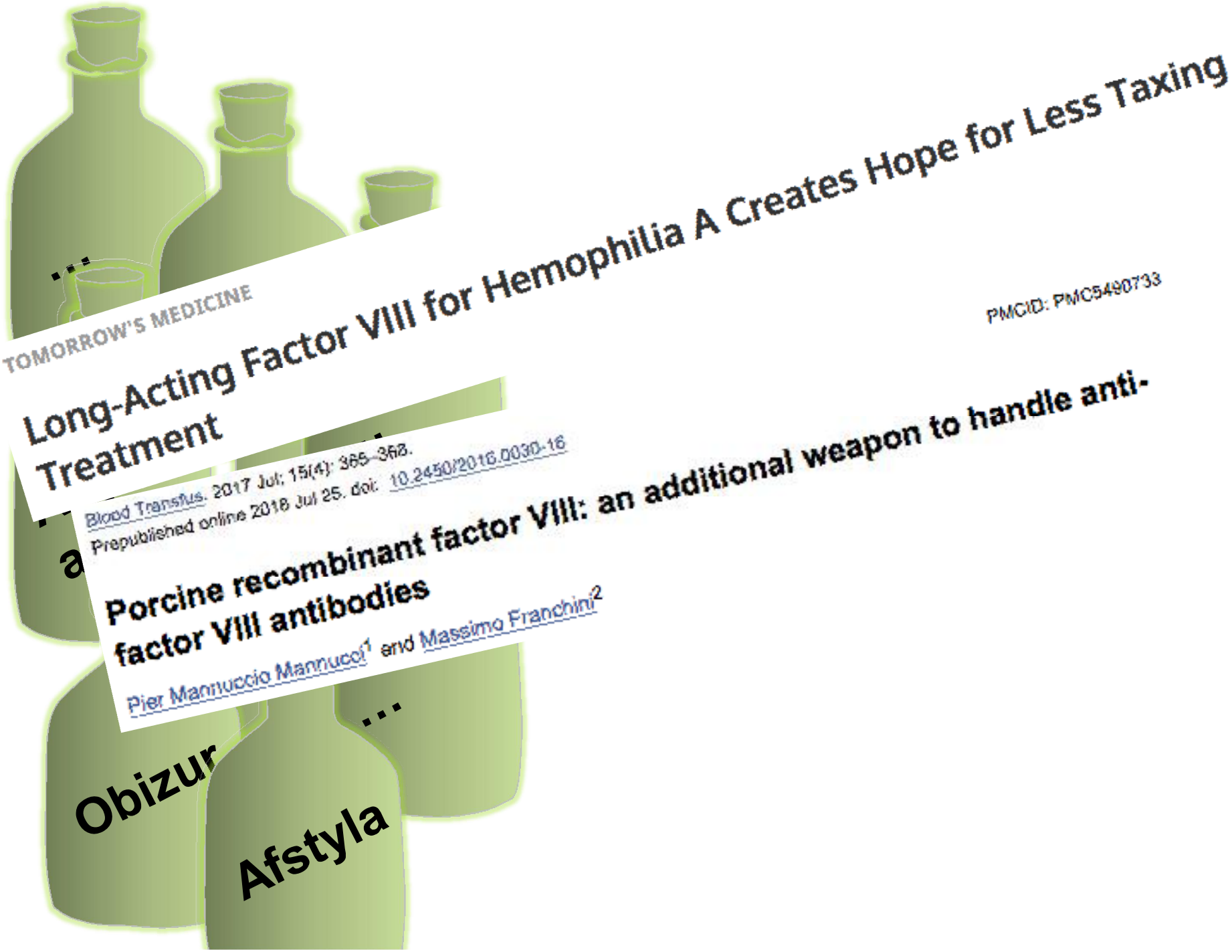
Le dosage du Facteur VIII: encore des défis?

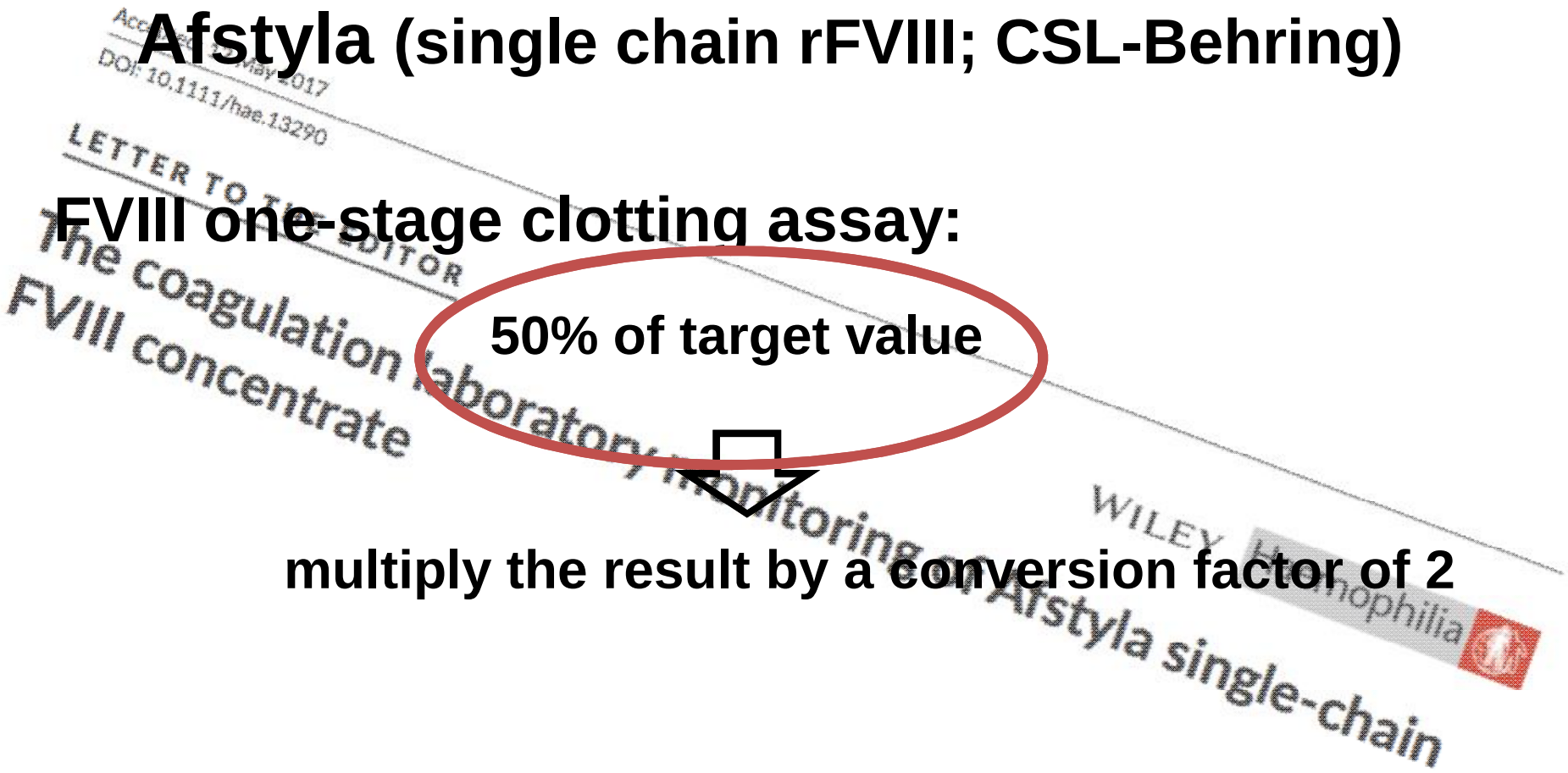
Marc Jacquemin

University of Leuven

Corata 2017


...
TOMORROW'S MEDICINE
Long-Acting Factor VIII for Hemophilia A Creates Hope for Less Taxing Treatment
PMCID: PMC5490733
Blood Transfus. 2017 Jul; 15(4): 365–368.
Prepublished online 2018 Jul 25. doi: 10.2450/2016.0030-16
Porcine recombinant factor VIII: an additional weapon to handle anti-factor VIII antibodies
Pier Mannuccio Mannucci[1] and Massimo Franchini[2]
...
Obizur
Afstyla

Afstyla (single chain rFVIII; CSL-Behring)



FVIII one-stage clotting assay:

50% of target value

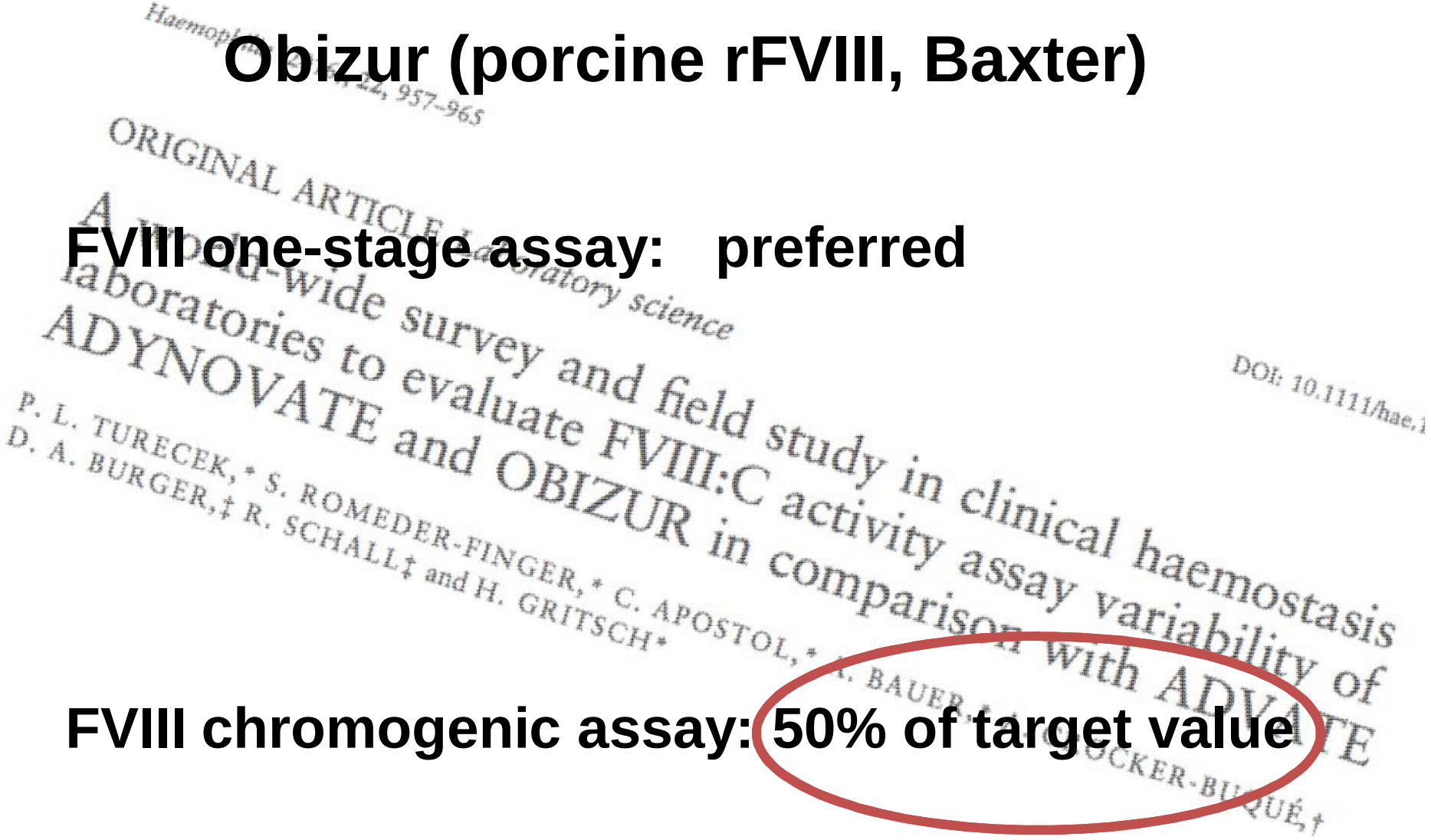
multiply the result by a conversion factor of 2

FVIII chromogenic substrate assay: preferred

Obizur (porcine rFVIII, Baxter)

FVIII one-stage assay: preferred

FVIII chromogenic assay: 50% of target value



Haemophilia (2014), 20, 593–600

ORIGINAL ARTICLE *Laboratory science*

Evaluation of the activated partial thromboplastin time assay for clinical monitoring of PEGylated recombinant factor VIII (BAY 94-9027) for haemophilia A

J-M. GU,* P. RAMSEY,* V. EVANS,* L. TANG,† H. APELER,† L. LEONG,* J. E. MURPHY,† V. LAUX* and T. MYLES*

**Hematology Research; and †Biological Research, US Innovation Center, Bayer HealthCare Pharmaceuticals, San Francisco, CA, USA*

DOI: 10.111

Bay 94-9027 (Peggylated rFVIII, Bayer)

FVIII one-stage assay:

STA^{R}-Cephascreen (Stago) can be used

Actin FSL (Siemens) can be used

APTT-SP (Werfen) 10% of target value

STA^{R}-PTT Automate (Stago) 10% of target value

FVIII chromogenic assay: preferred

Gu et al. Haemophilia 2014; 20: 593

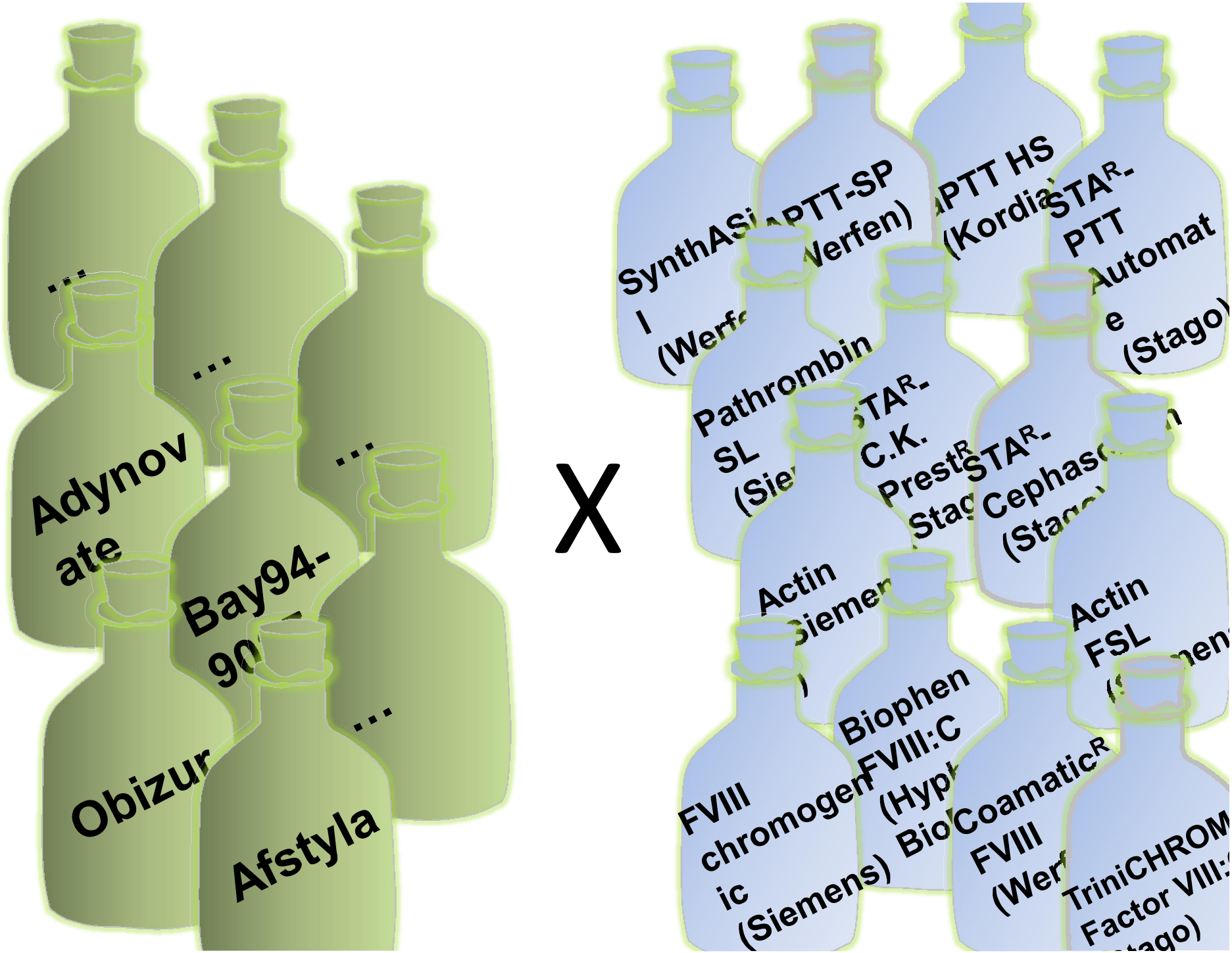
important underestimation of FVIII activity

unnecessary

additional dosing

inhibitor investigation

FVIII assays in Belgium	n° of labs
SynthASil (Werfen)	23
APTT-SP (Werfen)	2
aPTT HS (Kordia)	?
STA^{R}-PTT Automate (Stago)	3
Pathrombin SL (Siemens)	1
STA^{R}-C.K. Prest^{R} (Stago)	4
STA^{R}-Cephascreen^{R} (Stago)	6
Actin (Siemens)	3
Actin FS (Siemens)	13
Actin FSL (Siemens)	1
FVIII chromogenic (Siemens)	1
Biophen FVIII:C (Hyphen BioMed)	4
Coamatic^{R} FVIII (Werfen)	3
TriniCHROM Factor VIII:C (Stago)	3


...
...
...
Adynov
ate
Bay94-
Obizur
...
Afstyla
X
SynthASi
PTT-SP
(Werfen)
PTT HS
(Kordia)
STA®-
PTT
Automat
e
(Stago)
Pathrombin
SL
C.K.
Prest®
Stag
STA®-
Cephas
Actin
Actin
FSL
FVIII
chromogen
ic
(Siemens)
Biophen
FVIII:C
Coamatic®
FVIII
TriniCHROM
Factor VIII:

Communication with the clinicians

Communication with the clinicians

The grapevine

C.K.-Prest is the best

Communication with the clinicians

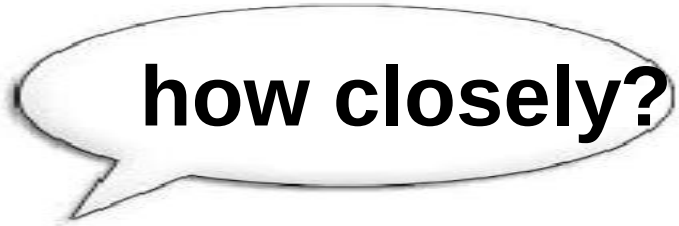
Interpretation of the guidelines

The laboratory should use an assay
in which the recovery of the product closely aligns
with the assay used by the pharmaceutical company
to assign potency to the product

Kitchen 2017 Semin Thromb Hemost 43: 331

Communication with the clinicians

Interpretation of the guidelines



The laboratory should use an assay
in which the recovery of the product closely aligns
with the assay used by the pharmaceutical company
to assign potency to the product

Kitchen 2017 Semin Thromb Hemost 43: 331

Communication with the clinicians

ñacceptableò assay:

± 30 % of the value
determined with the reference assay(s)

Kitchen 2017 Semin Thromb Hemost 43: 331

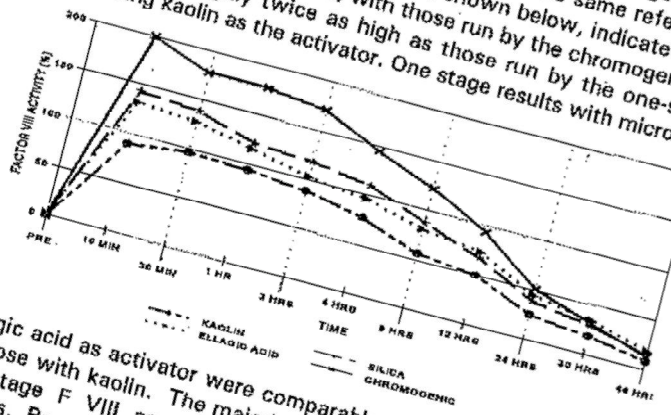
Communication with the clinicians

Will the real FVIII please stand up?

Lusher J 1995 Blood 86 supll 1 abstract 755

PLASMA FVIII LEVELS MEASURED AFTER INFUSION OF RECOMBINANT F VIII (rFVIII) VARY SIGNIFICANTLY WITH DIFFERENT ASSAY METHODS - (WILL THE REAL FVIII LEVEL PLEASE STAND UP!). J. M. Lusher, C. Hillman-Wiseman, P. Simpson*, D. Hurst, Children's Hospital of Michigan, Detroit, Mi. and Bayer Corp., Berkeley, Ca.

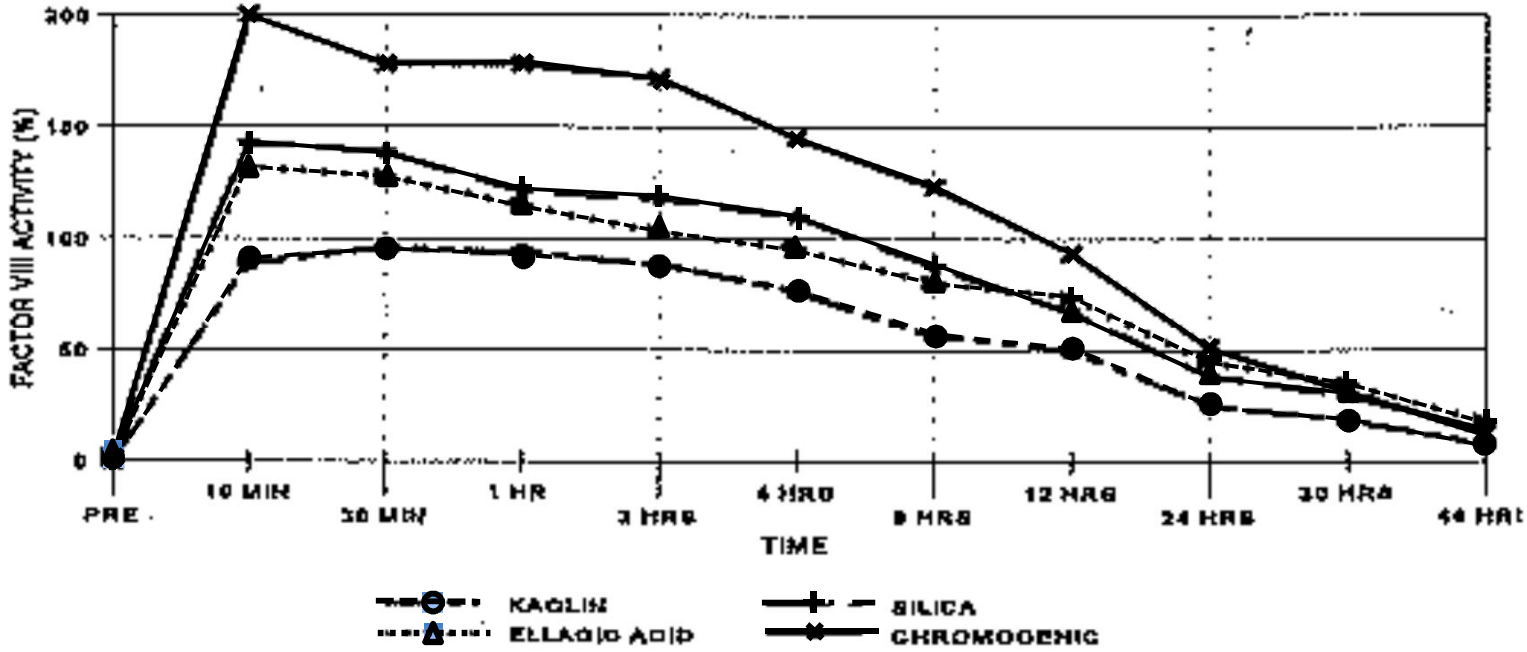
As part of a bioequivalence study comparing two lots of rFVIII (Kogenate®), 8 persons with hemophilia A were infused with rFVIII from each lot, and multiple plasma samples were then obtained from each subject for determination of FVIII levels over 48 hours. In view of reported discrepancies between FVIII levels measured by different assay methods, we assayed patient samples by 4 different methods: chromogenic (Coatest, F VIII, Kabi), and one stage APTT method using 3 different types of activators- micronized silica (Organon Teknika), ellagic acid (Dade), and kaolin (Diagnostica Stago). All samples were immediately centrifuged, snap frozen and stored at -70°C until assayed in duplicate. The same reference plasma standard was used throughout. Results, shown below, indicate a consistent difference in FVIII assay values, with those run by the chromogenic substrate method being roughly twice as high as those run by the one-stage APTT method using kaolin as the activator. One stage results with micronized silica



or ellagic acid as activator were comparable, and were consistently higher than those with kaolin. The majority of clinical laboratories in the U.S. use a one-stage F VIII assay, employing micronized silica or ellagic acid activators. Because significantly different results can be obtained depending on F VIII assay method used, multicenter studies must carefully standardize F VIII assay techniques and reagents in order to combine data for analysis.

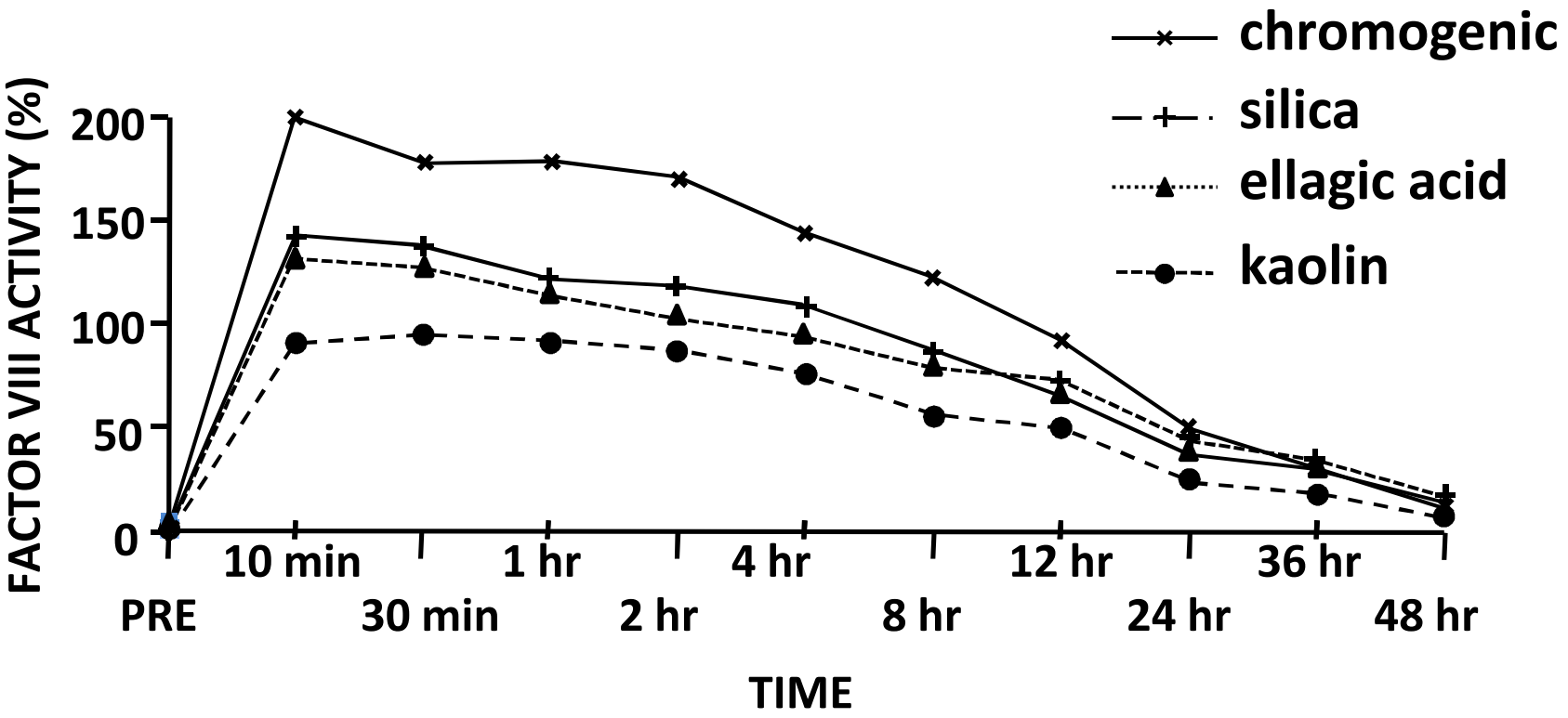
Will the real FVIII please stand up?

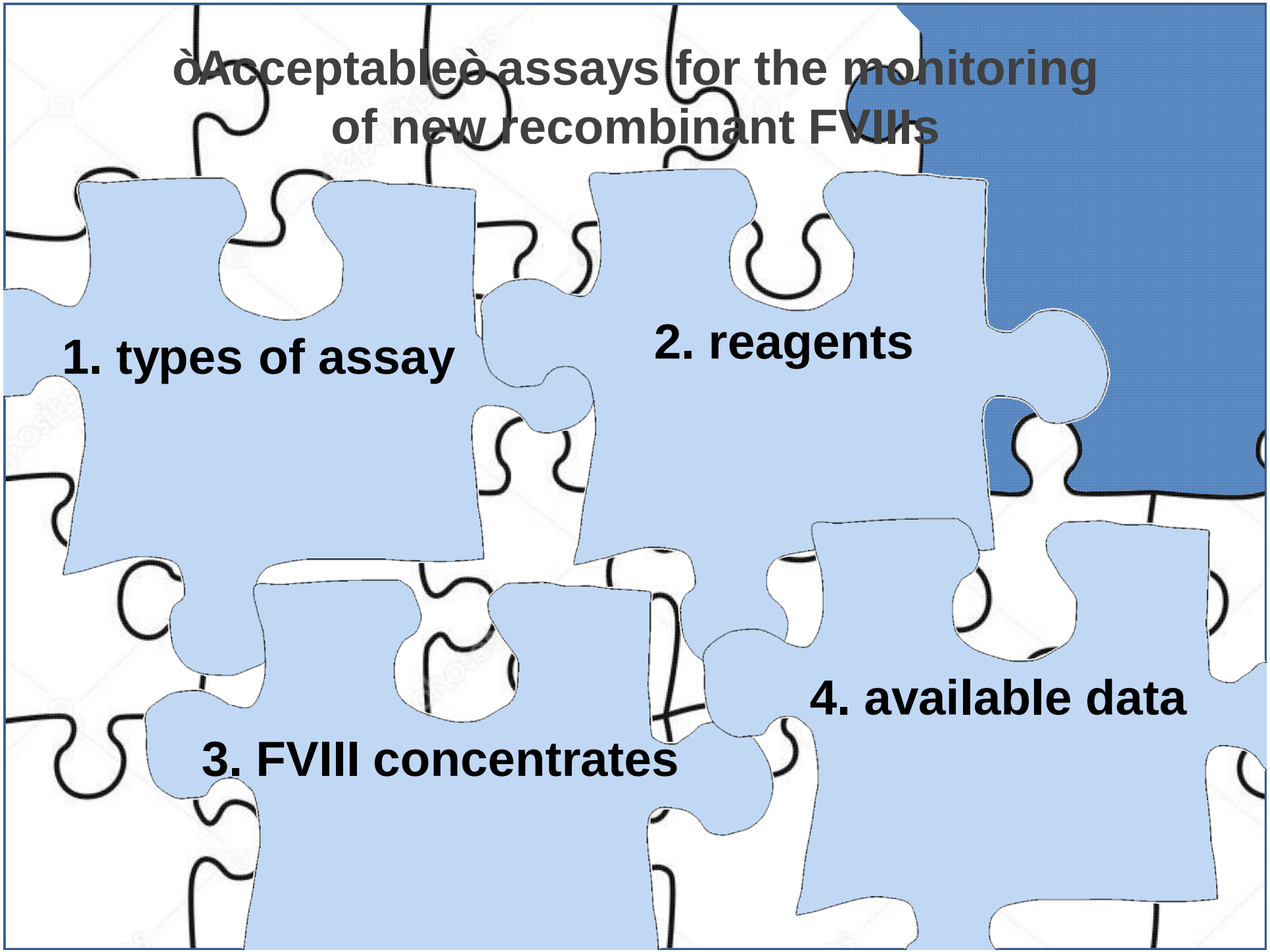
Lusher J 1995 Blood 86 supll 1 abstract 755

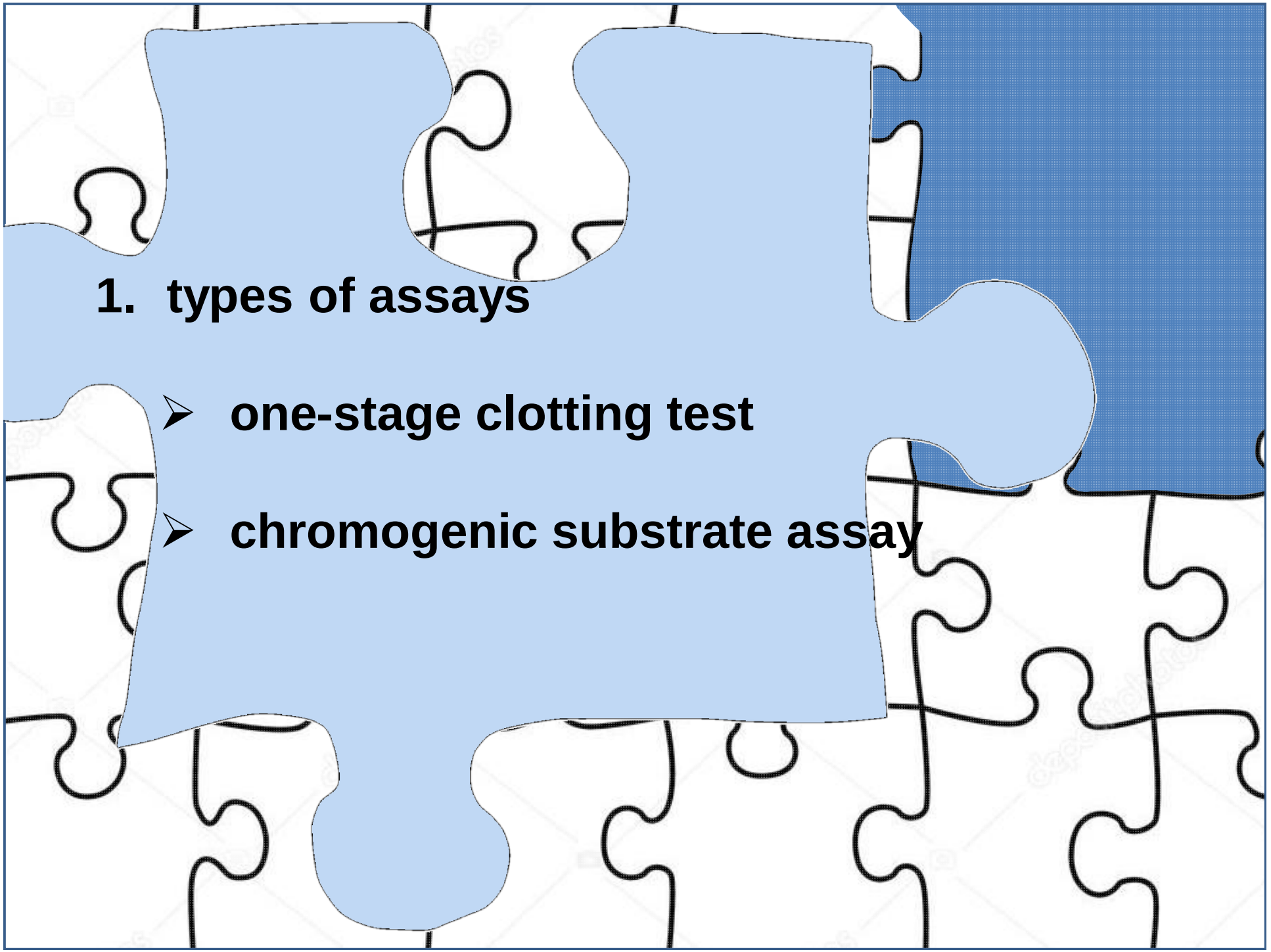


Will the real FVIII please stand up?

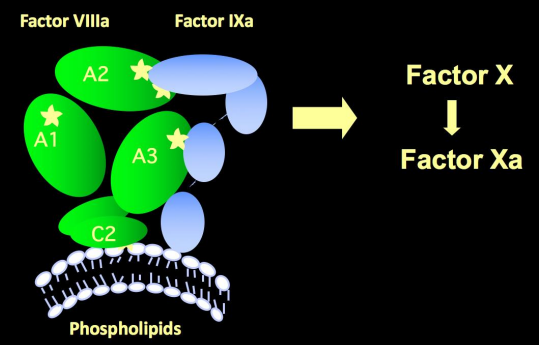
Lusher J 1995 Blood 86 supll 1 abstract 755




òAcceptableè assays for the monitoring of new recombinant FVIIIs
1. types of assay
2. reagents
3. FVIII concentrates
4. available data


1. types of assays
➢ one-stage clotting test
➢ chromogenic substrate assay

FVIII chromogenic assay

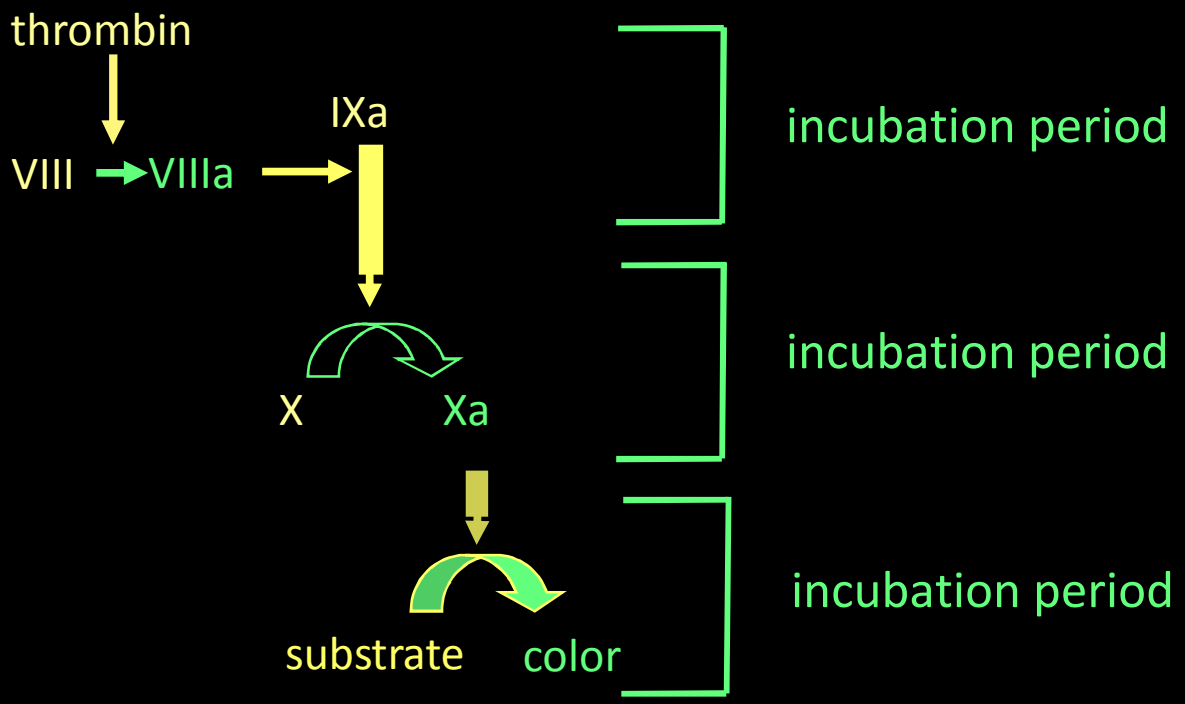


test sample (FVIII)

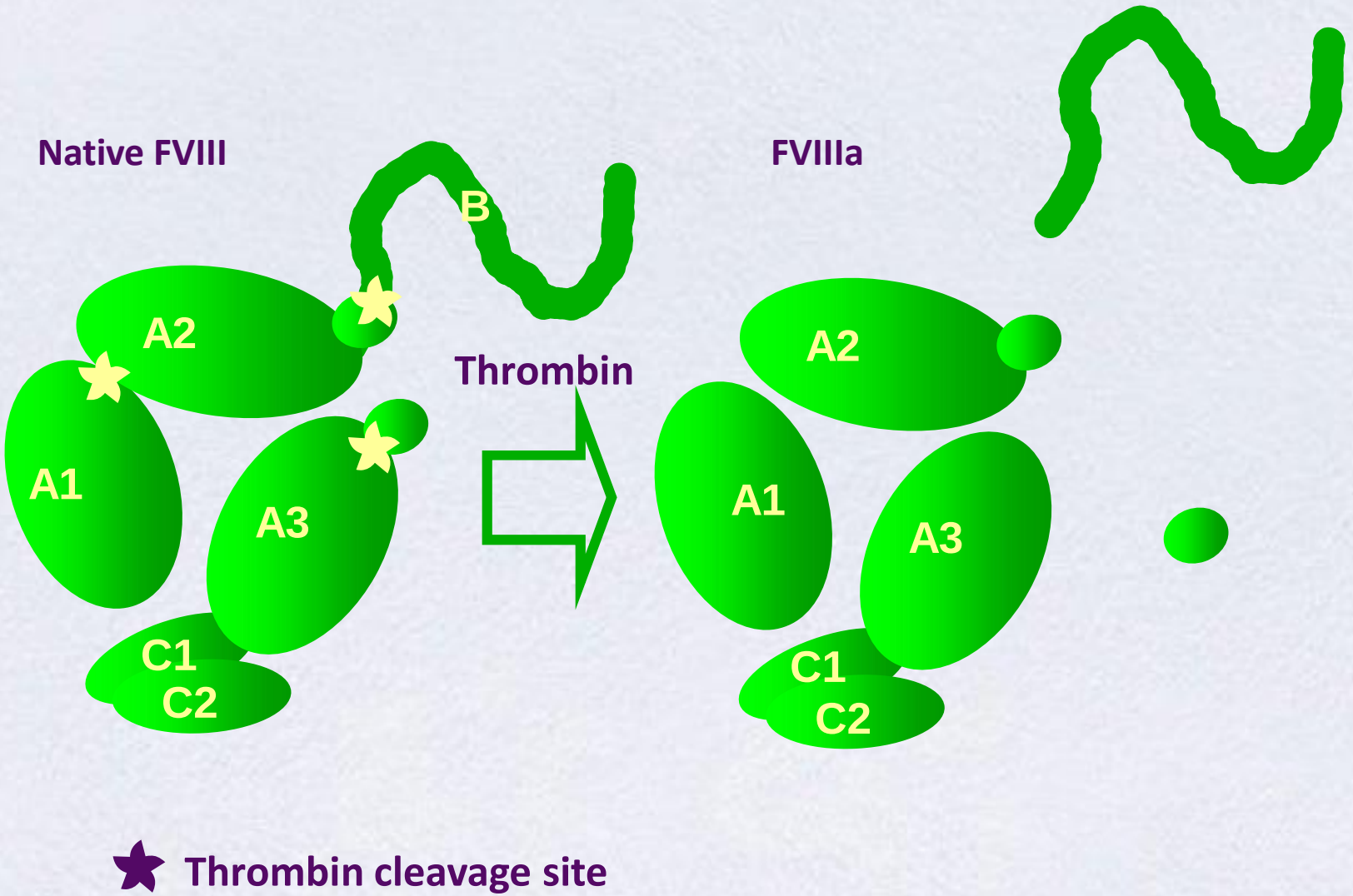
+ FIXa, FX
+ a little thrombin
+ phospholipids

+ Ca^{++}

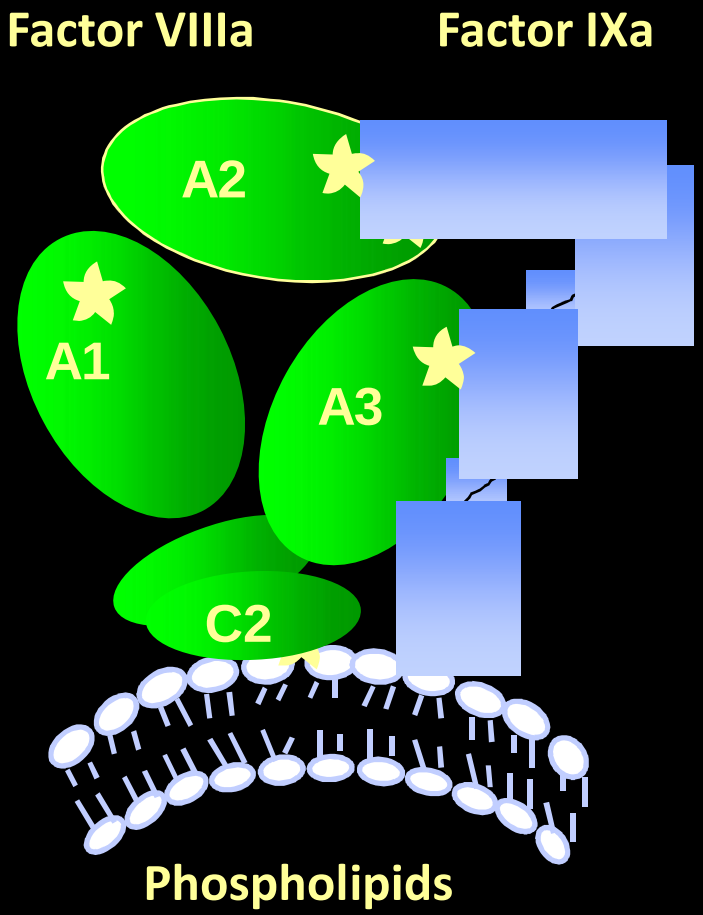
+ chromogenic substrate for FXa



Native and thrombin-activated FVIII



Activated Factor VIII as cofactor of Factor IXa



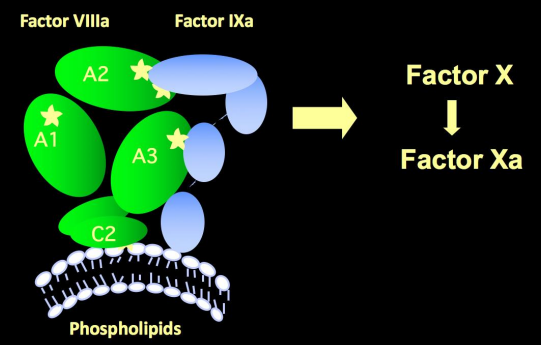
Factor X

Factor Xa

Haemostasis

X 100.000 by Factor VIII

FVIII chromogenic assay



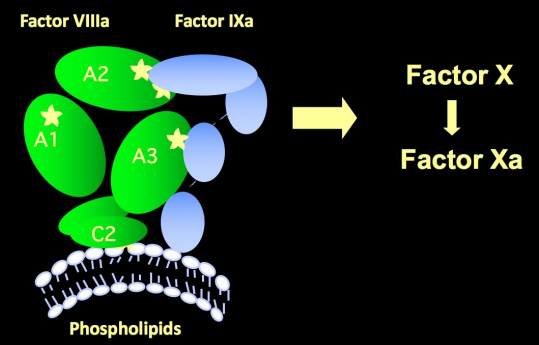
test sample (FVIII)

+ a little thrombin
+ FIXa, FX
+ phospholipids

+ Ca^{++}

+ chromogenic substrate
for FXa

FVIII chromogenic assay

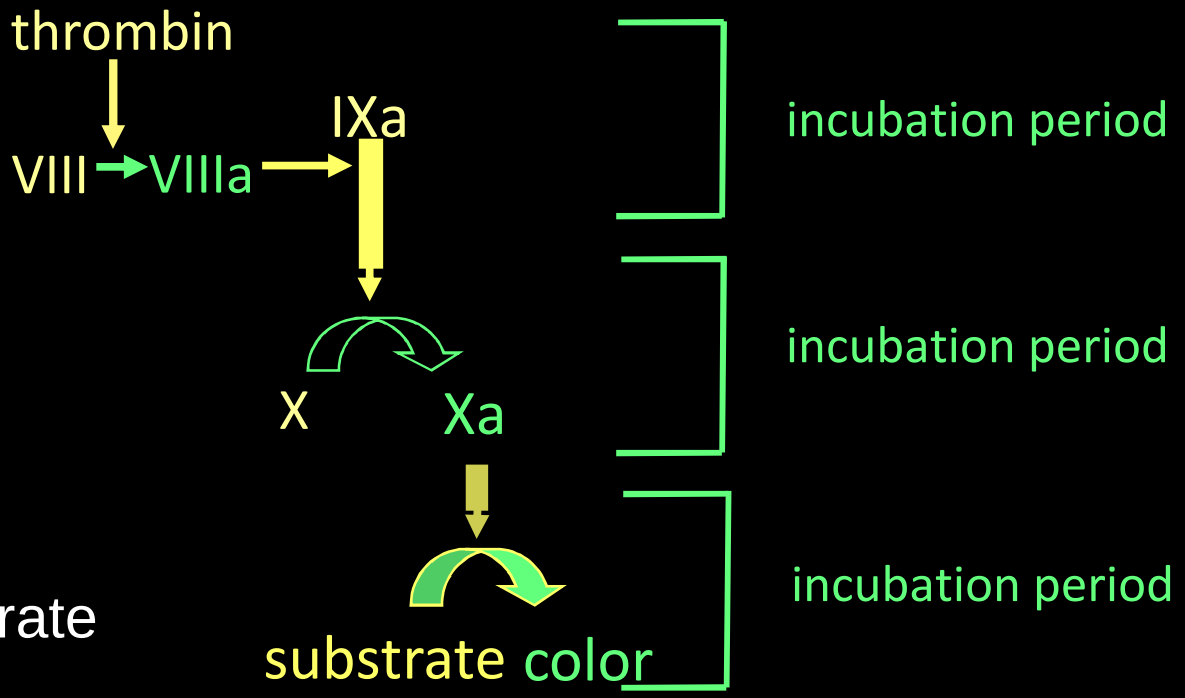


test sample (FVIII)

+ a little thrombin
+ FIXa, FX
+ phospholipids

+ Ca^{++}

+ chromogenic substrate for FXa



FVIII one-stage assay (APTT-based)

test sample (FVIII)

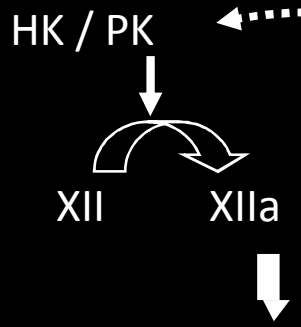
+ FVIII-deficient plasma

+ non physiological surface
silica, kaolin,
polyphenols, ellagic acid

+ phospholipids

+ Ca^{++}

FVIII one-stage assay (APTT-based)



test sample (FVIII)

+ FVIII-deficient plasma

+ non physiological surface
silica, kaolin,
polyphenols, ellagic acid

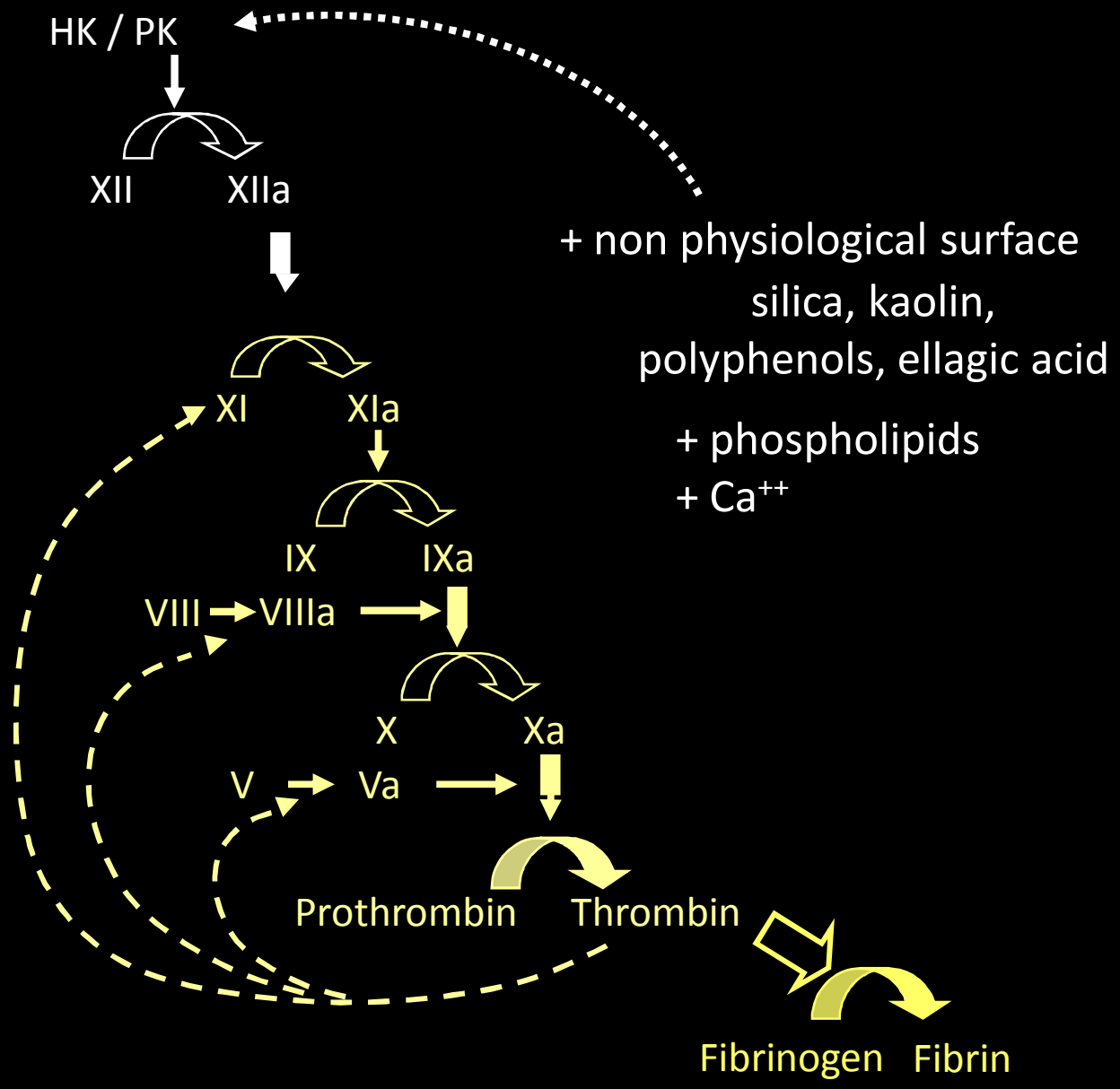
+ phospholipids

+ Ca^{++}

FVIII one-stage assay (APTT-based)

test sample (FVIII)

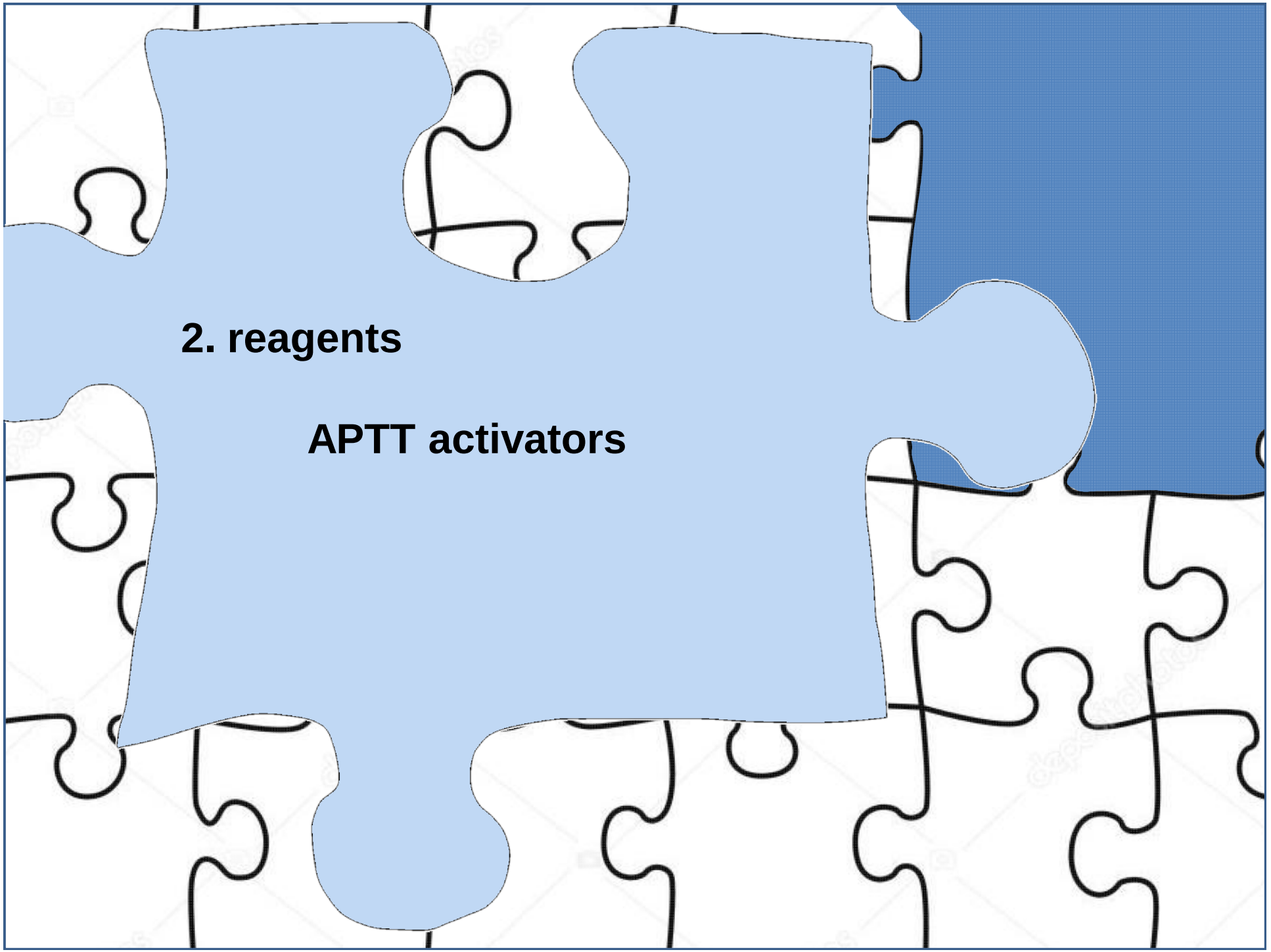
+ FVIII-deficient plasma

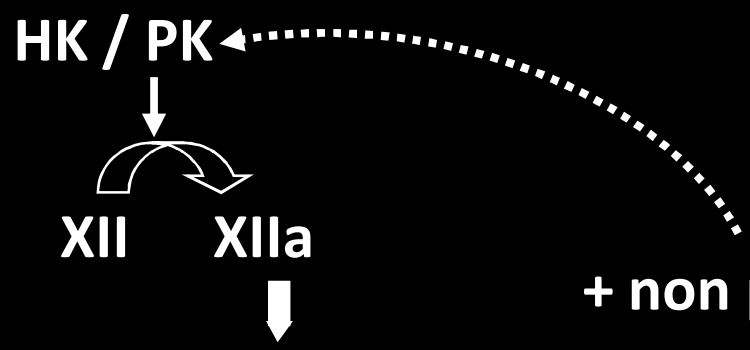


+ non physiological surface
silica, kaolin,
polyphenols, ellagic acid

+ phospholipids

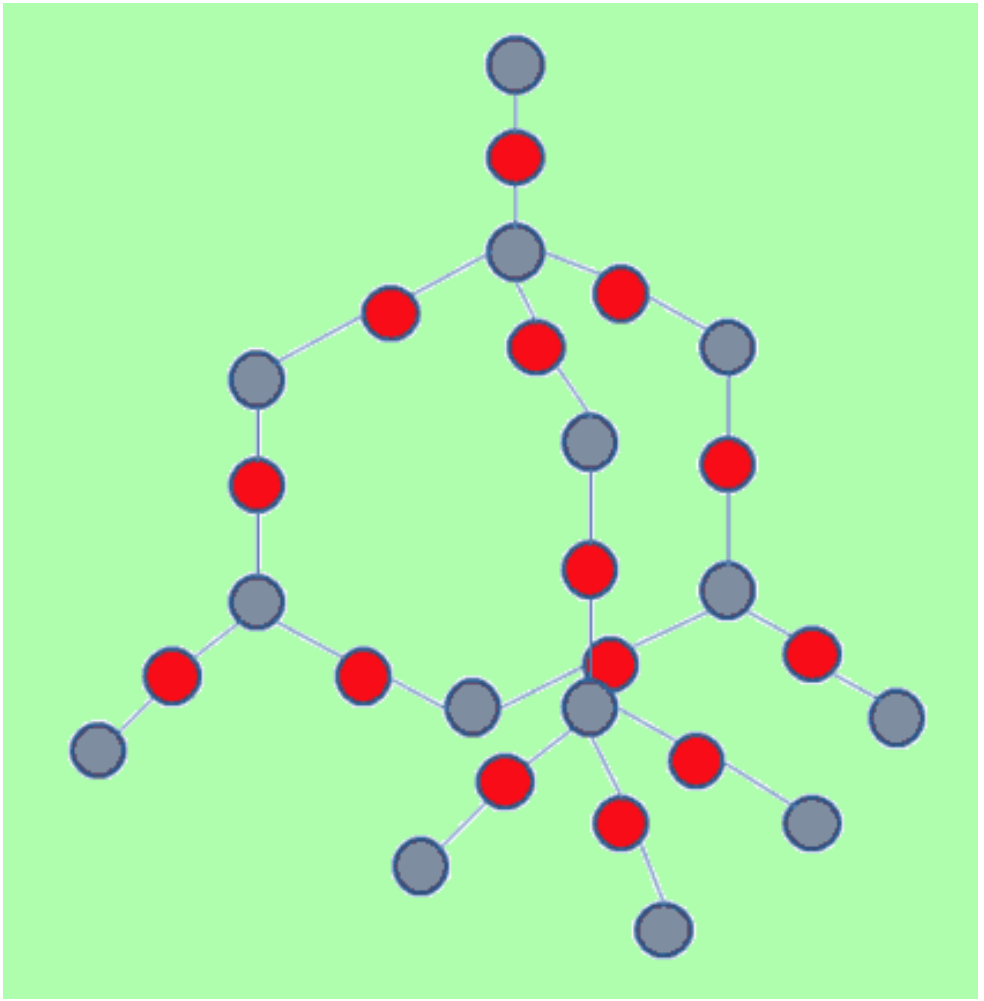
+ Ca^{++}


2. reagents
APTT activators



+ non physiological surfaces

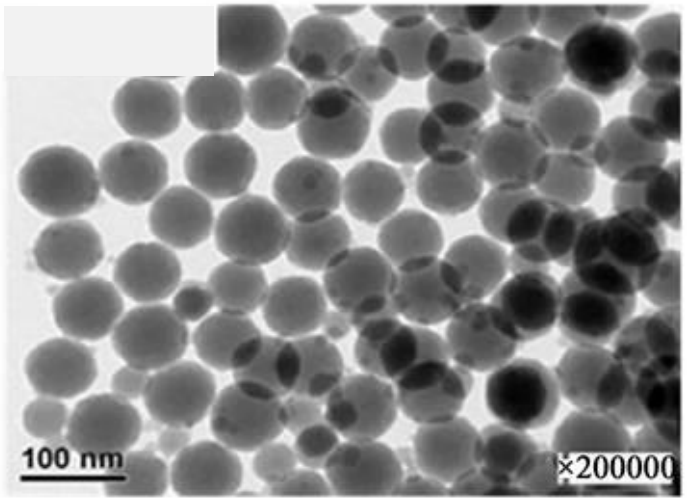
silica, kaolin,
polyphenols, ellagic acid



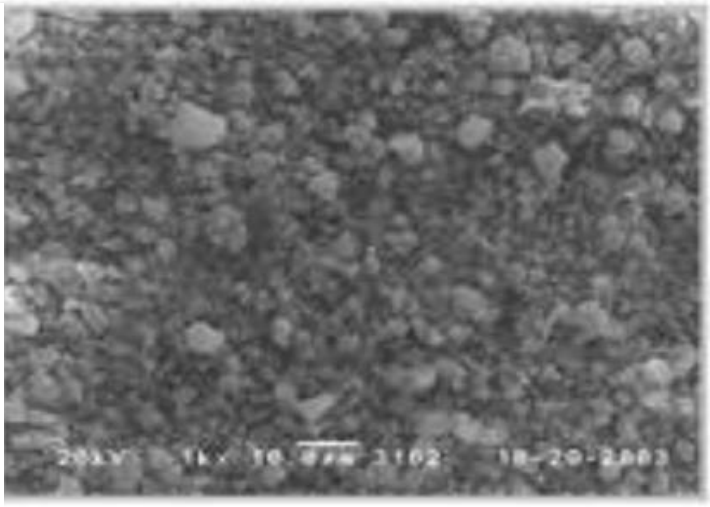
Silica: SiO_2

colloidal silica

Direct oxidation
of Silicon



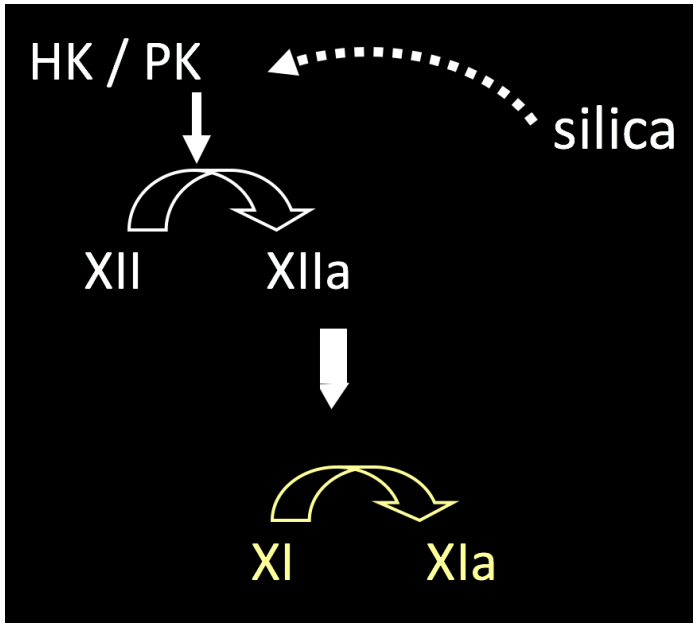
micronisated silica



Patent EP0566442B1 - Rouge à lèvres mat –

3 janv. 1996 - Composition de **rouge à lèvres mat** caractérisée par... un mica enrobé ... de sphères de **silice**.

Silica



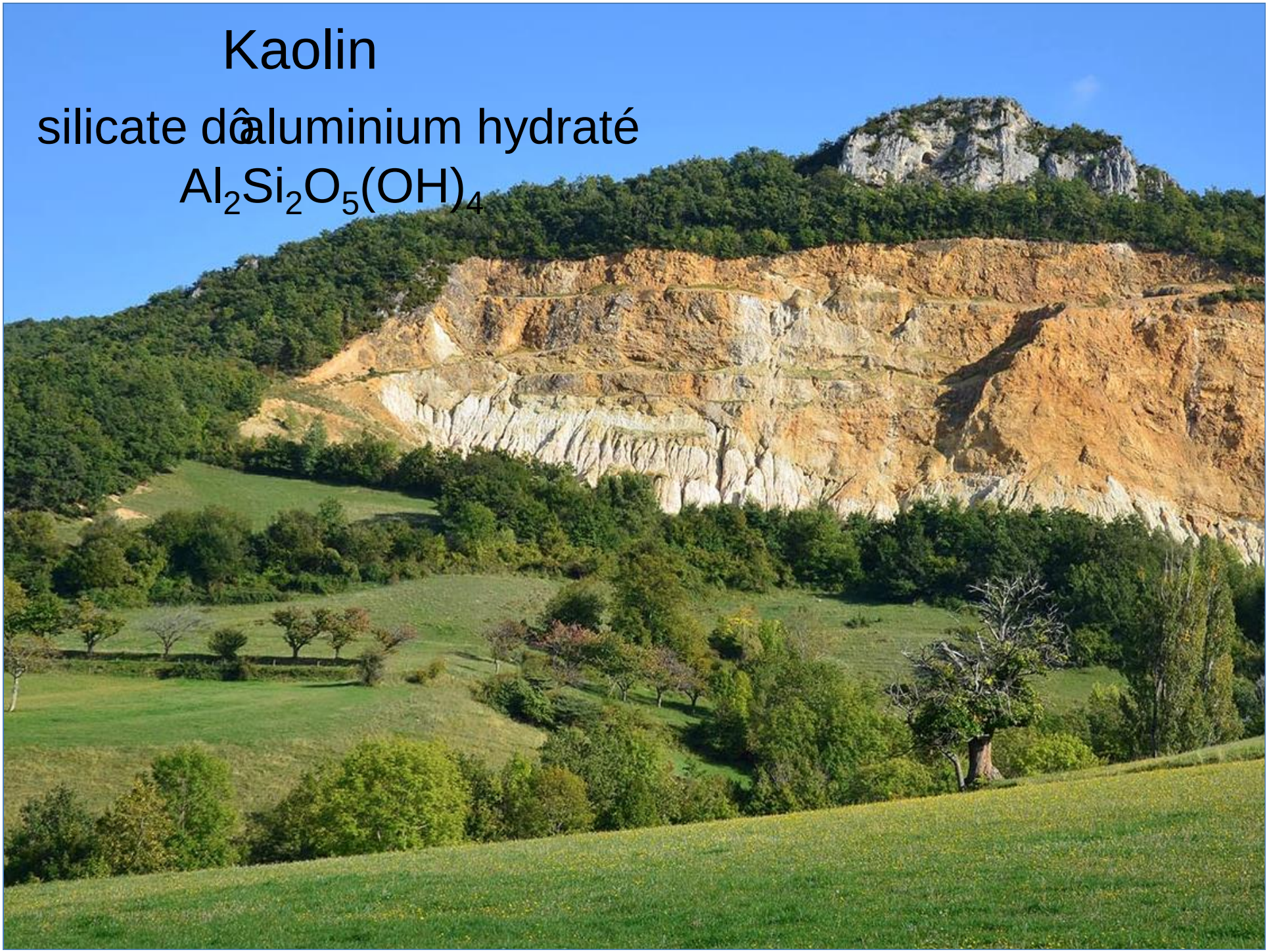
negatively charged material

contact pathway activation

Kaolin

silicate d'aluminium hydraté

$Al_2Si_2O_5(OH)_4$



Kaolin

silicate d'aluminium hydraté

$Al_2Si_2O_5(OH)_4$

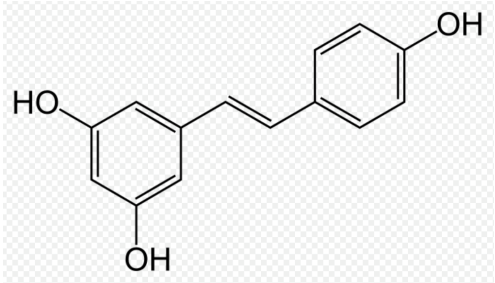
Polyphenols

PMCID: PMC2903024

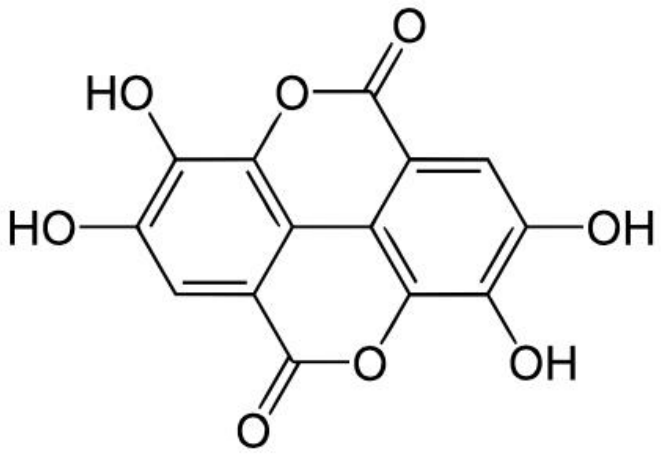
Int J Angiol. 2009 Autumn; 18(3): 111–117.

Polyphenols are medicine: Is it time to prescribe red wine for our patients?

Alfredo C Cordova, MD[1] and Bauer E Sumpio, MD PhD FICA[2]



Ellagic acid



Ellagic acid

Le whisky est riche en antioxydants, dont un en particulier que l'on connaît sous le petit nom d'acide ellagique. Non content de réduire

Pomegranate Powder Extract

Extrait de poudre de grenade avec des polyphénols d'acide ellagique pour antioxydant

Obtenir le Dernier Prix

Prix Unitaire:	
Commande Minimum:	25 kg
Conditions de Paiement:	LC, T/T, Western Union, PayPal
Marque Déposée:	Meiya

L'acide ellagique des fruits rouges : un super soin coup d'éclat | E-Santé

www.e-sante.fr › Beauté › Beauté de la peau

21 nov. 2016 - Puissant **antioxydant**, anti-taches, anti-rides, **l'acide ellagique** est un actif prisé en cosmétique. On le retrouve au cœur de nombreux fruits, et il ...

Ellagic acid (soluble) + Ca^{++}, Zn^{++}, Co^{++} or Fe^{++}

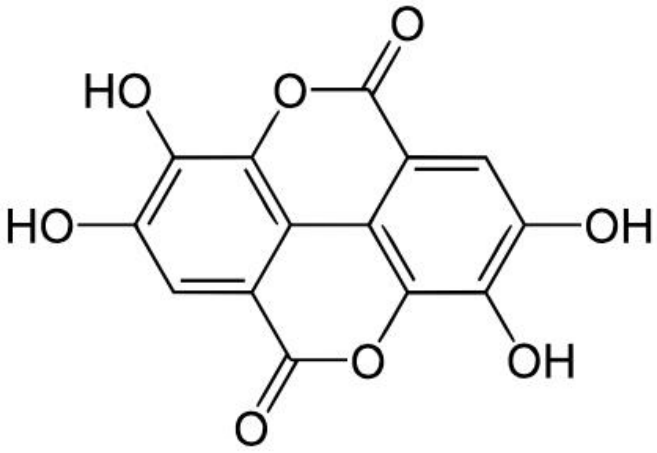
⇩

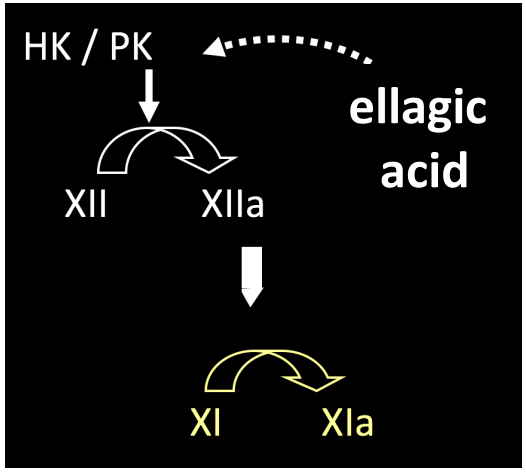
insoluble material

negatively charged

⇩

contact pathway activation

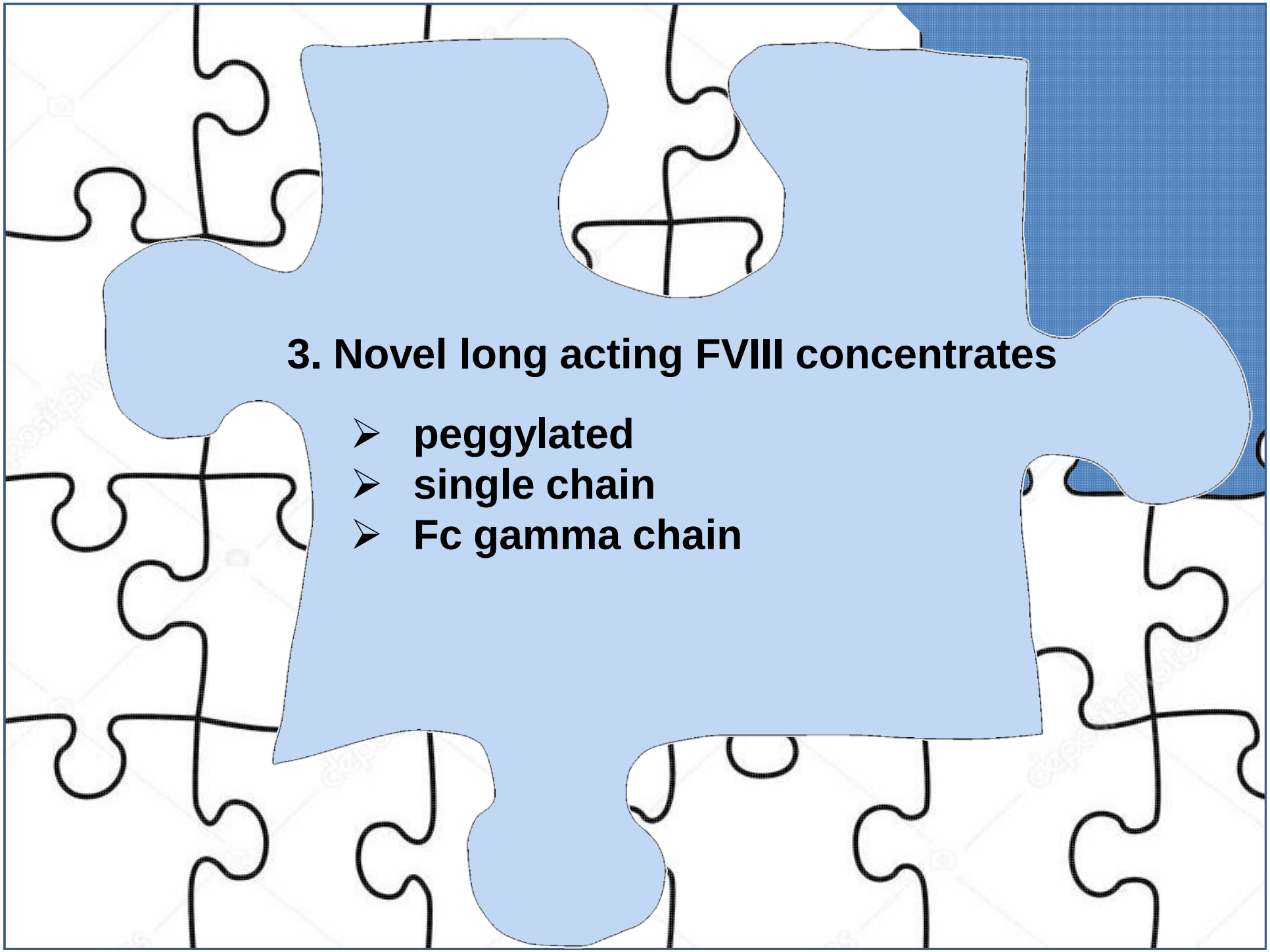




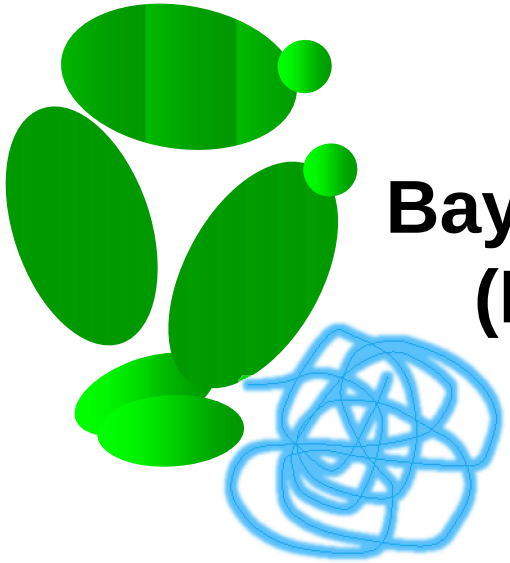
Bock P et al. Activation of intrinsic blood coagulation by ellagic acid: insoluble ellagic acid-metal ion complexes are the activating species. Biochemistry, 1981, 20:7258

FVIII assays in Belgium	n° of labs
SynthASil (Werfen)	23
APTT-SP (Werfen)	2
aPTT HS (Kordia)	?
STA^{R}-PTT Automate (Stago)	3
Pathrombin SL (Siemens)	1
STA^{R}-C.K. Prest^{R} (Stago)	4
STA^{R}-Cephascreen^{R} (Stago)	6
Actin (Siemens)	3
Actin FS (Siemens)	13
Actin FSL (Siemens)	1
FVIII chromogenic (Siemens)	1
Biophen FVIII:C (Hyphen BioMed)	4
Coamatic^{R} FVIII (Werfen)	3
TriniCHROM Factor VIII:C (Stago)	3

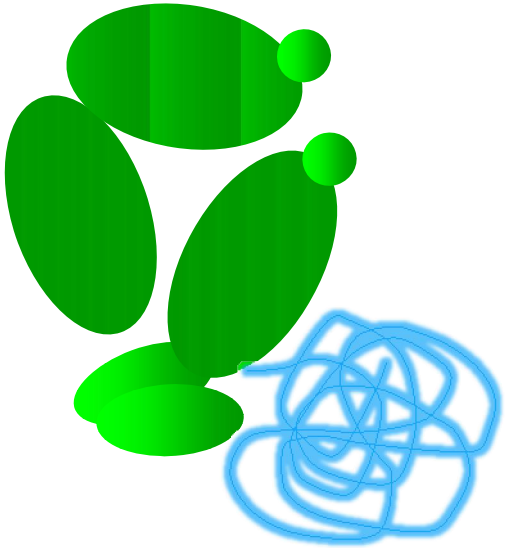
FVIII assays in Belgium	Activator
SynthASil (Werfen)	colloidal silica
APTT-SP (Werfen)	silica
aPTT HS (Kordia)	silica
STA^{R}-PTT Automate (Stago)	silica
Pathrombin SL (Siemens)	silica
STA^{R}-C.K. Prest^{R} (Stago)	kaolin
STA^{R}-Cephascreen^{R} (Stago)	polyphenols
Actin (Siemens)	ellagic acid
Actin FS (Siemens)	ellagic acid
Actin FSL (Siemens)	ellagic acid
FVIII chromogenic (Siemens)	.
Biophen FVIII:C (Hyphen BioMed)	.
Coamatic^{R} FVIII (Werfen)	.
TriniCHROM Factor VIII:C (Stago)	.

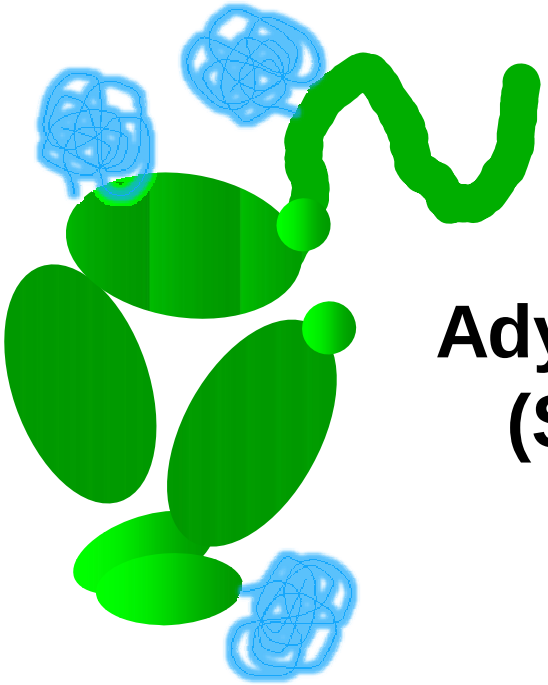

3. Novel long acting FVIII concentrates
peggylated
single chain
Fc gamma chain

Peggylated rFVIIIs

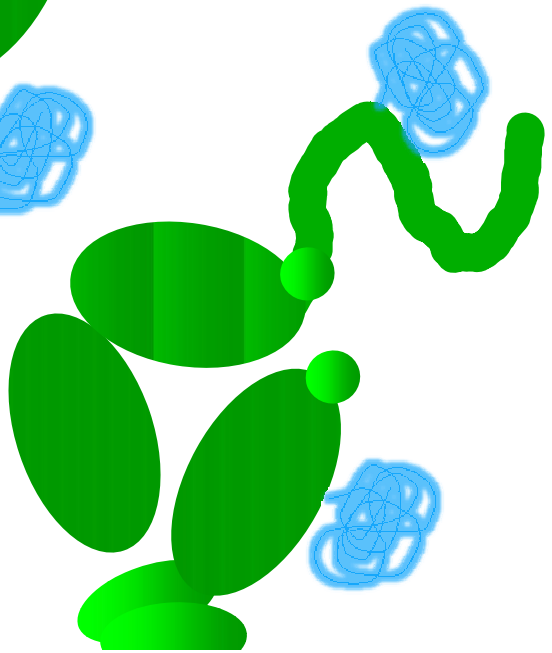


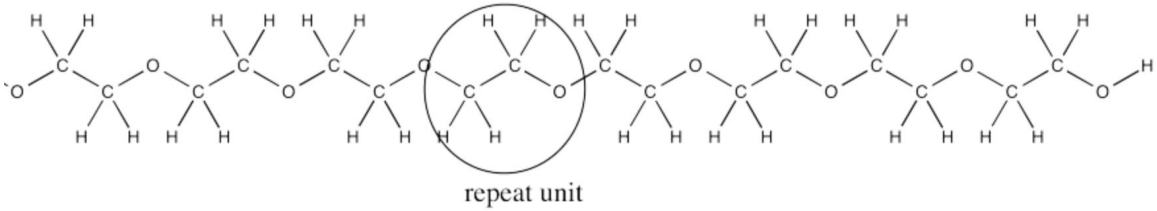
Bay 94-9027
(Bayer)

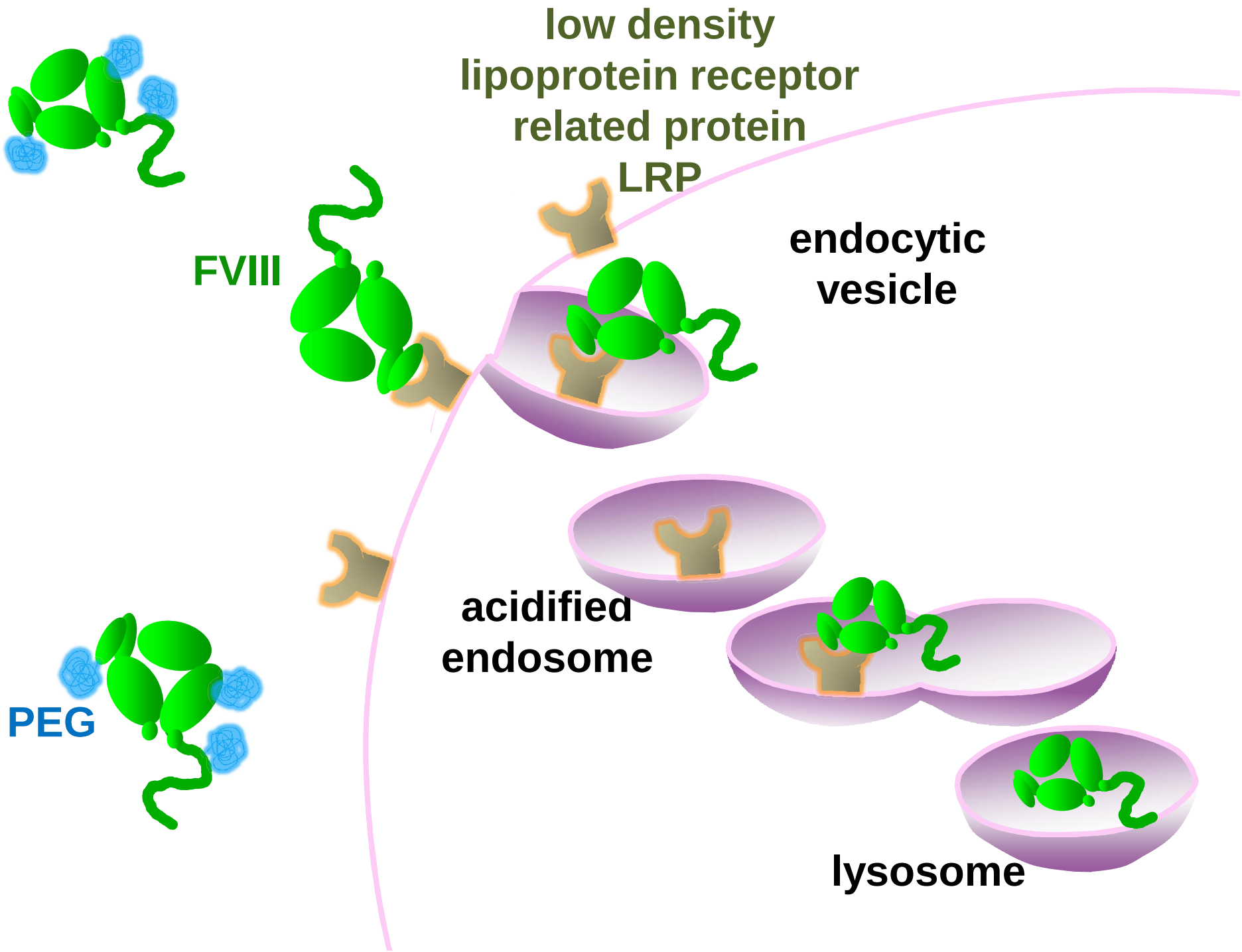




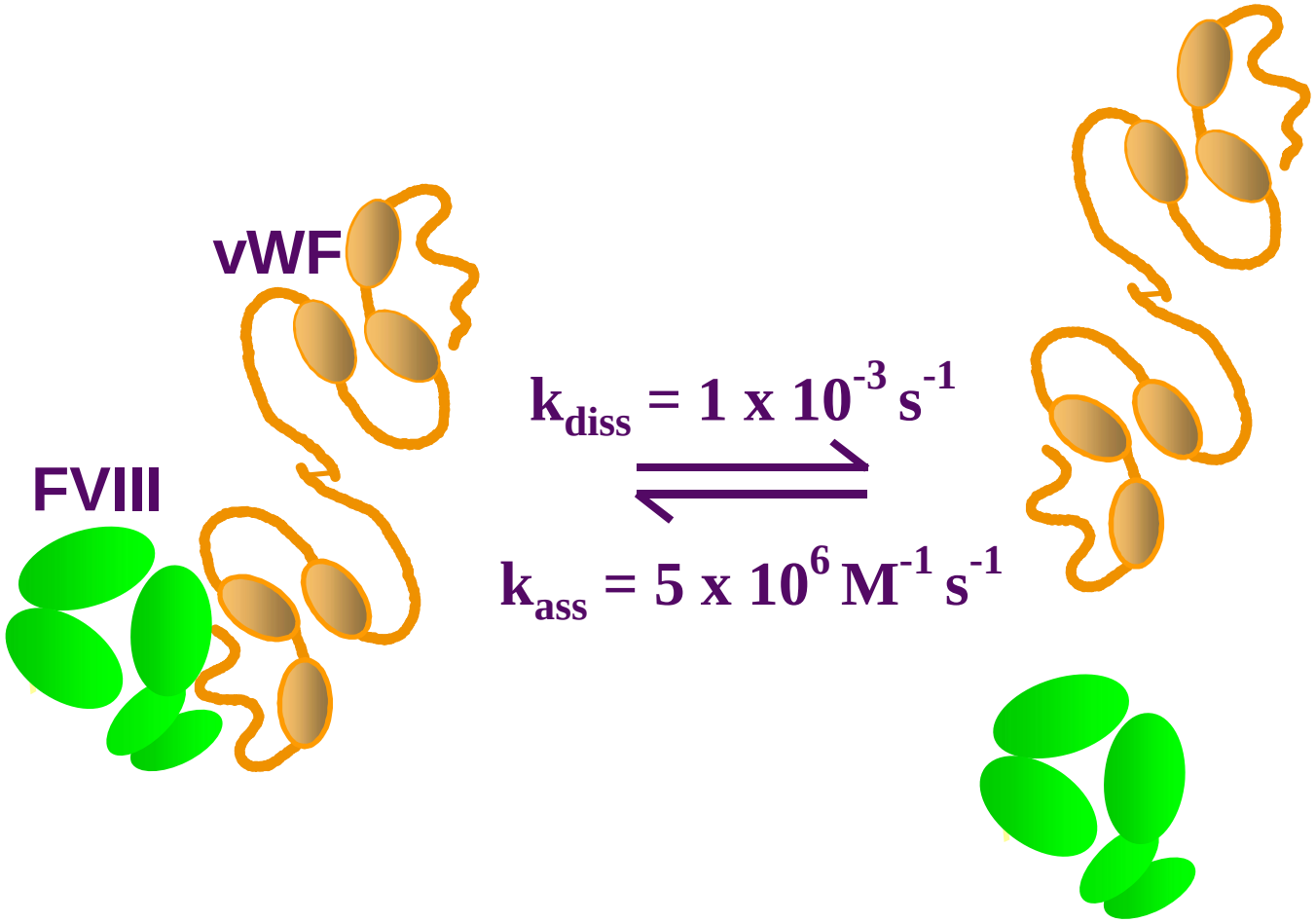
Adynovate
(Shire)





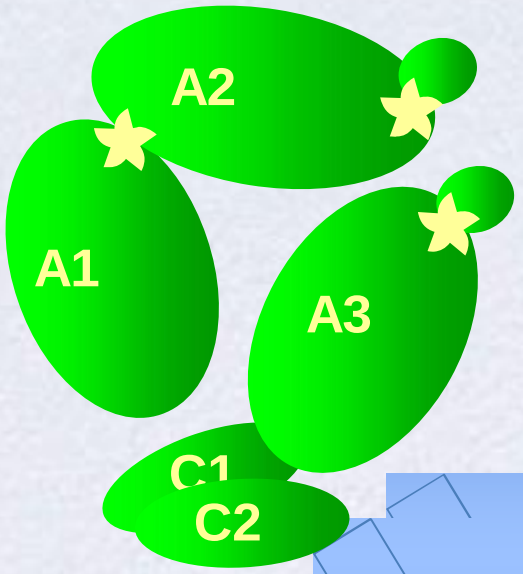

low density
lipoprotein receptor
related protein
LRP
FVIII
endocytic
vesicle
acidified
endosome
PEG
lysosome

FVIII binding to VWF

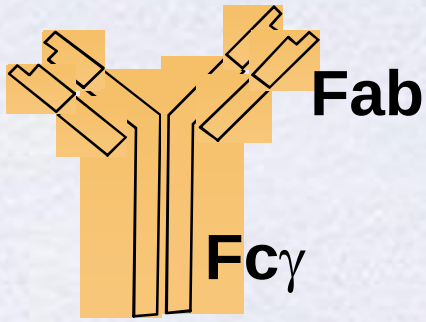


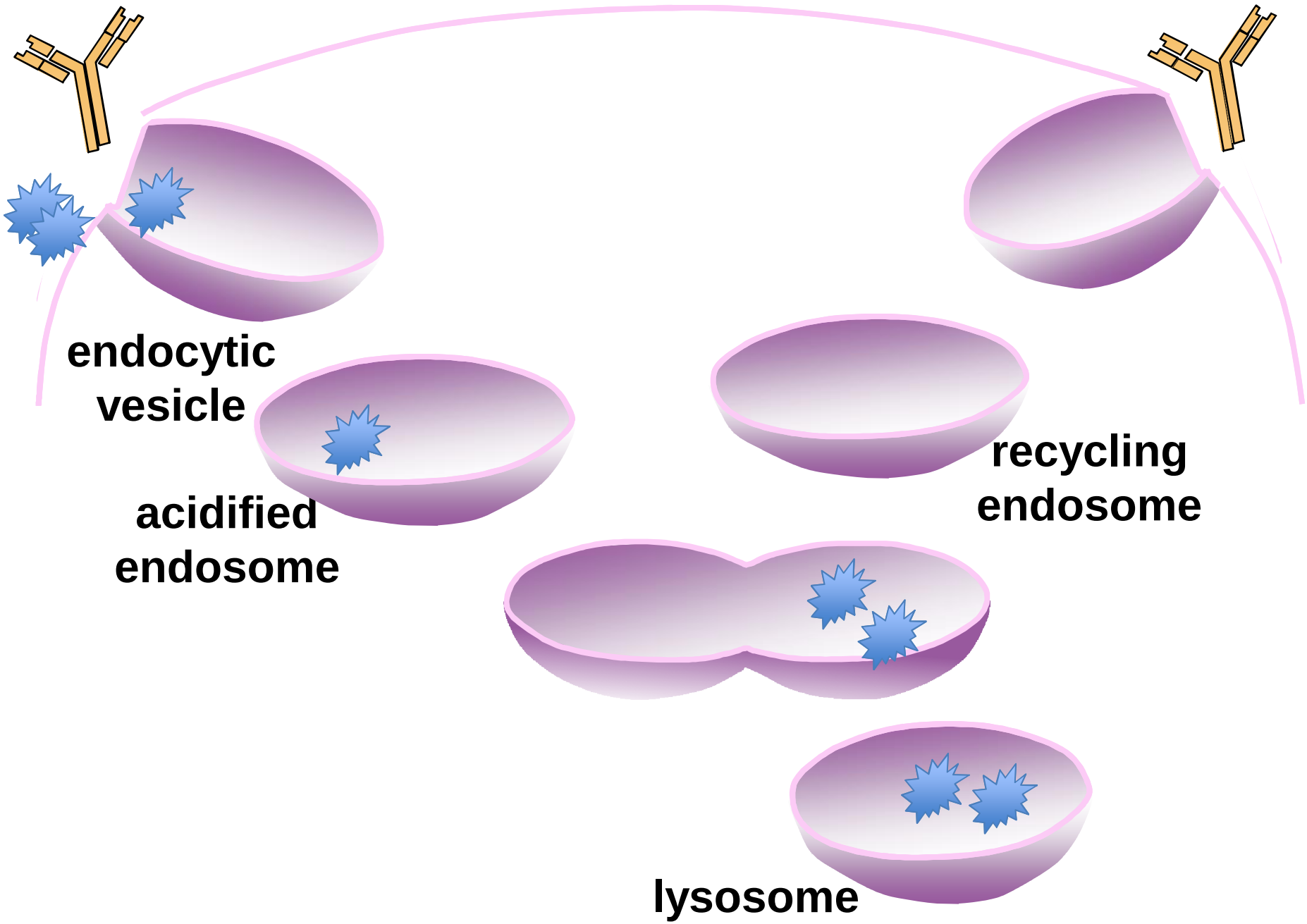
Vlot et al. Blood 1996

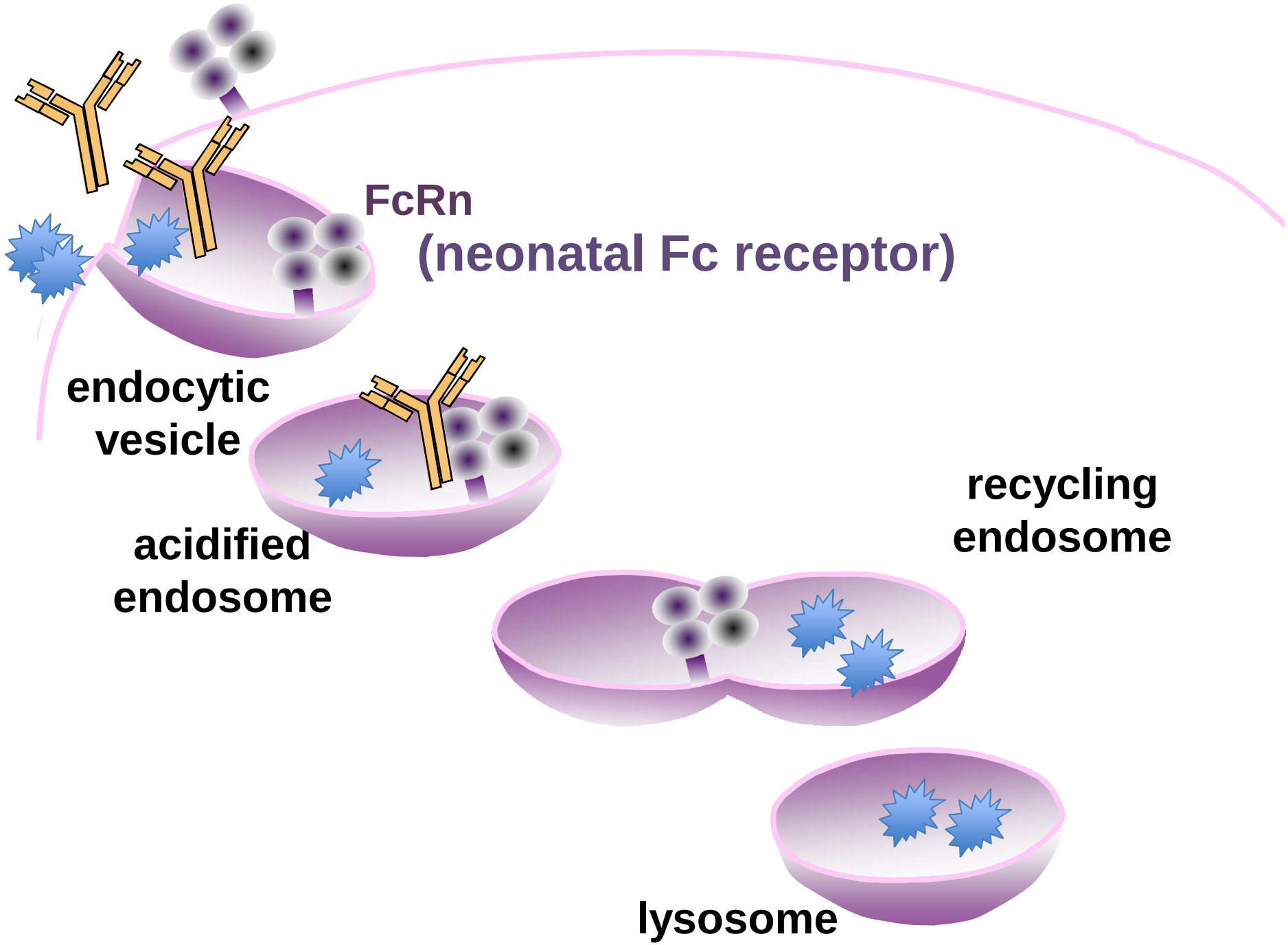
Fcγ-rFVIII



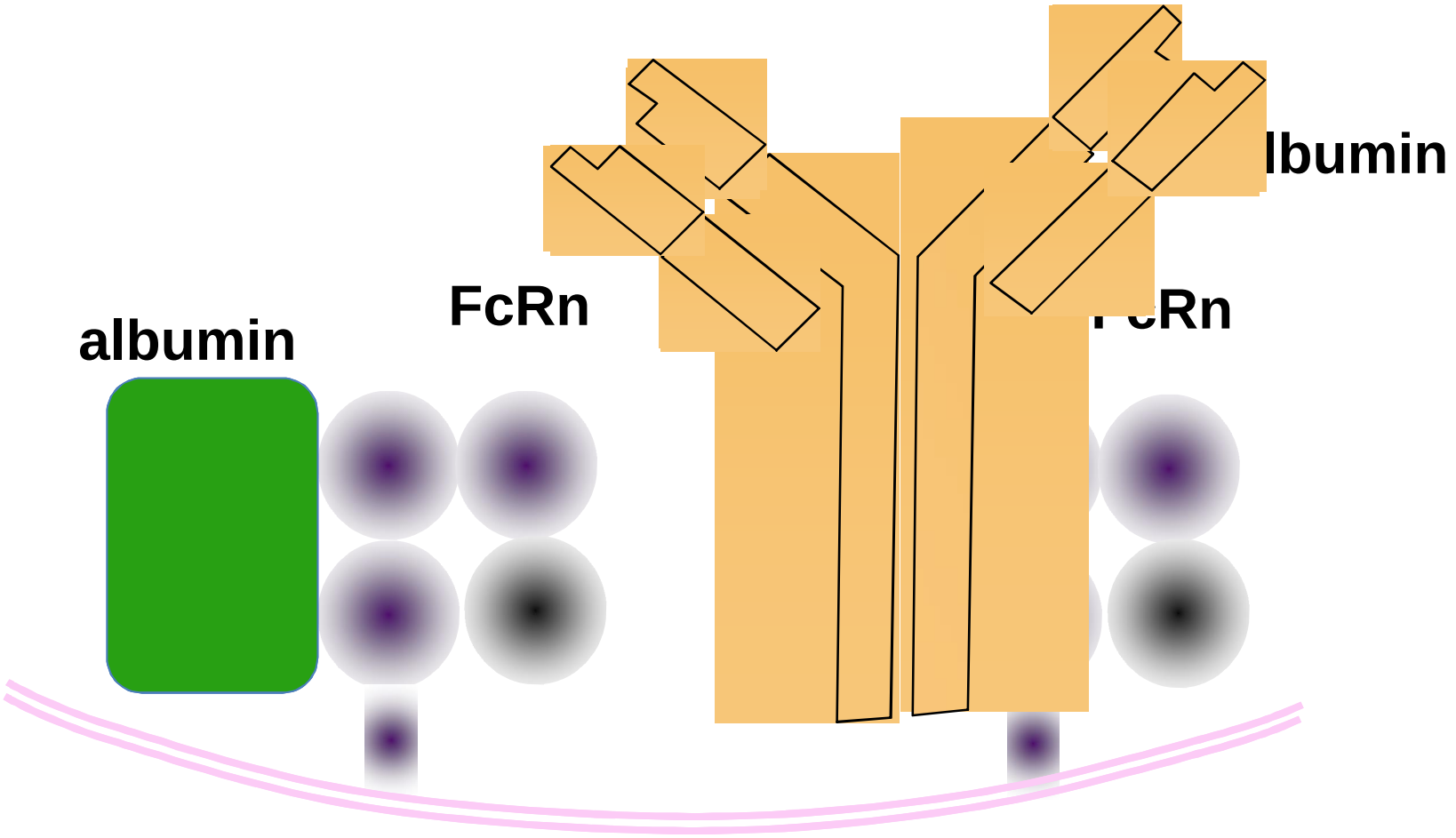
Elocta^{R} (Sobi)

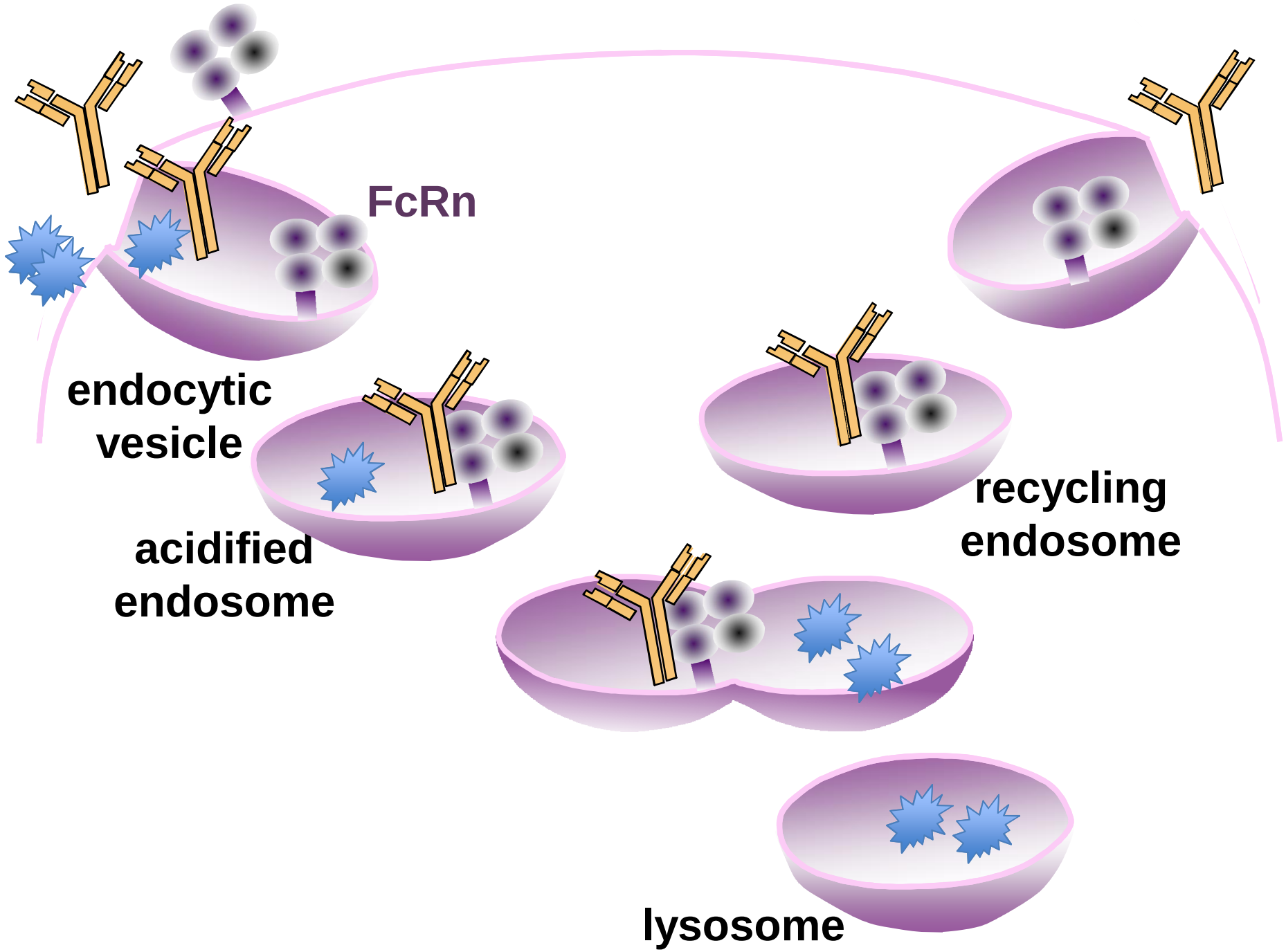


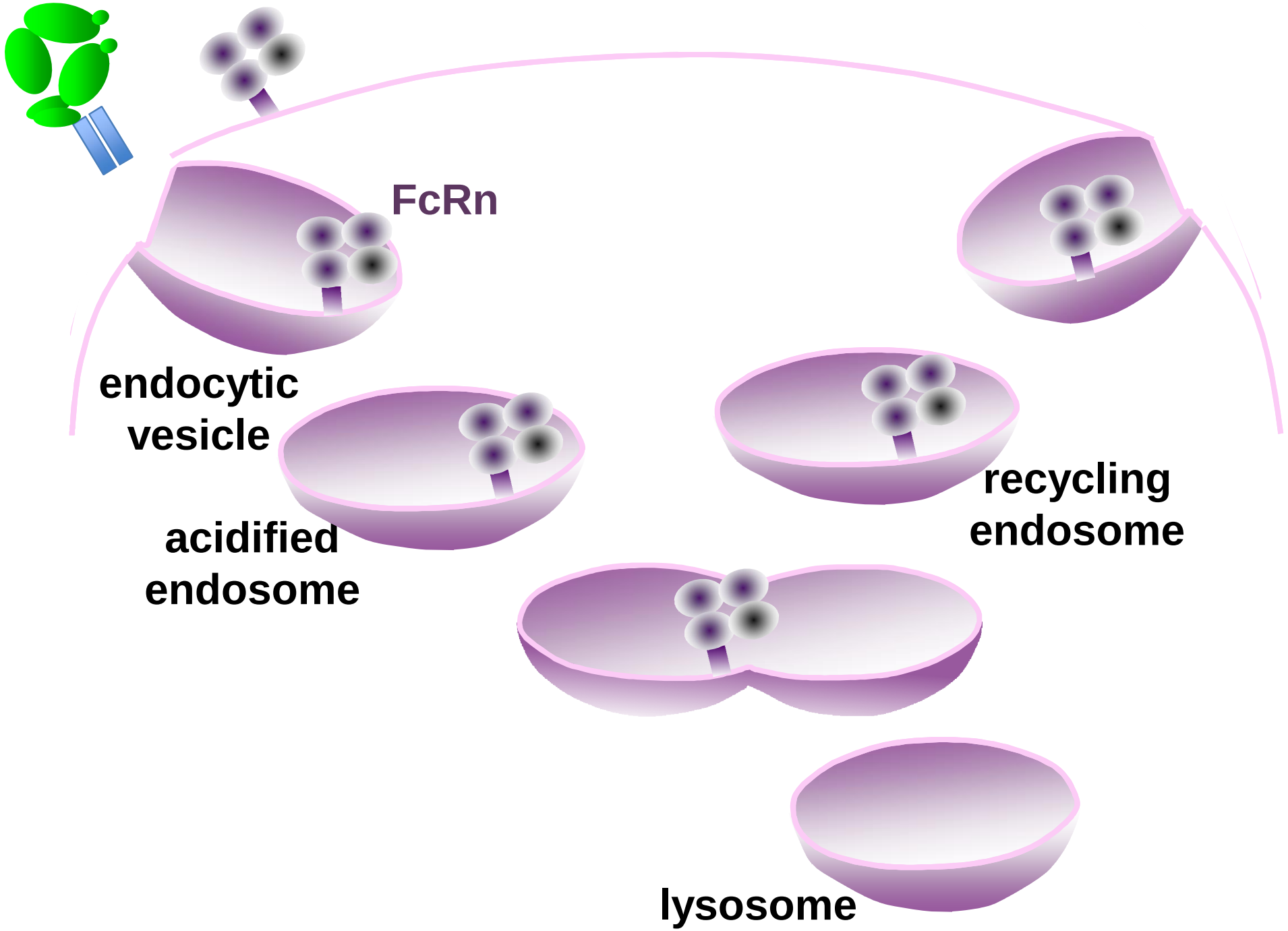

endocytic
vesicle
acidified
endosome
recycling
endosome
lysosome

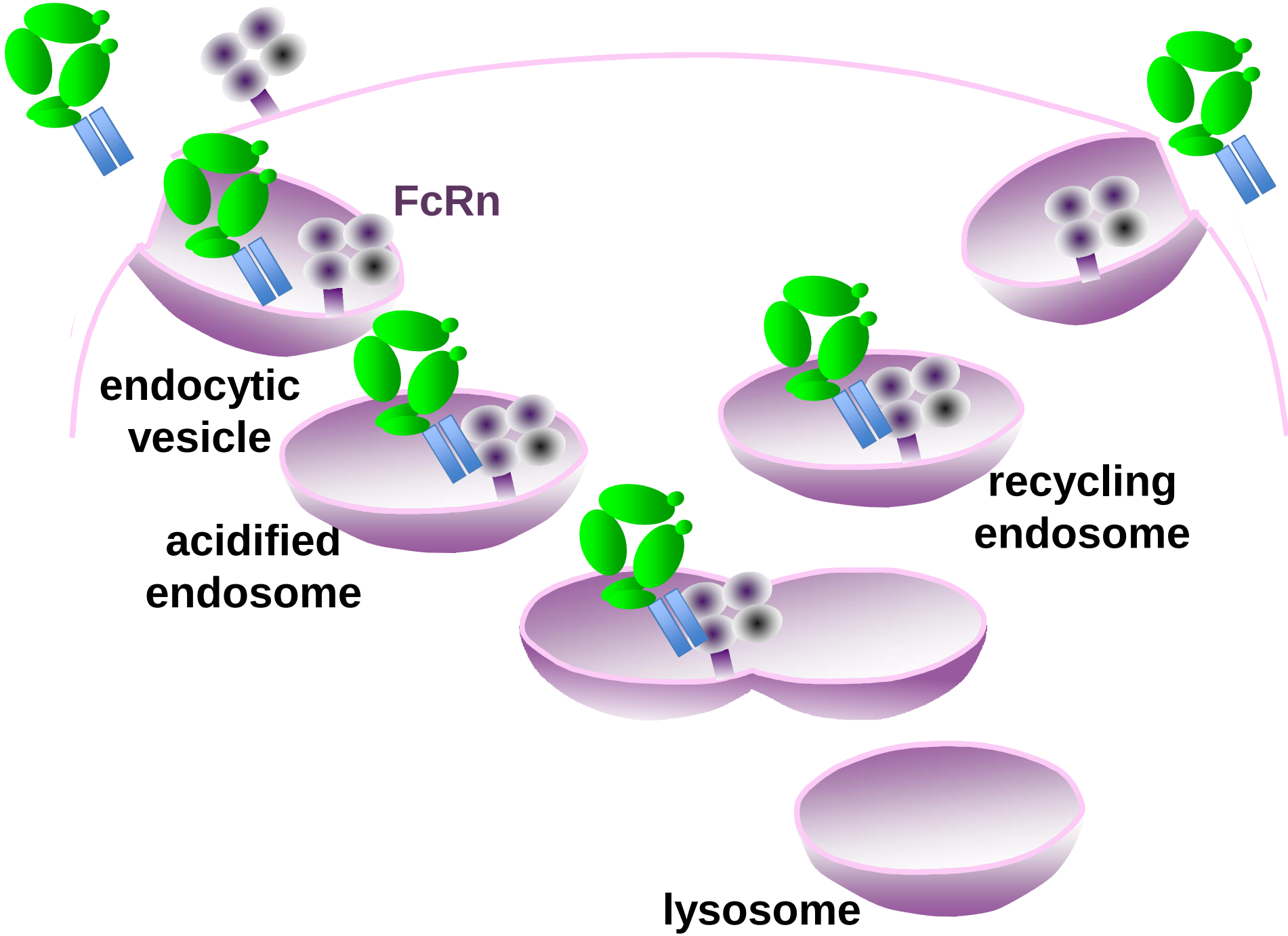

FcRn
(neonatal Fc receptor)
endocytic vesicle
acidified endosome
recycling endosome
lysosome

Neonatal Fc receptor (FcRn)

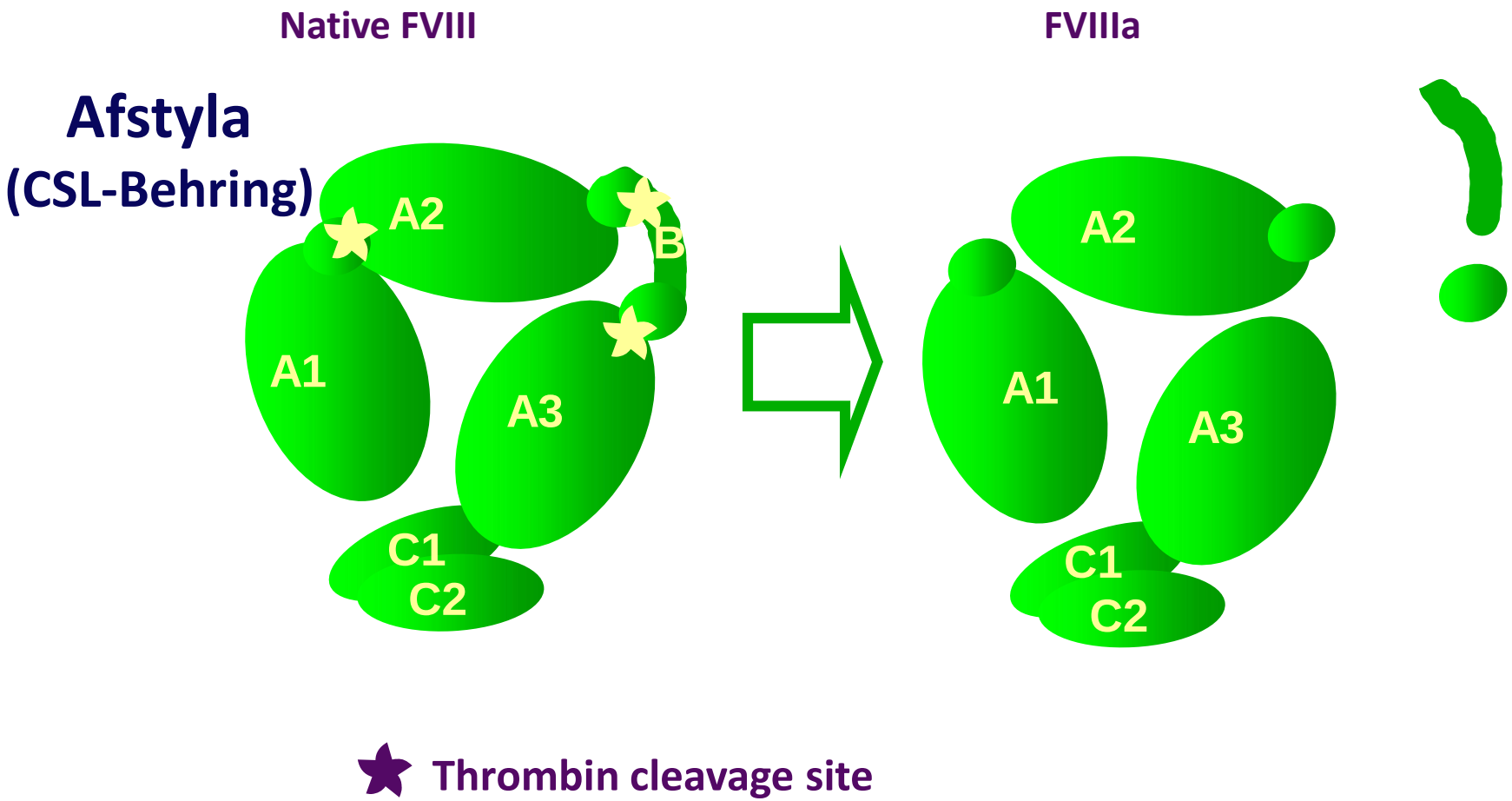



FcRn
endocytic vesicle
acidified endosome
recycling endosome
lysosome


FcRn
endocytic vesicle
acidified endosome
recycling endosome
lysosome

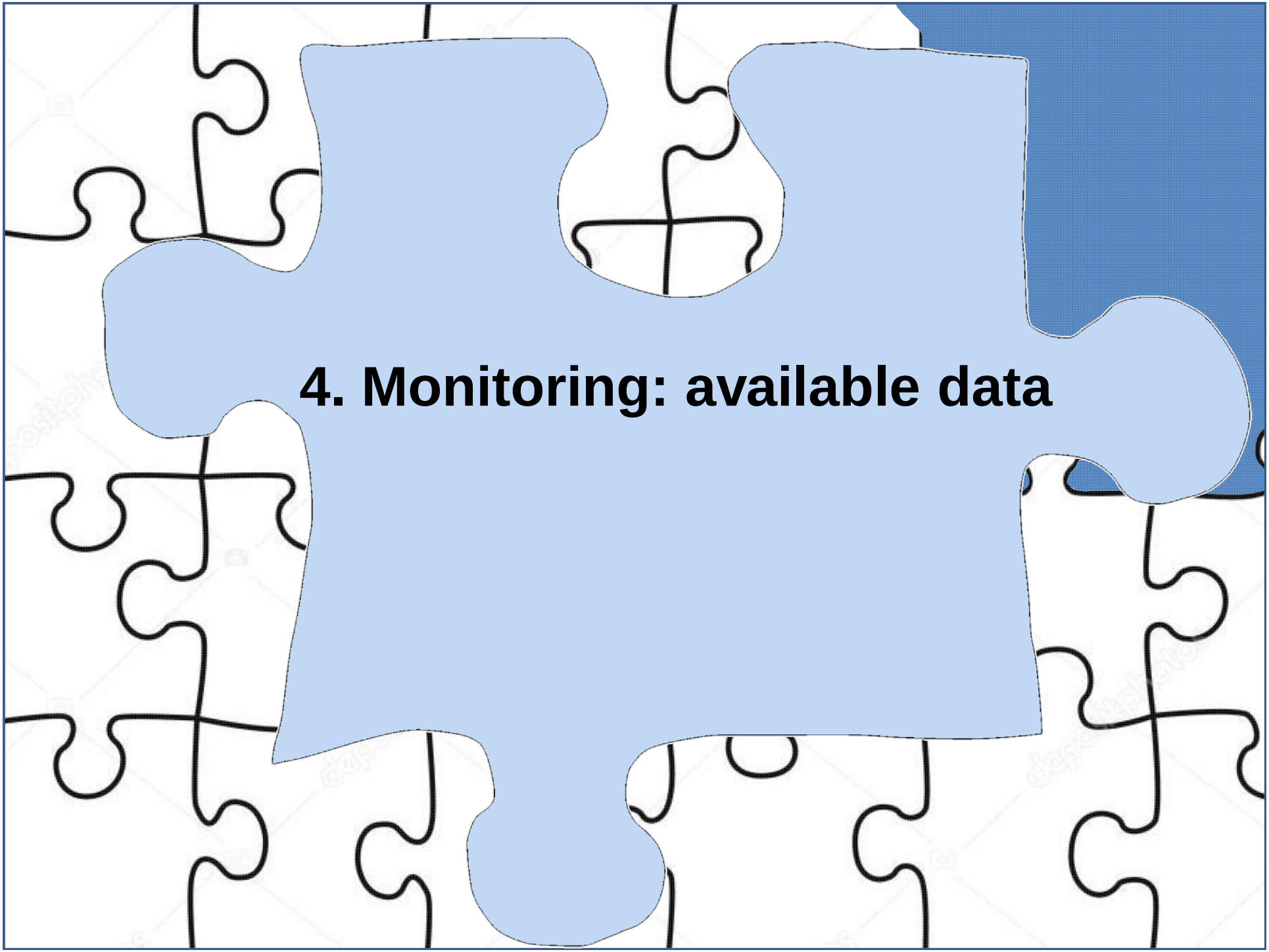

FcRn
endocytic vesicle
acidified endosome
recycling endosome
lysosome

Single chain-rFVIII



Half-life of new recombinant FVIIIs

Product	mean half-life (h)
Adynovate (Peg-rFVIII; Baxalta/Shire)	19
Bay 94-9027 (Peg-rFVIII; Bayer)	18
Elocta (Fc-rFVIII; Sobi)	18
Afstyla (sc-rFVIII;CSL-Behring)	14
wild type rFVIII	12


4. Monitoring: available data

rFVIII A

SynthASil (Werfen)

APTT-SP (Werfen)
aPTT HS (Kordia)
STA^{R}-PTT Automate (Stago)
Pathrombin SL (Siemens)

STA^{R}-C.K. Prest^{R} (Stago)

STA^{R}-Cephascreen^{R} (Stago)

Actin (Siemens)
Actin FS (Siemens)
Actin FSL (Siemens)

FVIII chromogenic (Siemens)
Biophen FVIII:C (Hyphen BioMed)
Coamatic^{R} FVIII (Werfen)
TriniCHROM Factor VIII:C (Stago)

rFVIII A

SynthASil (Werfen)

APTT-SP (Werfen)
aPTT HS (Kordia)
STA^{R}-PTT Automate (Stago)
Pathrombin SL (Siemens)

STA^{R}-C.K. Prest^{R} (Stago)

STA^{R}-Cephascreen^{R} (Stago)

Actin (Siemens)
Actin FS (Siemens)
Actin FSL (Siemens)

FVIII chromogenic (Siemens)
Biophen FVIII:C (Hyphen BioMed)
Coamatic^{R} FVIII (Werfen)
TriniCHROM Factor VIII:C (Stago)

rFVIII A

study 1

SynthASil (Werfen) — data

APTT-SP (Werfen)
aPTT HS (Kordia)
STA^{R}-PTT Automate (Stago)
Pathrombin SL (Siemens)

STA^{R}-C.K. Prest^{R} (Stago)

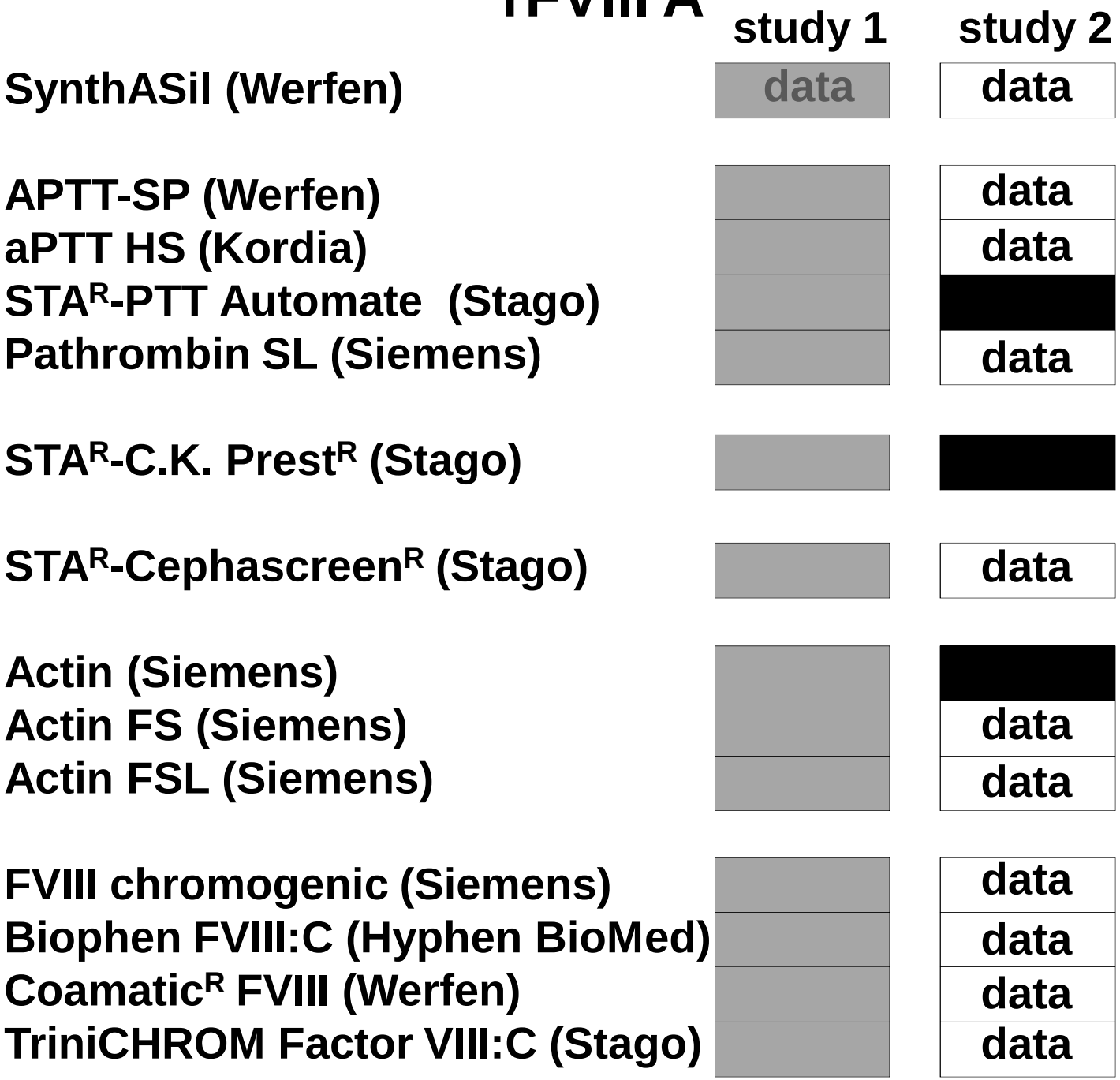
STA^{R}-Cephascreen^{R} (Stago)

Actin (Siemens)
Actin FS (Siemens)
Actin FSL (Siemens)

FVIII chromogenic (Siemens)
Biophen FVIII:C (Hyphen BioMed)
Coamatic^{R} FVIII (Werfen)
TriniCHROM Factor VIII:C (Stago)

only global results; no data about the individual reagents

rFVIII A


study 1
study 2
SynthASil (Werfen)
data
data
APTT-SP (Werfen)
aPTT HS (Kordia)
STA^R-PTT Automate (Stago)
Pathrombin SL (Siemens)
data
data
data
STA^R-C.K. Prest^R (Stago)
STA^R-Cephascreen^R (Stago)
data
Actin (Siemens)
Actin FS (Siemens)
Actin FSL (Siemens)
data
data
FVIII chromogenic (Siemens)
Biophen FVIII:C (Hyphen BioMed)
Coamatic^R FVIII (Werfen)
TriniCHROM Factor VIII:C (Stago)
data
data
data
data

rFVIII A

	study 1	study 2	conclusions
SynthASil (Werfen)	data	data	can be used
APTT-SP (Werfen)		data	DONôT
aPTT HS (Kordia)		data	DONôT
STA^{R}-PTT Automate (Stago)			DONôT
Pathrombin SL (Siemens)		data	DONôT
STA^{R}-C.K. Prest^{R} (Stago)			likely
STA^{R}-Cephascreen^{R} (Stago)		data	é
Actin (Siemens)			é
Actin FS (Siemens)		data	é
Actin FSL (Siemens)		data	é
FVIII chromogenic (Siemens)		data	reference
Biophen FVIII:C (Hyphen BioMed)		data	é
Coamatic^{R} FVIII (Werfen)		data	é
TriniCHROM Factor VIII:C (Stago)		data	é

	N8 GP	Bay 94–9027	rFVIIIFc
Relevant references	29, 30, 31, 34	35	25, 28, 29
Chromogenic FVIII assay	Yes[a]	Yes[a]	Yes[a]
One-stage reagents			
STA-PTT A	No	No	Yes[b]
STA-C.K. Prest	Yes	?	Yes[b]
Actin FS	Yes	?	Yes[b]
Actin FSL	Yes	?	Yes[a]
Pathromtin SL	?	?	Yes[a]
SynthASil	?	?	Yes[a]
SynthAFax	No	Yes	?
DG Synth	Yes	?	?
Cephascreen	Yes	Yes	Yes[a]
APTT Sp	No	No	?

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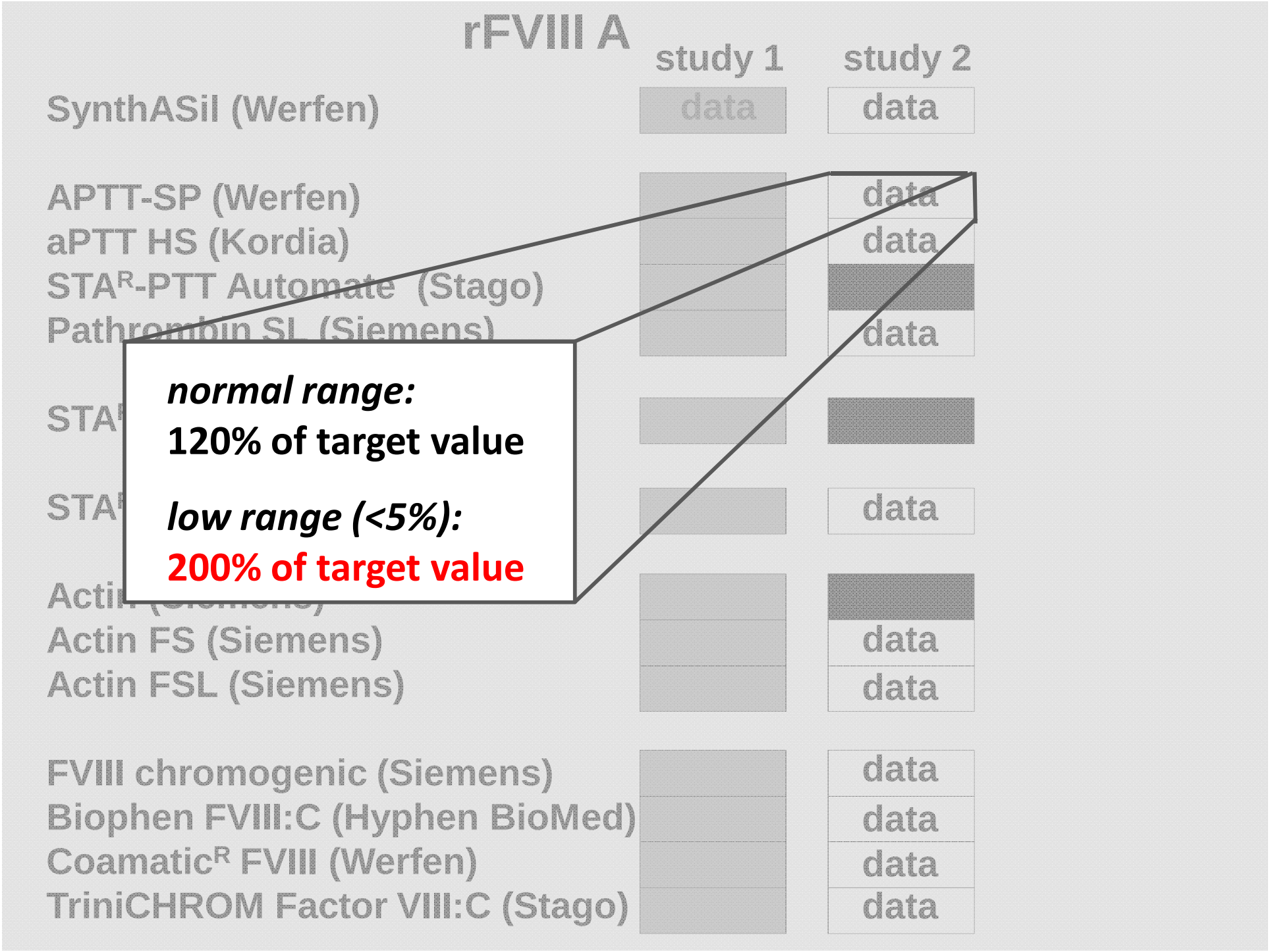
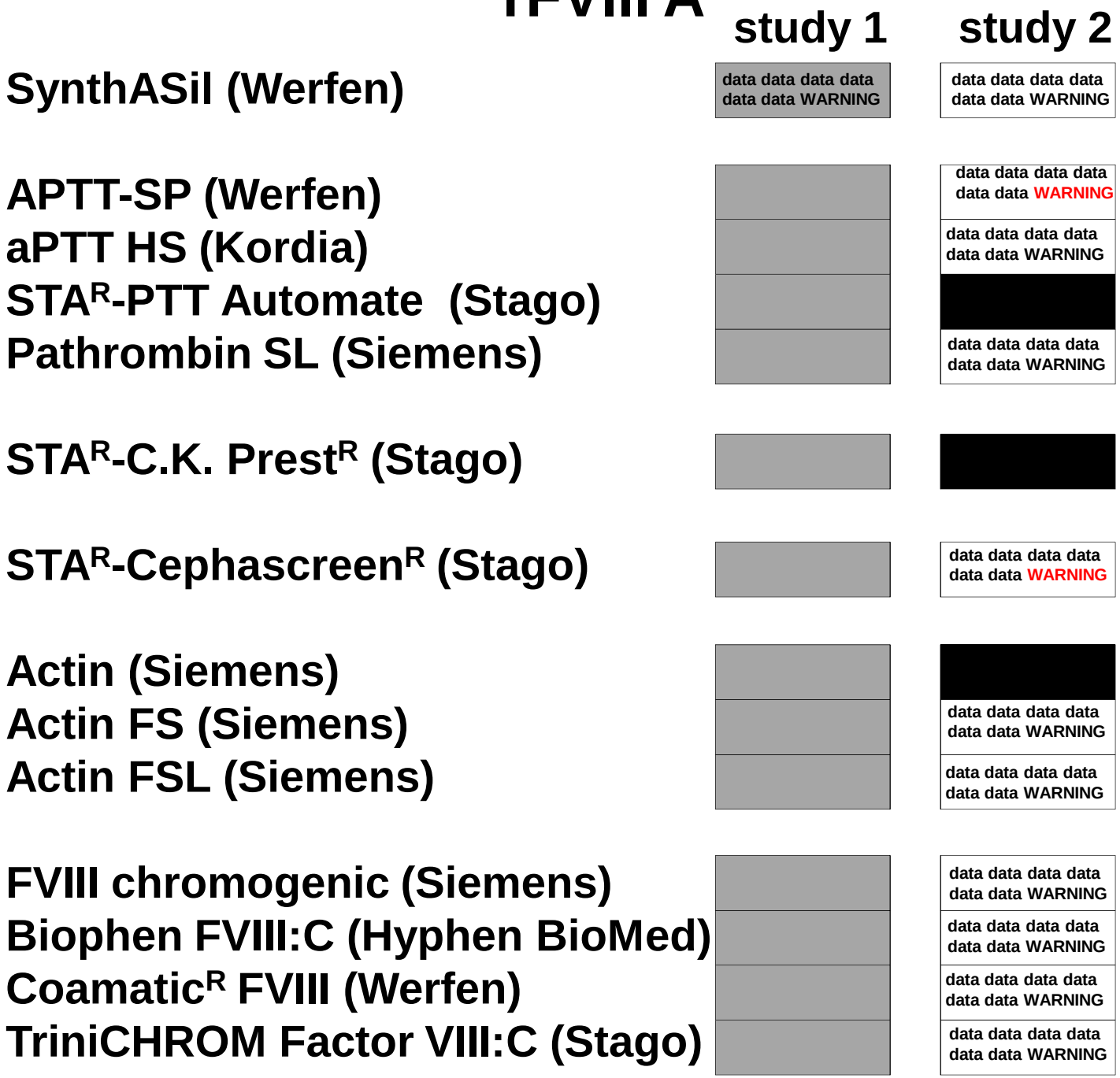
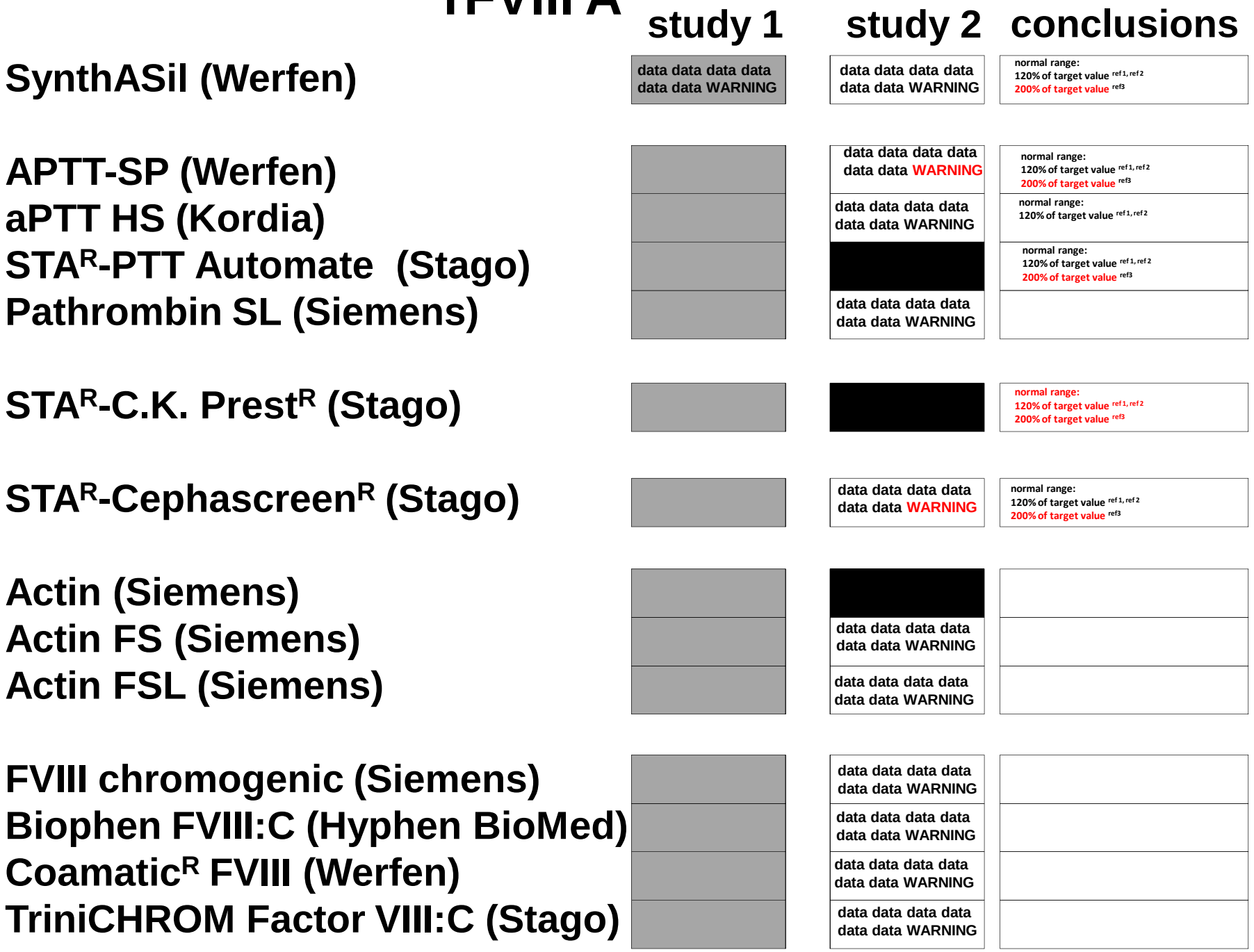
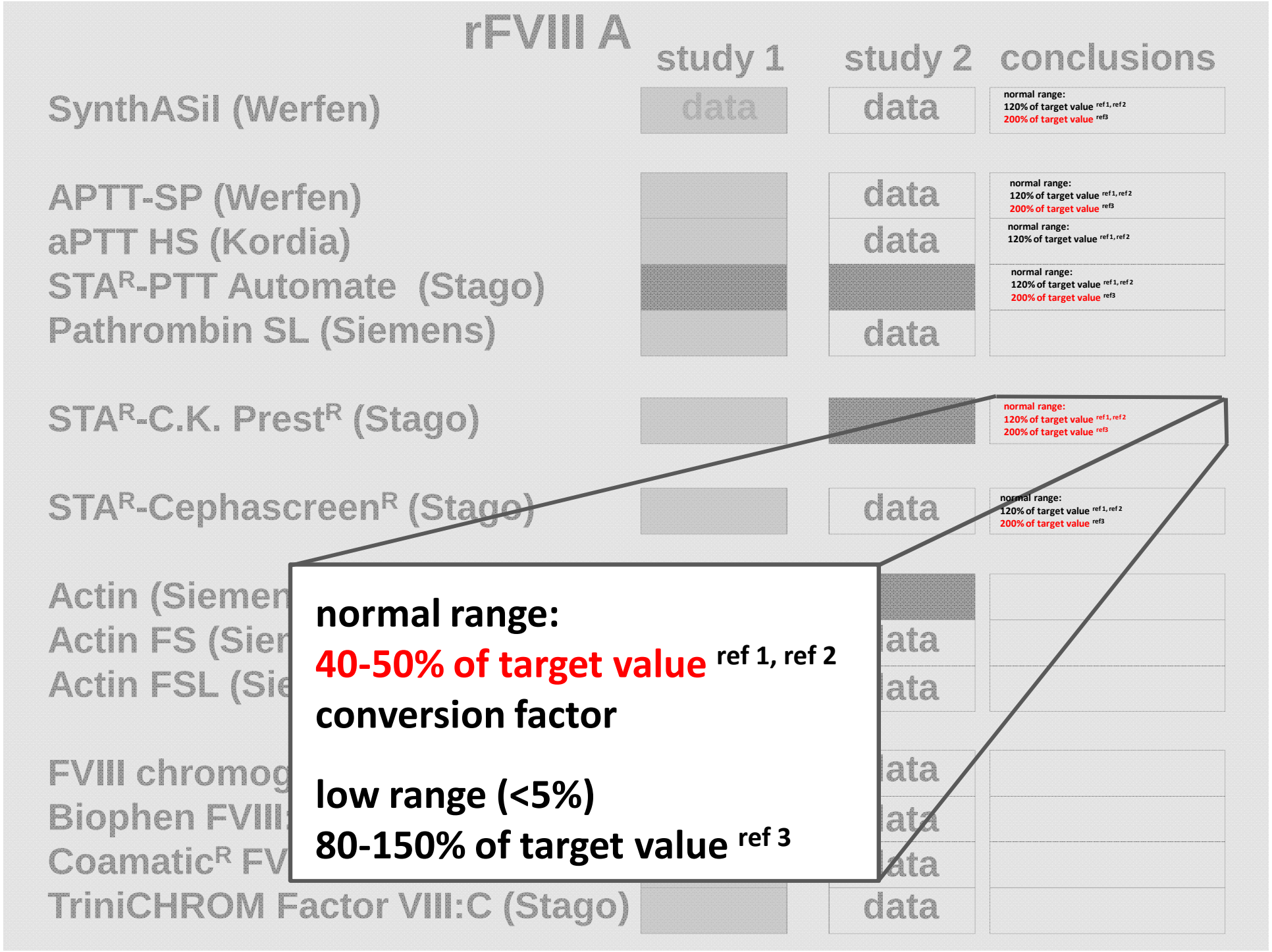

rFVIII A
study 1
study 2
SynthASil (Werfen)
data
data
APTT-SP (Werfen)
aPTT HS (Kordia)
STA^R-PTT Automate (Stago)
Pathrombin SL (Siemens)
data
data
data
normal range:
120% of target value
low range (<5%):
200% of target value
data
Actin FS (Siemens)
Actin FSL (Siemens)
data
data
FVIII chromogenic (Siemens)
Biophen FVIII:C (Hyphen BioMed)
Coamatic^R FVIII (Werfen)
TriniCHROM Factor VIII:C (Stago)
data
data
data
data

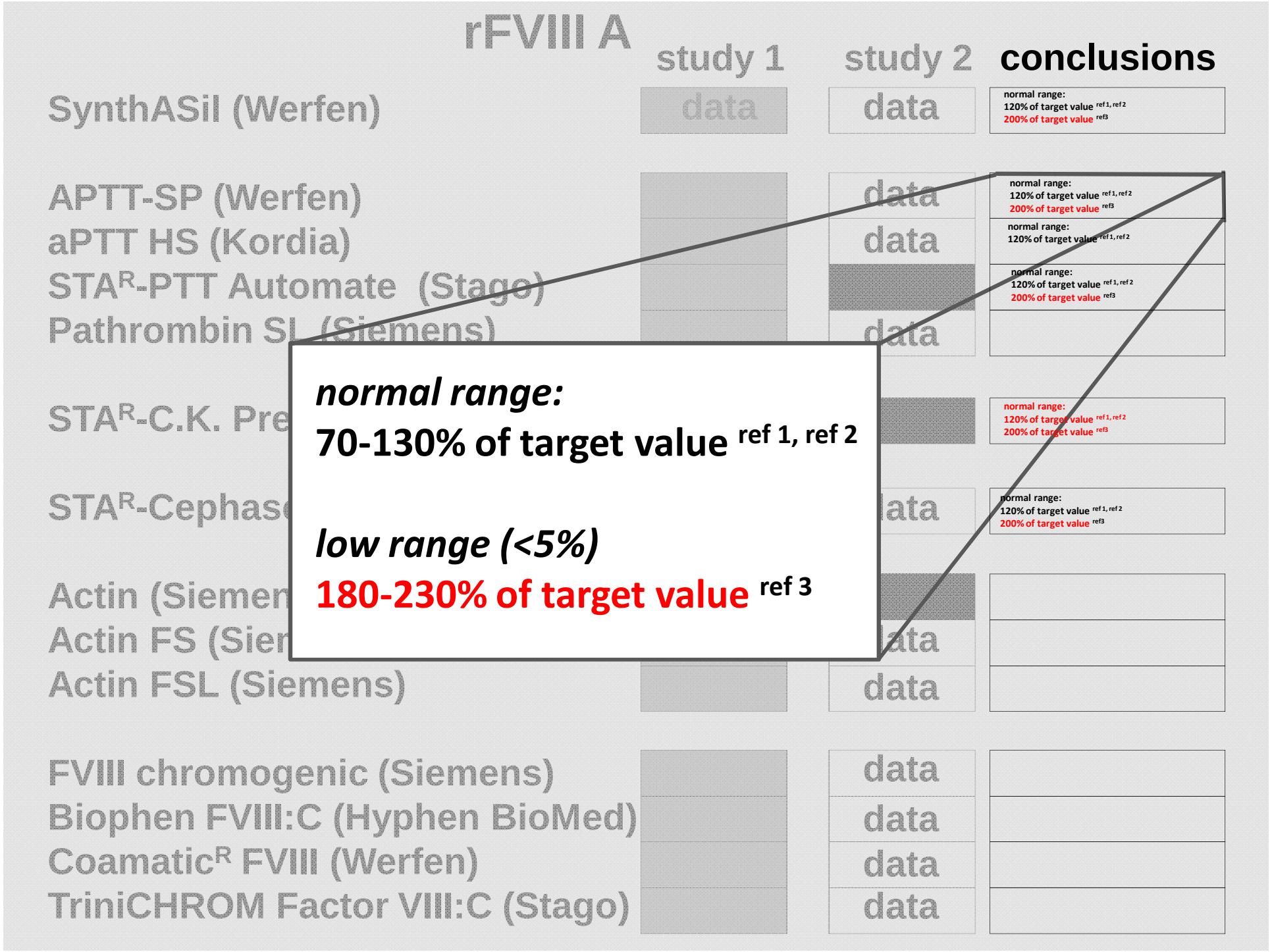
rFVIII A

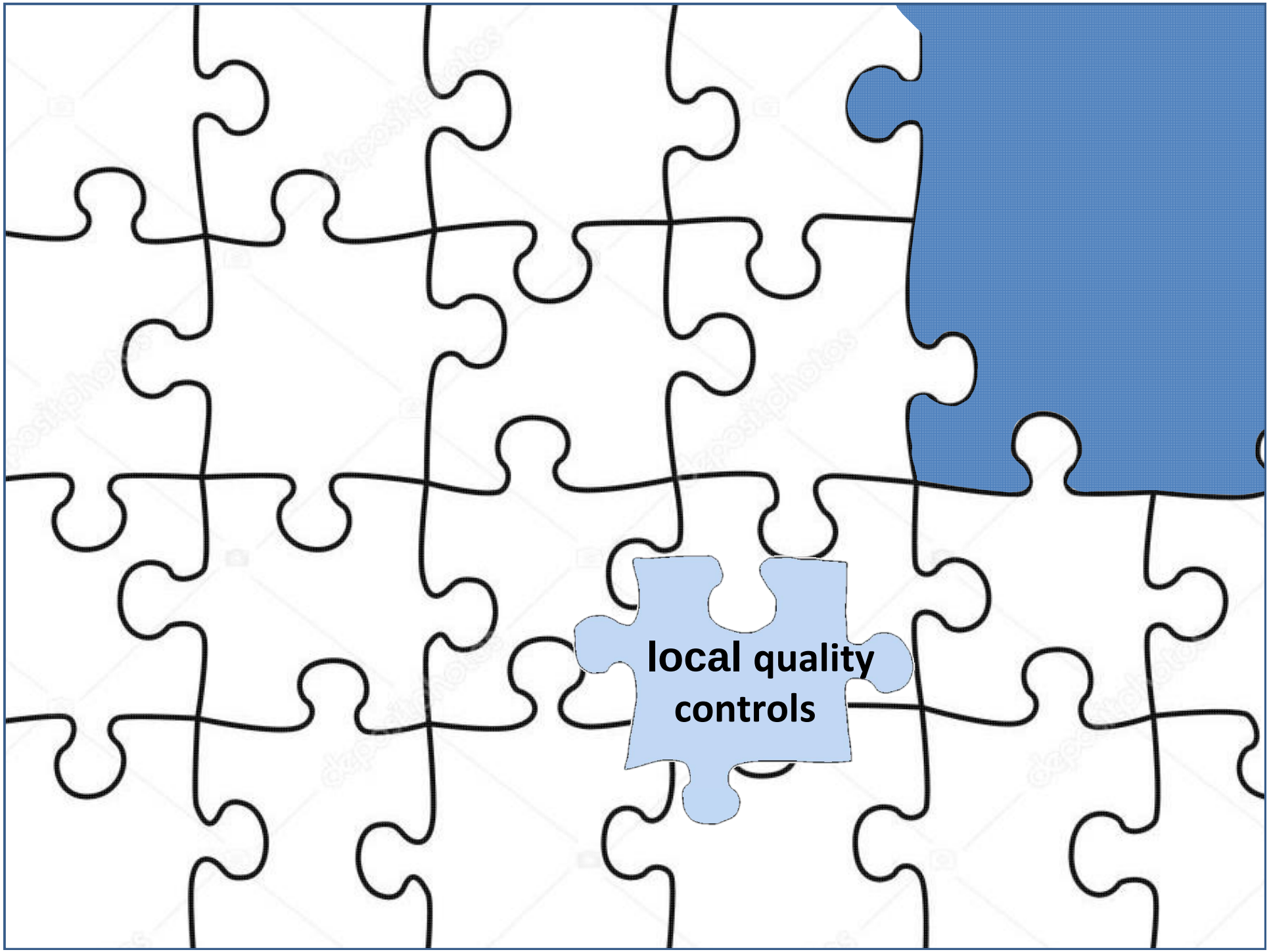

study 1
study 2
SynthASil (Werfen)
data data data data data data WARNING
data data data data data data WARNING
APTT-SP (Werfen)
aPTT HS (Kordia)
STA^R-PTT Automate (Stago)
Pathrombin SL (Siemens)
data data data data data data WARNING
data data data data data data WARNING
data data data data data data WARNING
STA^R-C.K. Prest^R (Stago)
STA^R-Cephascreen^R (Stago)
data data data data data data WARNING
Actin (Siemens)
Actin FS (Siemens)
Actin FSL (Siemens)
data data data data data data WARNING
data data data data data data WARNING
FVIII chromogenic (Siemens)
Biophen FVIII:C (Hyphen BioMed)
Coamatic^R FVIII (Werfen)
TriniCHROM Factor VIII:C (Stago)
data data data data data data WARNING
data data data data data data WARNING
data data data data data data WARNING
data data data data data data WARNING

rFVIII A


study 1
study 2
conclusions
SynthASil (Werfen)
data data data data data data WARNING
data data data data data data WARNING
normal range: 120% of target value ref 1, ref 2 200% of target value ref3
APTT-SP (Werfen)
aPTT HS (Kordia)
STA^R-PTT Automate (Stago)
Pathrombin SL (Siemens)
data data data data data data WARNING
data data data data data data WARNING
data data data data data data WARNING
normal range: 120% of target value ref 1, ref 2 200% of target value ref3
normal range: 120% of target value ref 1, ref 2
normal range: 120% of target value ref 1, ref 2 200% of target value ref3
STA^R-C.K. Prest^R (Stago)
normal range: 120% of target value ref 1, ref 2 200% of target value ref3
STA^R-Cephascreen^R (Stago)
data data data data data data WARNING
normal range: 120% of target value ref 1, ref 2 200% of target value ref3
Actin (Siemens)
Actin FS (Siemens)
Actin FSL (Siemens)
data data data data data data WARNING
data data data data data data WARNING
FVIII chromogenic (Siemens)
Biophen FVIII:C (Hyphen BioMed)
Coamatic^R FVIII (Werfen)
TriniCHROM Factor VIII:C (Stago)
data data data data data data WARNING
data data data data data data WARNING
data data data data data data WARNING
data data data data data data WARNING

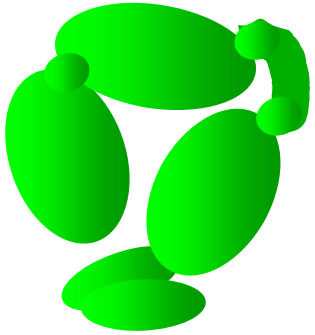

rFVIII A
study 1
study 2
conclusions
SynthASil (Werfen)
data
data
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
APTT-SP (Werfen)
data
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
aPTT HS (Kordia)
data
normal range:
120% of target value ref 1, ref 2
STA R -PTT Automate (Stago)
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
Pathrombin SL (Siemens)
data
STA R -C.K. Prest R (Stago)
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
STA R -Cephascreen R (Stago)
data
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
Actin (Siemen
Actin FS (Sier
Actin FSL (Sie
ata
ata
FVIII chromog
Biophen FVIII
Coamatic R FV
ata
ata
ata
TriniCHROM Factor VIII:C (Stago)
data
normal range:
40-50% of target value ref 1, ref 2
conversion factor
low range (<5%)
80-150% of target value ref 3


rFVIII A
study 1
study 2
conclusions
SynthASil (Werfen)
data
data
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
APTT-SP (Werfen)
aPTT HS (Kordia)
STA^R-PTT Automate (Stago)
Pathrombin SL (Siemens)
data
data
data
data
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
normal range:
120% of target value ref 1, ref 2
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
STA^R-C.K. Pre
STA^R-Cephase
Actin (Siemen
Actin FS (Sier
Actin FSL (Siemens)
data
data
data
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
normal range:
120% of target value ref 1, ref 2
200% of target value ref3
normal range:
70-130% of target value ref 1, ref 2
low range (<5%)
180-230% of target value ref 3
FVIII chromogenic (Siemens)
Biophen FVIII:C (Hyphen BioMed)
Coamatic^R FVIII (Werfen)
TriniCHROM Factor VIII:C (Stago)
data
data
data
data


local quality
controls

Spiked samples Afstyla (single chain rFVIII) provided by CSL-Behring

Target value		
90 U/dl	30 U/dl	9U/dl



Spiked samples Afstyla (single chain rFVIII) provided by CSL-Behring

	Target value		
	90 U/dl	30 U/dl	9U/dl
One stage assay (SynthAsil)	31 U/dl (40% of target)	13 U/dl	6U/dl (66% of target)

Spiked samples Afstyla (single chain rFVIII) provided by CSL-Behring

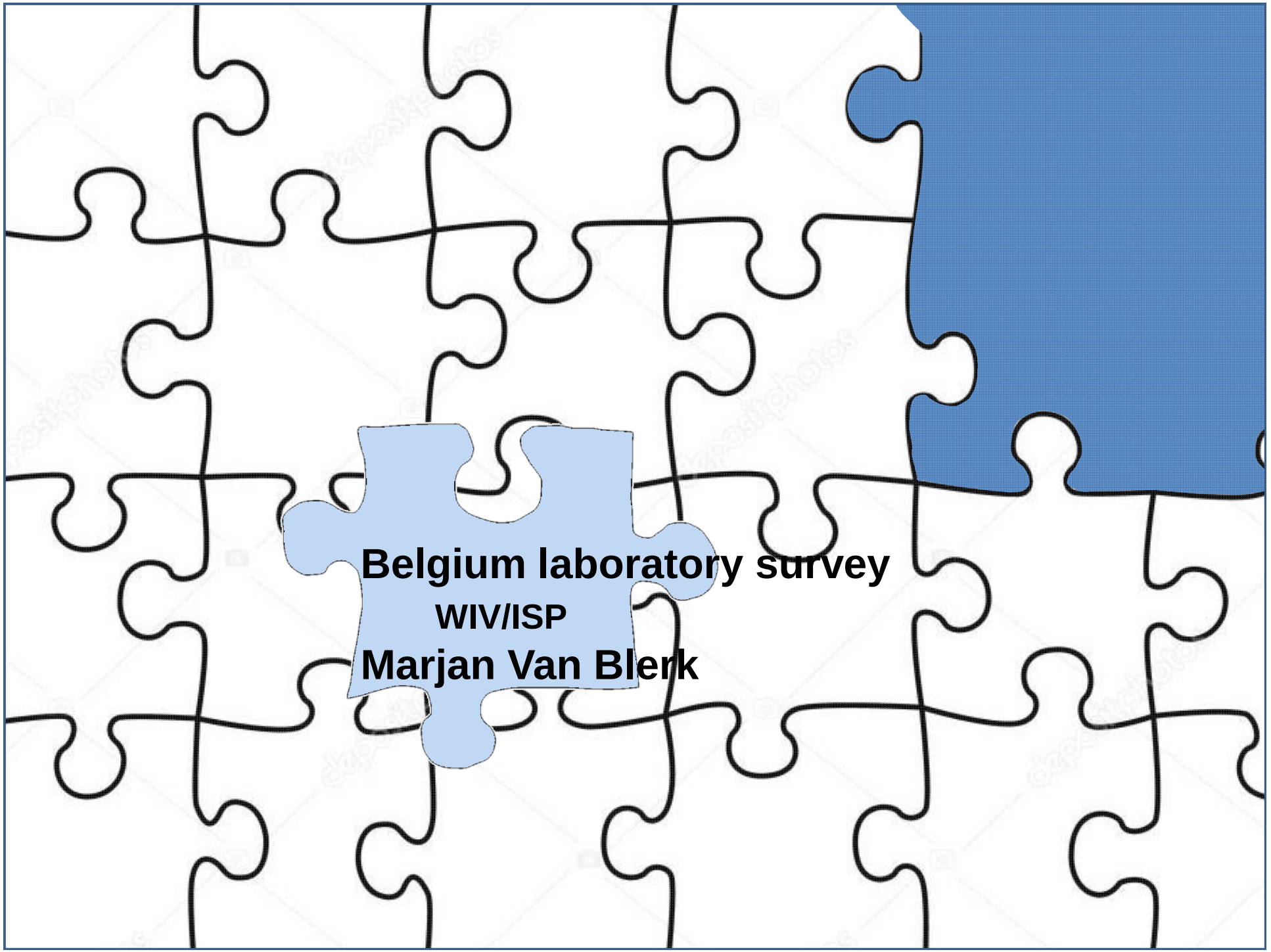
	Target value		
	90 U/dl	30 U/dl	9U/dl
One stage assay (SynthAsil)	31 U/dl (40% of target)	13 U/dl	6U/dl (66% of target)

with x2 correction factor

80% of target

Spiked samples Afstyla (single chain rFVIII) provided by CSL-Behring

	Target value		
	90 U/dl	30 U/dl	9U/dl
One stage assay (SynthAsil)	31 U/dl (40% of target)	13 U/dl	6U/dl (66% of target)
	with x2 correction factor		
	80% of target		
Chromogenic assay (Biophen FVIII)	82 U/dl	30 U/dl	<LOQ


Belgium laboratory survey
WIV/ISP
Marjan Van Blerk

plasma
after administration
of Elocta^{R}
(Fcγ-rFVIII;Sobi)

⇩

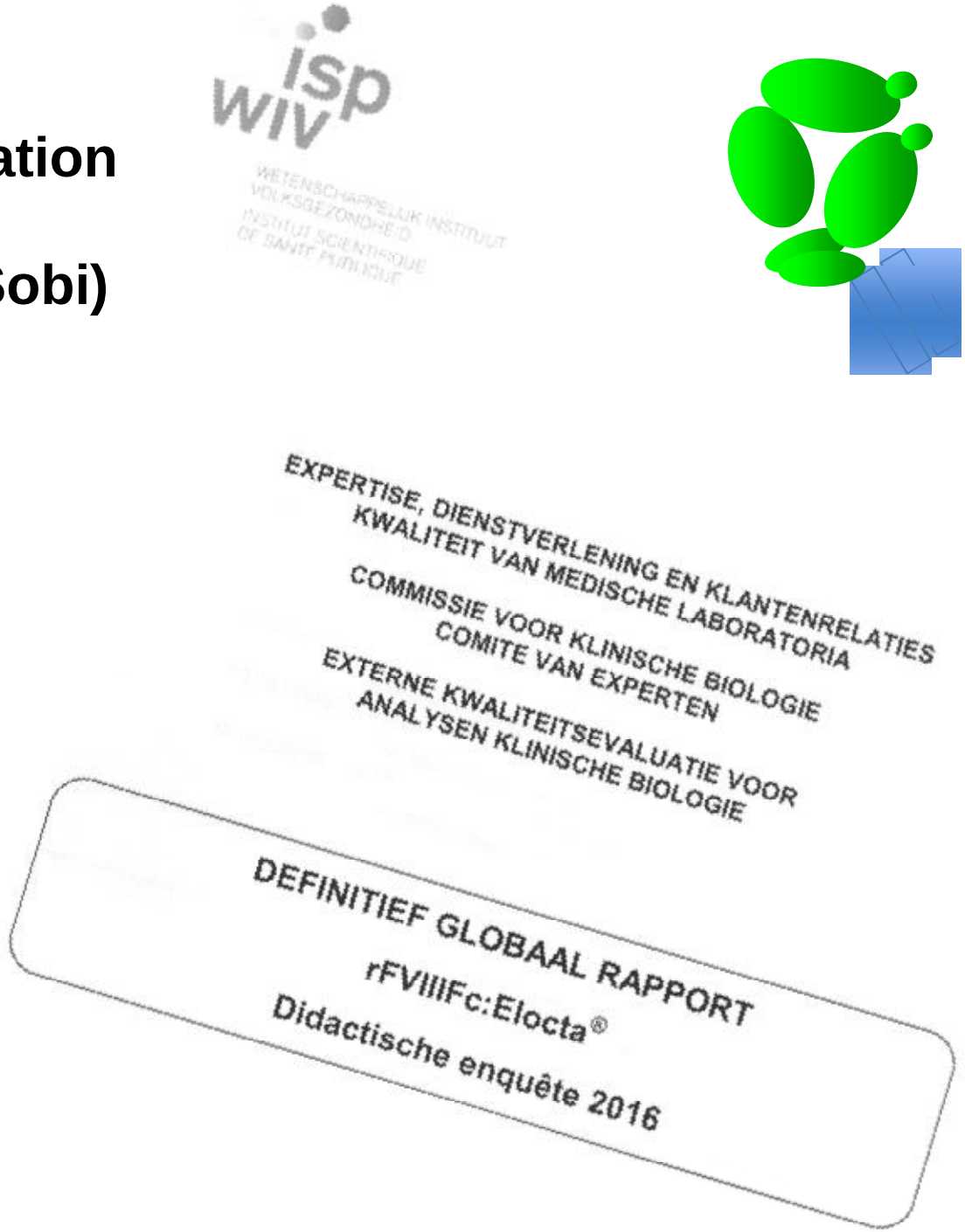
ISP/WIV

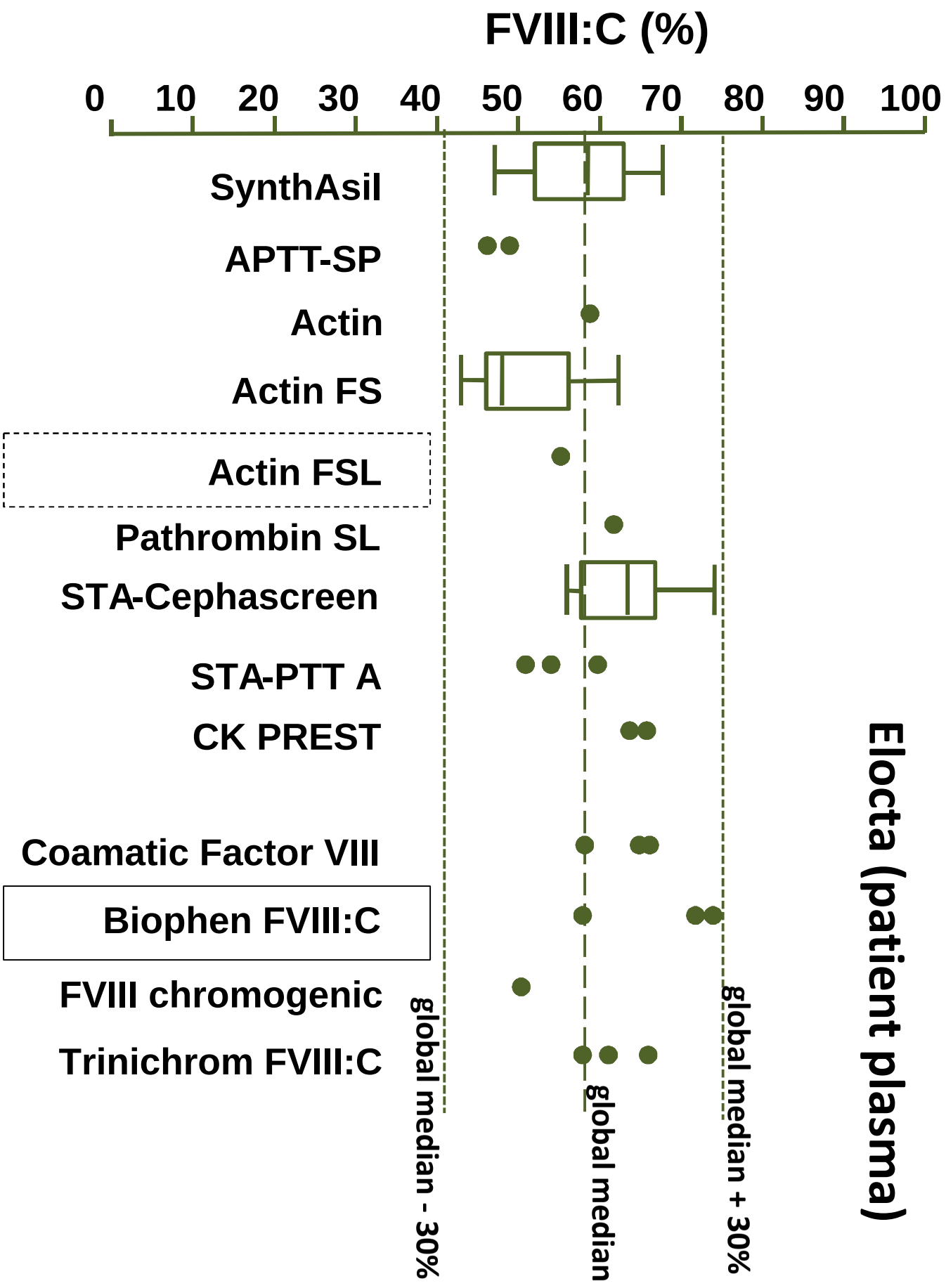
⇩

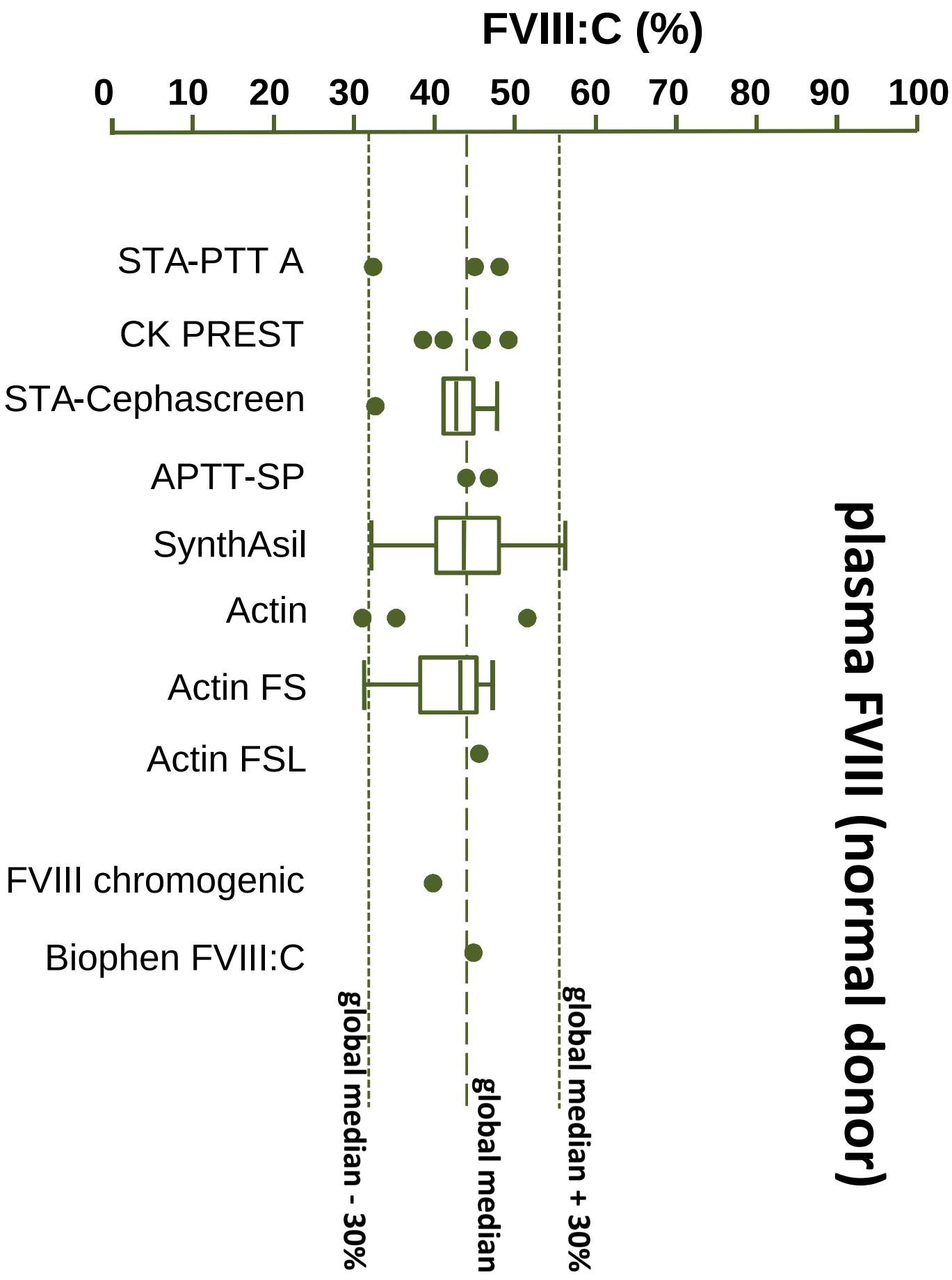
lyophilised

⇩

local labs




FVIII:C (%)
0
10
20
30
40
50
60
70
80
90
100
SynthASil
APTT-SP
Actin
Actin FS
Actin FSL
Pathrombin SL
STA-Cephascreen
STA-PTT A
CK PREST
Coamatic Factor VIII
Biophen FVIII:C
FVIII chromogenic
Trinichrom FVIII:C
global median - 30%
global median
global median + 30%
Elocta (patient plasma)


FVIII:C (%)
0
10
20
30
40
50
60
70
80
90
100
STA-PTT A
CK PREST
STA-Cephascreen
APTT-SP
SynthAsil
Actin
Actin FS
Actin FSL
FVIII chromogenic
Biophen FVIII:C
global median - 30%
global median
global median + 30%
plasma FVIII (normal donor)

Interaction with the clinicians

Interaction with the clinicians

- for which rFVIIIs can we garantee acceptable results (70-130% of the target value in the normal range)?
- for which rFVIIIS are we unable to give any result?
- accuracy in the low range?

Measurement of "long acting" rFVIII

	activator	**Afstyla** **ScrFVIII** **CSL-Behring**	**Adynovate** **8-Peg** **Shire**	**Elocta** **F8-Fc** **Sobi**	Bay 94-9027
SynthASil (Werfen)	colloidal silica	*Normal range:* **!!! 40% of target** [20,21] if multiply as recommended by a conversion factor of 2: 80% of target [20] *Low range (≤5%):* **!!! if multiply as recommended by a conversion factor of 2: 2-fold overestimatation** [20]	*Normal range:* 95-120% of target value[50] *Low range (≤5%):* 116-132% of target value[50] NB: not tested in [51]	*High range* Median: 101% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	can be used [10]
APTT-SP (Werfen)	silica	*Normal range:* **!!! 50% of target** [20] if multiply as recommended by a conversion factor of 2: 100% of target [20] *Low range (≤5%):* **!!! if multiply as recommended by a conversion factor of 2: 2-fold overestimatation** [20]	*Normal range:* 95-120% of target value[50] 97-160% of target value[51] but better with specific standard[51] *Low range (≤5%):* 116-132% of target value[50] **165-262% of target value[51]**	*High range* Median: 82% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	**10%** (bad 2d derivative)[11]

STA[R]-PTT Automate (Stago)	Silica°	-----	*Normal range:* 95-120% of target value[50] *Low range (≤5%):* 116-132% of target value[50] NB: not tested in [51]	*High range* Median: 93% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	<<< (bad 2d derivative)[11]
aPTT HS (Kordia)	micronisated silica		------	Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	
Pathrombin SL (Siemens)	Silica*	*Normal range:* **!!! 40% of target** [20] if multiply as recommended by a conversion factor of 2: 80% of target [20] *Low range (≤5%):* **!!! if multiply as recommended by a conversion factor of 2: 2-fold overestimatation** [20]	*Normal range:* 97-160% of target value[51] but better with specific standard[51] *Low range (≤5%):* **165-262% of target value[51]**	*High range* Median: 107% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	

STA[R]-C.K. Prest[R] (Stago)	kaolin		*Normal range:* 97-160% of target value[51] but better with specific standard[51] *Low range (≤5%):* **165-262% of target value[51]**	*High range* Median: 110% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	
STA[R]-Cephascreen[R] (STAGO)	polyphenols		*Normal range:* 95-120% of target value[50] *Low range (≤5%):* 116-132% of target value[50] NB: not tested in [51]	*High range* Median: 109% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	OK[11]
Actin (Siemens)	Ellagic acid		------	*High range* Median: 102% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	OK[11]
Actin FS (Siemens)	Ellagic acid		*Normal range:* 95-120% of target value[50] *Low range (≤5%):* 116-132% of target value[50] NB: not tested in [51]	*High range* Median: 83% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	

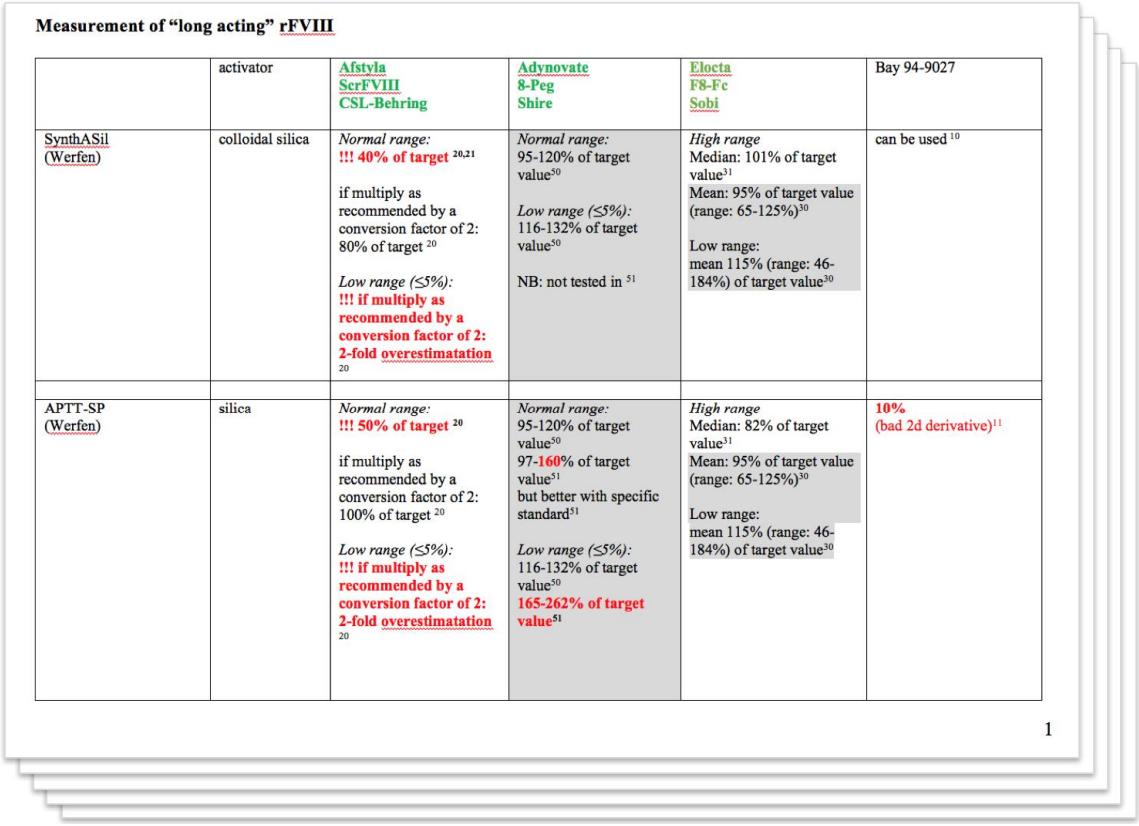
Actin FSL (Siemens)	Ellagic acid	*Normal range:* **!!! 60% of target** [20] if multiply as recommended by a conversion factor of 2: 120% of target [20] *Low range (≤5%):* **!!! if multiply as recommended by a conversion factor of 2: 2-fold overestimatation** [20]	*Normal range:* 95-120% of target value[50] 97-160% of target value[51] but better with specific standard[51] *Low range (≤5%):* 116-132% of target value[50] **165-262% of target value[51]**	Reference assay *High range* Median: 96% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	
SynthAFax (Werfen)	Ellagic acid	*Normal range:* **!!! 60% of target** [20] if multiply as recommended by a conversion factor of 2: 120% of target [20] *Low range (≤5%):* **!!! if multiply as recommended by a conversion factor of 2: 2-fold overestimatation** [20]		*High range* Median: 110% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	OK[11]

FVIII chromogenic (Siemens)			*Normal range:* 115-133% of target value[50] 144-**221**% of target value[51] but better with specific standard[51] *Low range (≤5%):* 76-120% of target value[50] **Up to 289% of target value[51]** But better with specific standard[51]	*High range* Median: 86% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	
Biophen FVIII:C (Hyphen BioMed)		*Normal range:* 100% of target [21] *Low range:* No data	*Normal range:* 115-133% of target value[50] 144-**221**% of target value[51] but better with specific standard[51] *Low range (≤5%):* 76-120% of target value[50] **Up to 289% of target value[51]** But better with specific standard[51]	*Reference assay* *High range* Median: 112% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	

Coamatic® FVIII (Chromogenix; Werfen)		Reference assay[22]	*Normal range:* 115-133% of target value[50] *Low range (≤5%):* 76-120% of target value[50] NB: not tested in [51]	*High range* Median: 112 of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	
Coatest® SP (Werfen)			------		
Trinichrom Factor VIII:C (nom à verifier) (Stago)				*High range* Median: 105% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	
Technochrom® FVIII:C (Technoclone) nom à vérifier				Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	
DG-Chrom FVIII (Grifols					

updated summary tables available at

ñmarc.jacquemin@kuleuven.beò



Measurement of "long acting" rFVIII

	activator	Afstyla ScrFVIII CSL-Behring	Adynovate 8-Peg Shire	Elocta F8-Fc Sobi	Bay 94-9027
SynthASil (Werfen)	colloidal silica	*Normal range:* **!!! 40% of target** [20,21] if multiply as recommended by a conversion factor of 2: 80% of target [20] *Low range (≤5%):* **!!! if multiply as recommended by a conversion factor of 2: 2-fold overestimatation** [20]	*Normal range:* 95-120% of target value[50] *Low range (≤5%):* 116-132% of target value[50] NB: not tested in [51]	*High range* Median: 101% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	can be used [10]
APTT-SP (Werfen)	silica	*Normal range:* **!!! 50% of target** [20] if multiply as recommended by a conversion factor of 2: 100% of target [20] *Low range (≤5%):* **!!! if multiply as recommended by a conversion factor of 2: 2-fold overestimatation** [20]	*Normal range:* 95-120% of target value[50] 97-160% of target value[51] but better with specific standard[51] *Low range (≤5%):* 116-132% of target value[50] **165-262% of target value[51]**	*High range* Median: 82% of target value[31] Mean: 95% of target value (range: 65-125%)[30] Low range: mean 115% (range: 46-184%) of target value[30]	**10%** (bad 2d derivative)[11]

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Conclusions

- ñreference assayò: potency of the rFVIII concentrate
- òacceptable assayò: ± 30% of the target value
- in the ñnormal rangeò (50-150%):
  severe biases with SOME rFVIIIs/reagents combinations
- in the ñlow rangeò (through level):
  difficult to avoid important overestimation

Conclusions

- **quality controls for rFVIIIs should be available**

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