shire)**
  16. *Wilate®* **(Octapharma)** *
  17. Xyntha® **(Pfizer)**

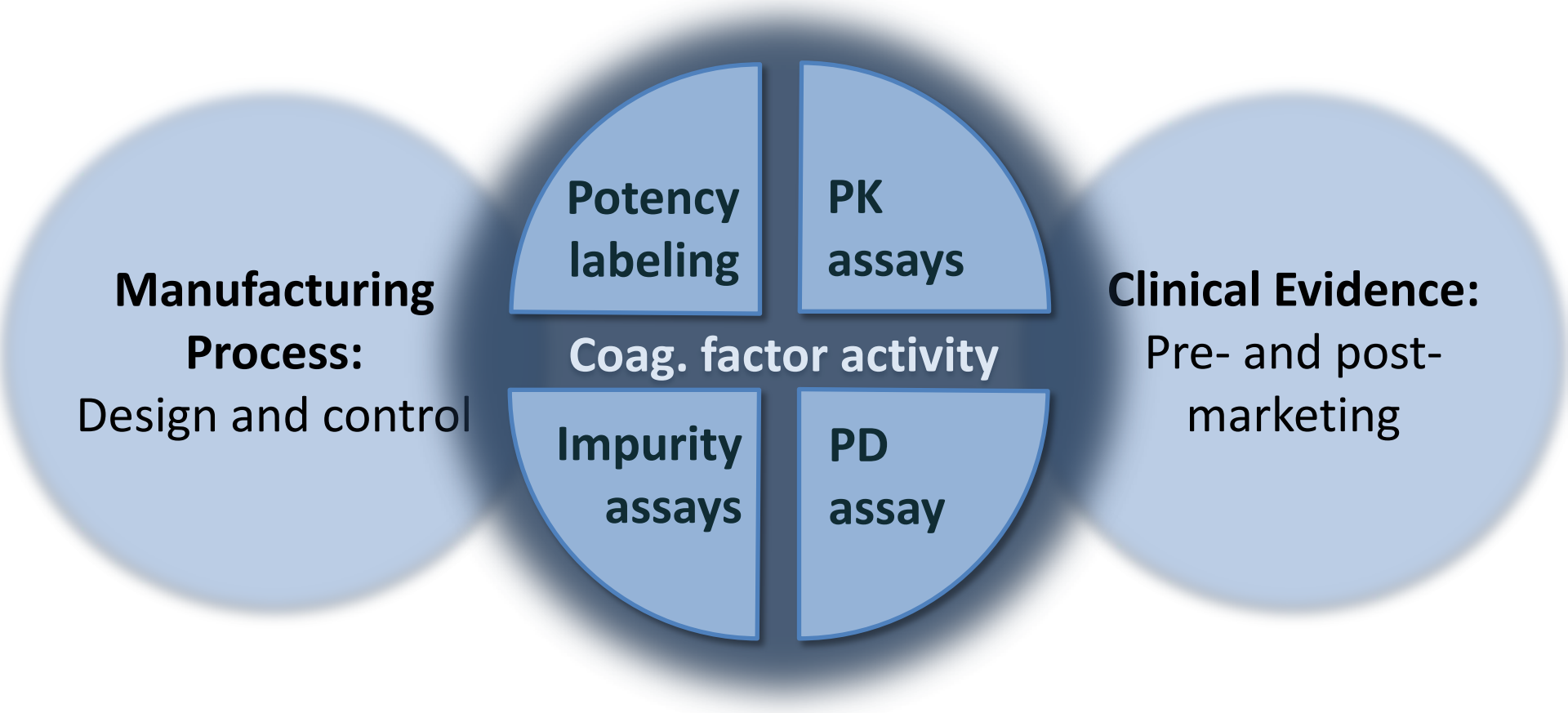
  + several in the pipeline[1]

- **Factor IX-containing products:**
  1. *Alphanine® SD* **(Grifols)**
  2. Alprolix® **(Bioverativ)** Fc-fusion
  3. *Bebulin® VH* **(Shire)**
  4. BeneFix® **(Pfizer)**
  5. Idelvion® **(CSL Behring)** albumin-fusion
  6. Ixinity® **(Aptevo)**
  7. *Kcentra®* **(CSL Behring)** *
  8. Mononine® **(CSL Behring)**
  9. *Profilnine® SD* **(Grifols)**
  10. Rebinyn® **(Novo Nordisk)** PEGylated
  11. Rixubis™ **(Shire)**

  *) not FDA licensed for hemophilia treatment

Reference: 1. www.ema.europa.eu “EMA/135928/2014”

Why coagulation factor activity assays are important



Why coagulation factor activity assays are important for regulation and use of factor VIII and IX concentrates

- **Potency**

DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only. (2)

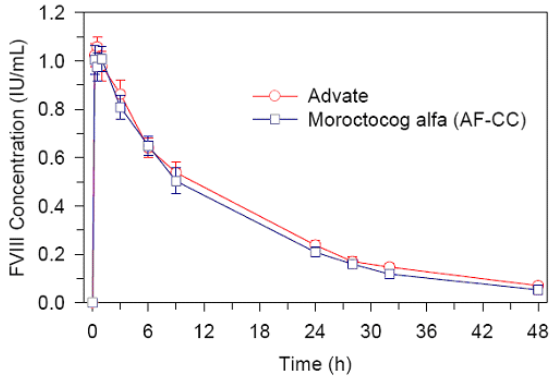
- Each vial of ADVATE contains the labeled amount of recombinant Factor VIII in International Units (IU). (2)
- The required dosage is determined using the following formulas:

  Desired increment in Factor VIII concentration (IU/dL or % of normal)=[Total Dose (IU)/body weight (kg) x 2 [IU/dL]/[IU/kg]

  OR

  Required Dose (IU) = body weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL). (2)

- **Pharmacokinetics**



- **Pharmacodynamics**

Hemophilia B is a bleeding disorder characterized by a deficiency of functional coagulation Factor IX (FIX), which leads to a prolonged clotting time in the activated partial thromboplastin time (aPTT) assay, an established *in vitro* test for the biological activity of Factor IX. Treatment with ALPROLIX™ shortens the aPTT over the effective dosing period.

References: www.fda.gov Prescribing Information (PI) for ADVATE®, XYNTHA® and ALPROLIX ®

Discrepancies in coagulation factor activity assignment for new coagulation products

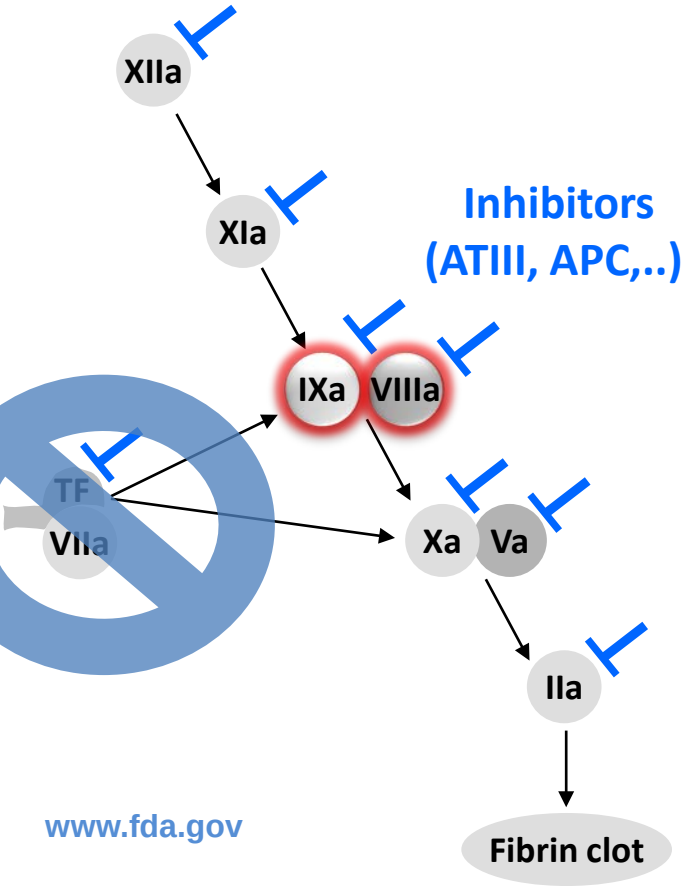
- In general, coagulation factor products are well characterized and International Standards of their biological activity are available
- However, new genetically or chemically modified coagulation factors can demonstrate discrepancies in potency assignment and post-infusion monitoring
- Similar issues were reported for some gene therapies

Presentation outline

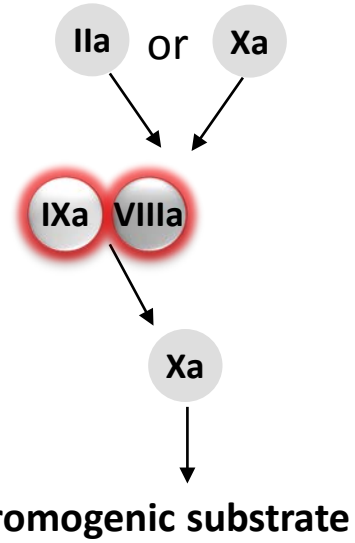
1. Licensed coagulation factor VIII & IX products
2. **Potency assay discrepancy for early recombinant products**
3. Choosing the right potency assay for new products

Clotting and Chromogenic assays for factor activity

One stage clotting [OC] in plasma (aPTT, 1953)

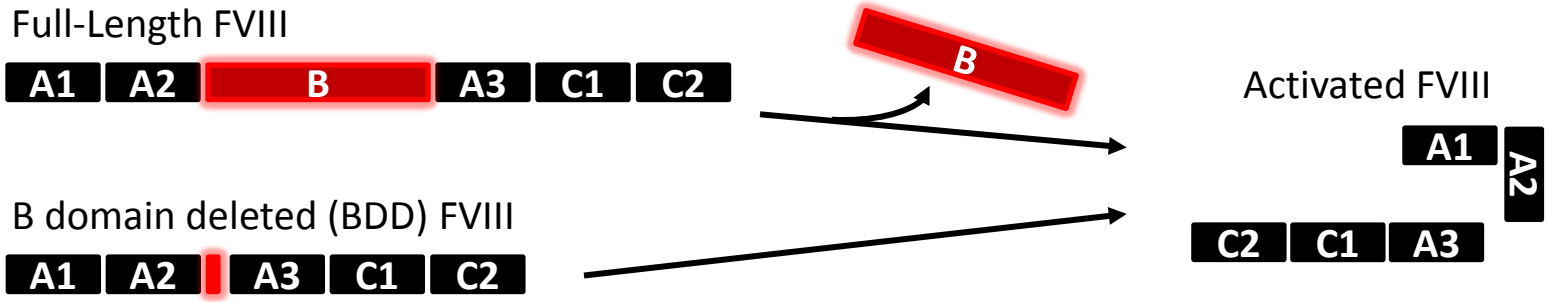


Chromogenic substrate [CS] in purified protein mixture (1980s)#



#) Chromogenic substrate assay is based on a two-stage assay developed in 1956

Example: Clotting vs. Chromogenic discrepancy for BDD-FVIII



- Chromogenic potency is ~50% higher than clotting potency [1] but the chromogenic assay was used for labeling of the product licensed in 2000
- Soon, reports of the lack of effect were published [2,3].
- In 2003, product standard was changed, increasing the amount of protein by 20% [4]. Uncertain relevance to the lack of effect.

References:
1. www.fda.gov 1998 Blood Products Advisory Committee 61st Meeting
2. Gruppo et al. Haemophilia (2003), 9, 251–260
3. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2003/14229a-eng.php
4. www.ema.europa.eu May 27 2003. CPMP/2337/03

Example: Clotting vs. Chromogenic discrepancy for BDD-FVIII

- "Lack of effect" in European and Canadian product information [1,2]:

  "Reports of lack of effect, mainly in prophylaxis patients, have been received in the clinical trials and in the post-marketing setting … The reported lack of effect …. has been described as bleeding into target joints, bleeding into new joints or a subjective feeling by the patient of new onset bleeding."

- In 2008, diverged unitage: **1 IU** in North America is **1.38 IU** in Europe

  "Due to the difference in methods used to assign product potency .., 1 IU of the .. product (one-stage assay calibrated) is approximately equivalent to 1.38 IU of the .. product (chromogenic assay calibrated)" [2]

References:
1. www.blood.ca 2009 "Xyntha anouncement letter"
2. www.ema.europa.eu 2009 "ReFacto AF : EPAR - Product Information"

Presentation outline

1. Licensed coagulation factor VIII & IX products
2. Potency assay discrepancy for early recombinant products
3. **Choosing the right potency assay for new products**

Strategies for choosing the right potency assay

"Product Z should be labeled with Assay Y (and not Assay X) because…"

1. Considerations about bioassay validity (vs. WHO Standard)
2. To "maintain"
   a) globally harmonized assay
   b) International Unit
   c) standard of treatment
3. Considerations of patient safety
4. Theoretical and clinical considerations of assay relevance
5. Clinical validation

Consideration #1 of 5: Bioassay validity (vs. WHO Standard)

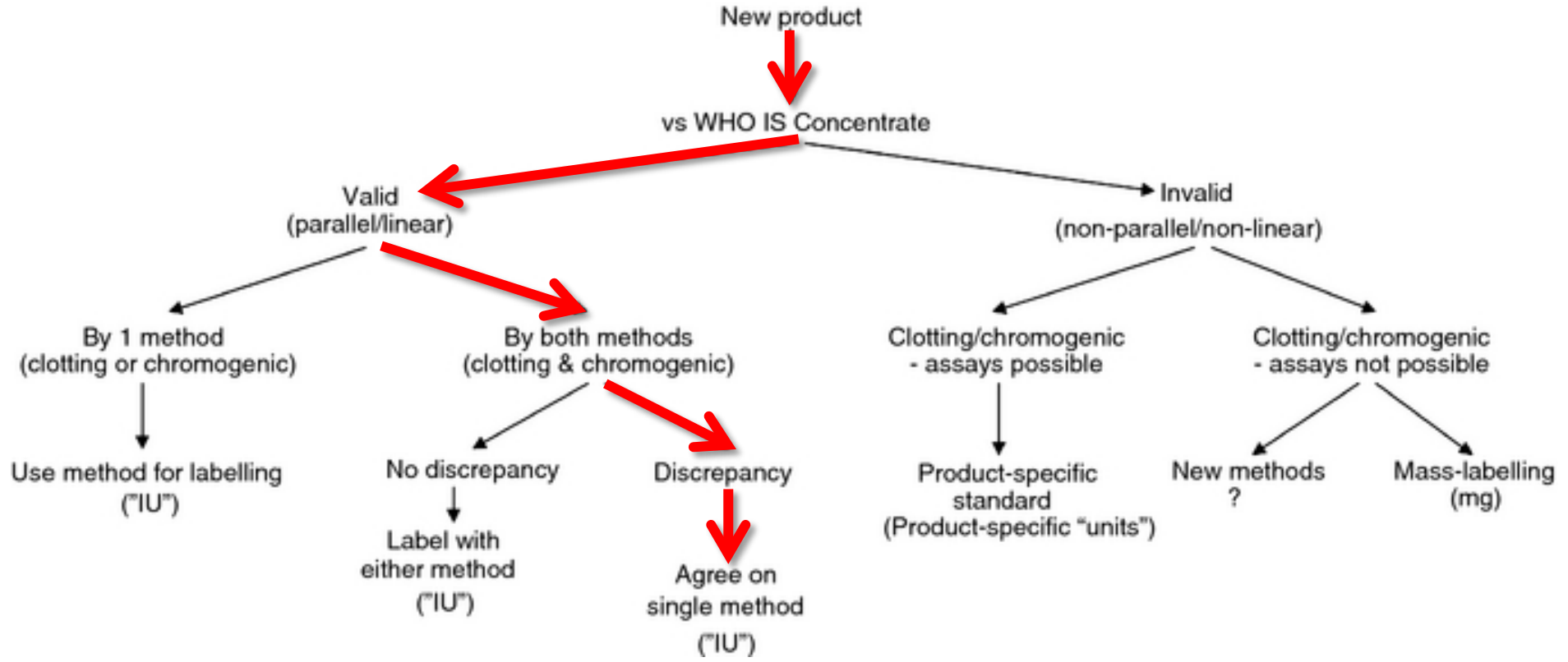
Journal of Thrombosis and Haemostasis, 11: 988–989 (2013) DOI: 10.1111/jth.12167

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



The decision tree misses every new product

Consideration #2 of 5: Maintain…
a) globally harmonized assay

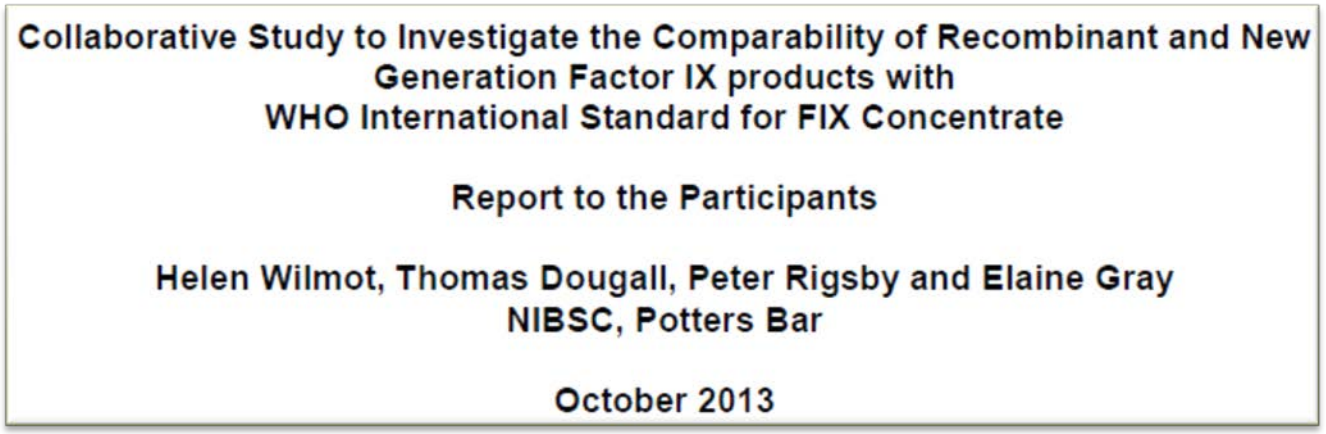
- European Pharmacopeia potency assays
  - Chromogenic assay for Factor VIII
  - Clotting assay for Factor IX
- US FDA recommends evidence-based and product-specific approach:
  - Chromogenic: 4 FVIII products
  - Chromogenic using clotting units: 1 FVIII product
  - Two-stage clotting: 1 FVIII product
  - One stage clotting: 7 FVIII and 8 FIX products

→ Harmonization of regulatory requirements is lacking

Consideration #2 of 5: Maintain…
a) globally harmonized assay

Reagent harmonization is lacking too: ~60 clotting reagents

"*Factor IX potency* ***results can be affected by the type of aPTT reagent and reference standard*** *used in the assay; differences of up to 40% have been observed.*"[1]


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

Helen Wilmot, Thomas Dougall, Peter Rigsby and Elaine Gray
NIBSC, Potters Bar

October 2013

50 fold!

Reference: 1. www.fda.gov 2013 Rixubis Prescribing Information

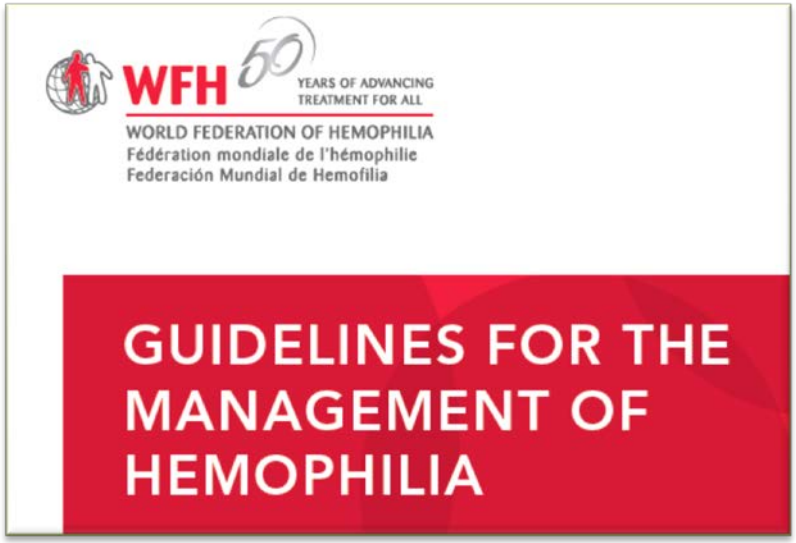
Consideration #2 of 5: Maintain…
b) International Unit

- Assay disagreement simply reflects structural and functional differences vs. international plasma-derived standards [1]
- A non-IU product-specific potency standard may be established for potency labeling. Single example: porcine FVIII [2]
- Non-IU labeling may be disruptive for clinical practice

References: 1. Farrugia A. Potency assessment of the new generation of coagulation factor concentrates--time for a new paradigm? Thromb Haemost. 2003 Dec;90(6):968-70
2. Prescribing Information for OBIZUR [Antihemophilic Factor (Recombinant), Porcine Sequence] (October, 2014) Sequence] (October, 2014)

Consideration #2 of 5: Maintain…
c) standard of treatment

- Standard dosing recommendations harmonize treatment and potentially may help patients
- If possible, labeled doses in a clinical trial should agree with the standard of treatment



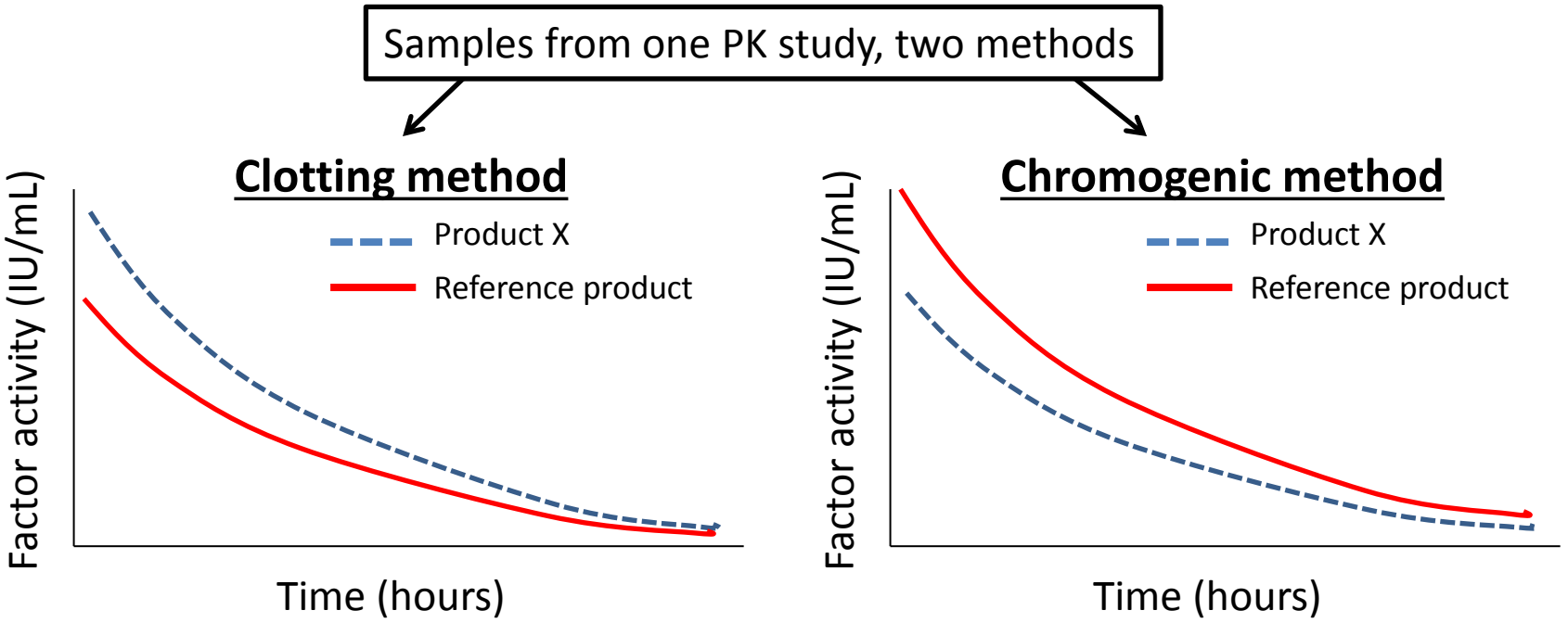
Recommendations can be broad enough to accommodate assay discrepancy

The *WFH guidelines* for Hemophilia A prophylactic management (2012):

- Malmö protocol: 25-40 IU/kg 3 times a week
- Utrecht protocol: 15-30 IU/kg 3 times a week

Consideration #3 of 5:
Focus on patient safety

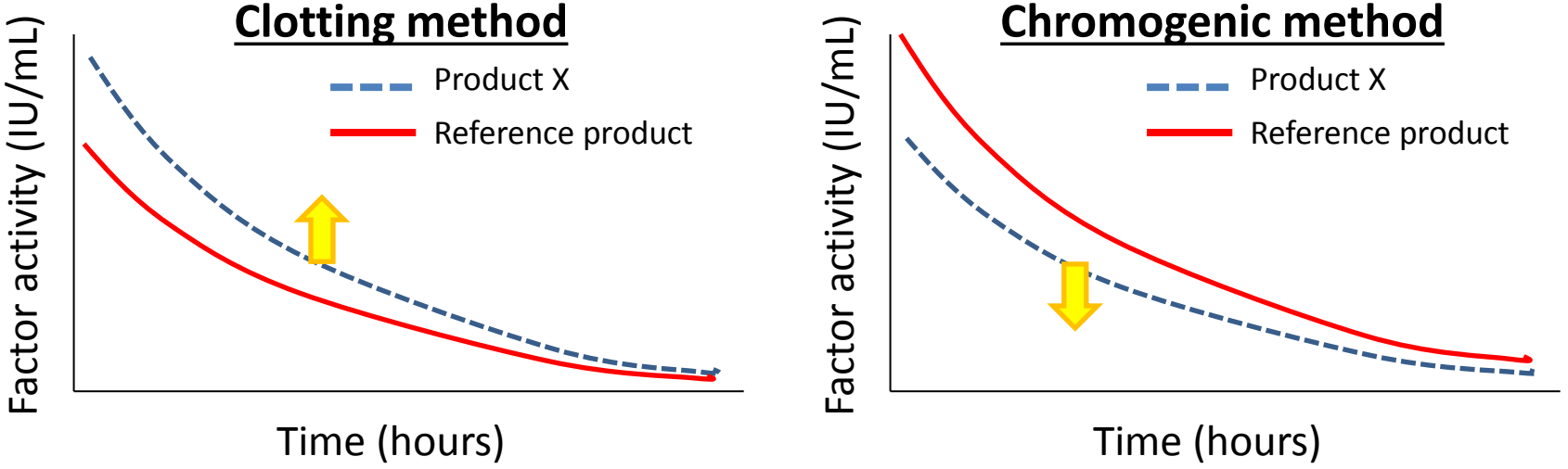
- Under-dosing may result in the lack of effect (potentially fatal)
- Over-dosing carries low risks (for FVIII) or theoretical thrombotic risk (FIX)



Consideration #3 of 5:
Focus on patient safety

- Under-dosing may result in the lack of effect (potentially fatal)
- Over-dosing carries low risks (for FVIII) or theoretical thrombotic risk (FIX)

Product X: Are we overdosing (OK) or underdosing (not OK)?



Consideration #4 of 5:
a) *In vitro* diagnostic relevance of potency assays

Clotting vs. Chromogenic factor activity IVD assays:

1. In rare cases of confirmed mild hemophilia, only chromogenic assay detects deficiency while clotting assay reports normal value. An opposite also happens.
2. Analytical characteristics are also comparable: both methods are automated, robust and accurate
3. Use by clinical laboratories:
   - Clotting assay is routinely used by all clinical laboratories
   - Chromogenic is recommended by the World Federation for Haemophilia & the National Hemophilia Foundation

Consideration #4 of 5:
b) theoretical relevance of the potency assays

- *"Assay A reflects the **true activity** of Product Z because Assay B is not physiological…"*
- Physiological relevance of either assay is questionable:

1. Clotting assay

   [+] hemostatic end-point (clotting time) in a relevant matrix (plasma)

   [-] activated by artificial pathway (contact) with artificial lipids

2. Chromogenic assay

   [+] clear mechanism of action in a system of purified components

   [-] lacks complexity of plasma matrix

Consideration #5 of 5: Clinical validation

5.3 Monitoring Laboratory Tests

- Monitor plasma Factor VIII activity in patients receiving AFSTYLA using either the chromogenic assay or the one-stage clotting assay, which is routinely used in US clinical laboratories. The chromogenic assay result most accurately reflects the clinical hemostatic potential of AFSTYLA and is preferred. The one-stage clotting assay result underestimates the Factor VIII activity level compared to the chromogenic assay result by approximately one-half. If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level. Incorrect interpretation of the Factor VIII activity obtained by the one-stage clotting assay could lead to unnecessary additional dosing, higher chronic dosing, or investigations for an inhibitor.

- **Clinical studies** demonstrated the safe and effective dosage by Chromogenic Assay
- **Clinical Lab Field study:** Clotting assays give 1.8-2.2 fold lower value vs. chromogenic assays
- **Therefore,** clotting assay underestimates vs. the clinical trial's/potency assay

Reference: Package insert of AFSTYLA

Conclusions

1. The analytical root cause for the potency assay discrepancy: **new factor products are labeled in IU but they are not "like" WHO IS**
2. Labeling decision is made during the review of the BLA
3. We recommend using both clotting and chromogenic factor activity methods at all stages of product development and undertaking a clinical laboratory field study
4. Clinical trials are indispensable but limited in scope, meaning that the risk/benefit assessment may become important

Acknowledgements

OTAT:

Tim Lee

Dov Golding

Bindu George

Wilson Bryan

NIBSC (UK):

Elaine Gray

OBRR alumni

Nisha Jain

Mark Weinstein

Nancy Kirschbaum

Ginette Michaud

Jay Epstein