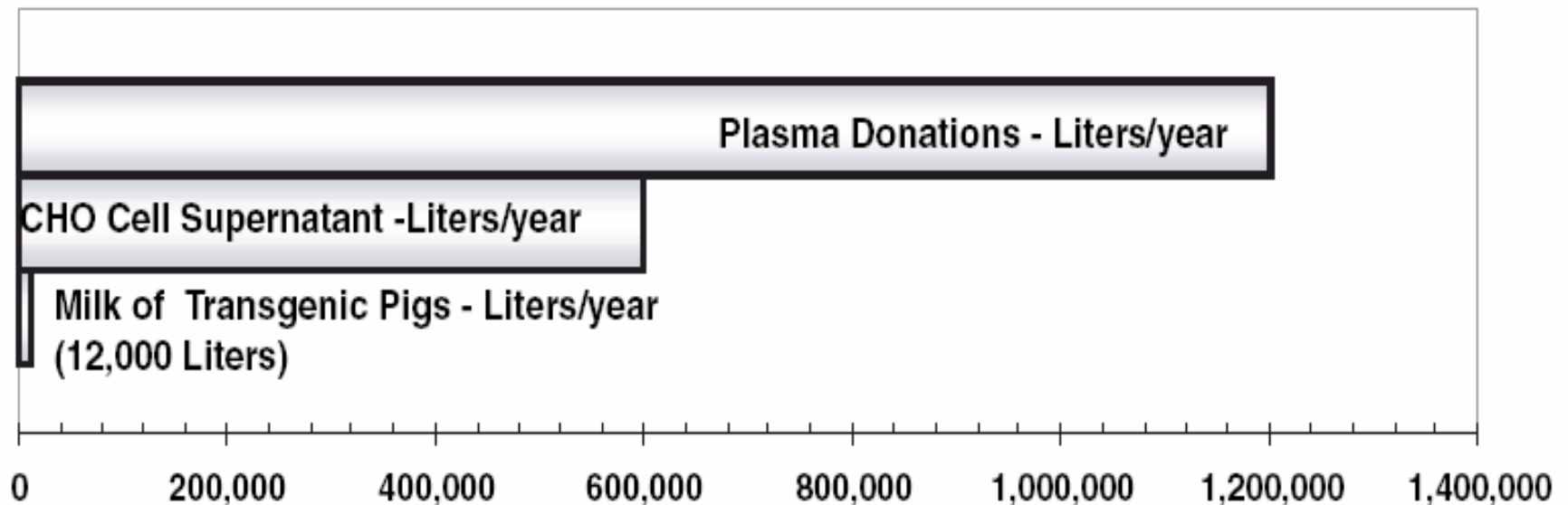


Trends in the plasma-derived and recombinant markets Regulator's perspective

A Farrugia
Head, Blood and Tissues Unit
Australian Therapeutic Goods
Administration

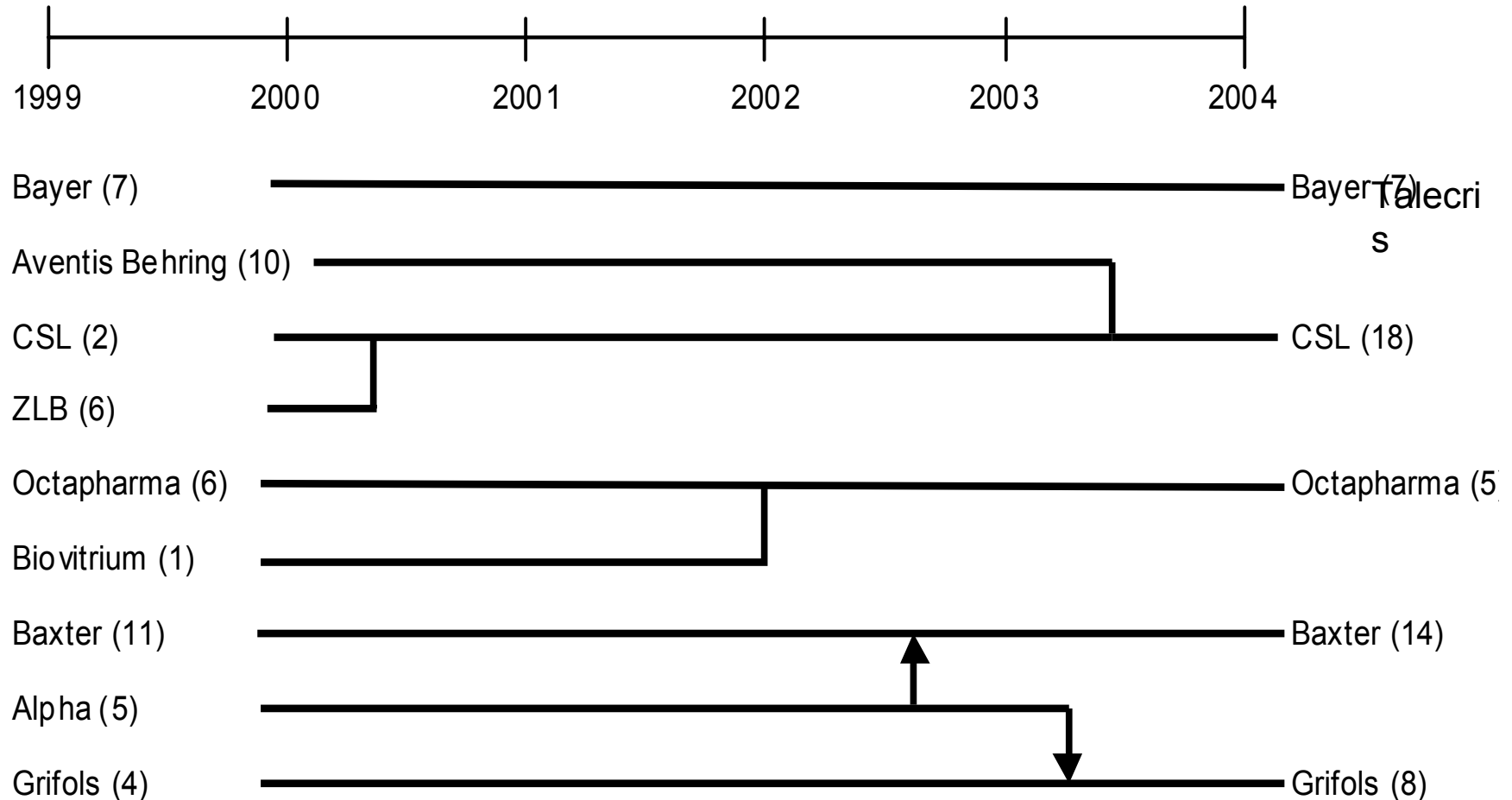
Volumes of source materials for FIX required to meet the needs for prophylactic therapy of all haemophilia B patients in the US



Van Cott et al Haemophilia (2004), 10, (Suppl. 4), 70–76

PLASMA FRACTIONATORS- MERGERS AND ACQUISITIONS, 1999-2004

Percent share of world capacity indicated in parentheses



Dangers of the shrinking plasma industry

- **Insufficiency**

- **No single manufacturer can generate sufficiency of all products**
- **Niche products cannot be manufactured economically**

- **Risk of poor quality**

- **Quality failures lead to inadequate therapy**
- **No access to new technology**
- **Regulators have difficulty in acquiring traction**

Plasma and recombinant products

Similarities

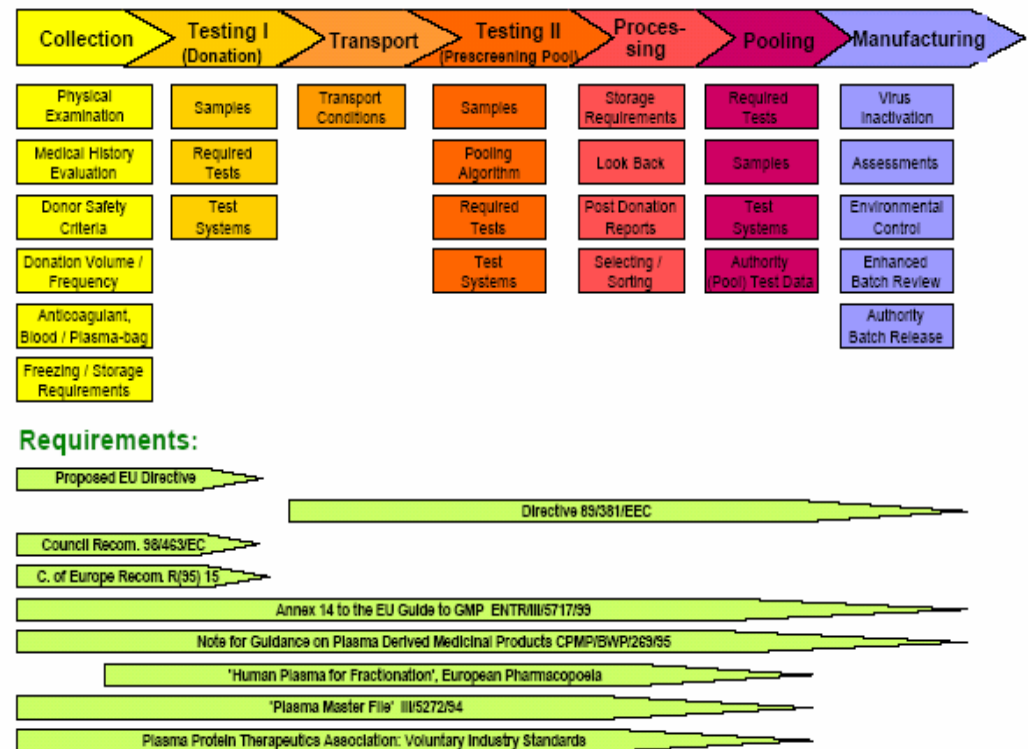
- Pharmaceutical manufacture
- End product QC, GMP
- Biological source – pathogen issues

Differences

- Source material
- Manufacturing issues – recombinants are more standardised
- Characterisation issues – recombinants are easier specified

Product Regulation

- Heavily regulated environment
- Dominated by
 - FDA in North America
 - EMEA in Europe
- Influenced by
 - Public/political pressure
 - Industry competition



Regulation of Haemophilia concentrates

- As a general principle, all regulatory authorities strive to assure that products demonstrate:
 - Safety
 - Quality
 - Efficacy
- This is generally addressed through:
 - Facility Licensure (GMP)
 - Pre-Market Product assessment
 - Post-Market surveillance
- In general, these principles are similar for plasma and recombinant products

Assuring quality, safety & efficacy

- Establishment and maintenance of a (national) system of licensing and control, including
 - Facility and product registration
 - Inspection and enforcement
 - Where appropriate, arrangements for sampling and analysis
- Provision of appropriate (national) standards and guidelines, against which licensing and control may be seen to happen
- Require licence holders to adopt and implement quality systems appropriate to the products being supplied
- Provision of competent and consistent arrangements for post-marketing surveillance of products

Factors contributing to product safety and quality

- The assurance of product quality is multifactorial:
 - Controlling the quality of plasma for fractionation
 - Use of a robust, validated, process incorporating virus elimination and/or inactivation
 - Application of appropriate tests to raw materials, to in-process samples (and, perhaps, to samples of finished product)
 - Implementation of effective quality systems and adherence to the principles of current good manufacturing practice (cGMP) at the active ingredient manufacturer and by the final manufacturer
- Internal, as well as control agency audit, ensures the effectiveness of all of the above
- Deficiencies in any of the above compromise quality

Common strengths of US & EU regulatory provision

- Review of data in marketing authorisation application:
 - Commitments on plasma source - “plasma master file”
 - Process/batch consistency including effectiveness of VI/VE steps
 - Review data on safety & efficacy and of pharmacokinetics
- Inspection & enforcement in respect of:
 - Plasma donor base, collection facilities and quality systems
 - Manufacturing facility, process and quality systems
- Control agency batch review & release
 - Batch specific review of protocols and testing of samples
 - Availability of trend information on batch performance over time
- Post-marketing surveillance – mandatory follow-up

Regulation of haemophilia concentrates

Products of large-scale plasma fractionation

- Produced in large batches from a homogeneous pool of starting material, through well-defined processes subject to standard pharmaceutical quality control.
- Biologic drugs such as factor concentrates cannot be considered as generic agents, and each manufacturing process requires individual assessment with full product specification.
- General properties leading to quality and safety may be reflected in standards of the pharmacopoeia.
- But range of approaches to the manufacture of FVIII and factor IX (FIX) concentrates results in significant differences between products.
- This necessitates thorough evaluation for the potential effect of the process on the factors of interest and the impurities in the products.

Facility licensure

- Done through reference to codes of good manufacturing practice (GMP) –
 - generic documents specifying quality standards for manufacture
 - common to all medicinal products.
- GMP seeks to ensure that manufacture is consistently carried out to high standards ensuring product safety, quality, and consistency.
- Inspections may identify deficiencies - regulator and manufacturer collaborate to ensure the issue of a manufacturing license, indicating production to a high standard.
- Recently, the Pharmaceutical Inspectorate Convention has adopted a GMP for medicinal products that includes a chapter specifically addressing plasma-derived products .

Principles of good manufacturing practice for plasma fractionation agencies

(Pharmaceutical Inspectors Convention Scheme 2003)

- Quality management
- Premises and equipment
- Blood and plasma collection
- Traceability and post collection measures
- Production and quality control
- Retention of samples
- Disposal of rejected blood, plasma or intermediates

RECOMBINANT COAGULATION FACTORS RELEVANT CONSIDERATIONS

- **Ensure structure as similar as necessary to the natural substance:**
 - **structure and conformation**
 - **posttranslational changes:**
 - **glykosylation**
 - **phosphorylation**
 - **Gla-residues**
- **Avoid during expression and purification:**
 - **alteration of biologic function**
 - **activation**
 - **enhanced antigenicity**
 - **neo-antigens**
 - **host cell impurities**

Note for guidance on production and quality control of medicinal products derived by recombinant technology III/3477/92, rev. 1994

- **Development genetics**
 - **Gene construct, vector, host cell**
 - **expression and genetic stability**
- **Control of cell banks**
- **Fermentation**
- **Purification**
- **Active ingredient, characterization**
 - **physico-chemical, structure, conformation**
- **Active ingredient, characterization**
 - **posttranslational modification**
 - **biological function**
 - **purity**
- **Consistency of production**
- **Specifications, reference materials**
- **Finished Product and development pharmaceuticals**

CPMP/ICH/295/95:

Note for guidance on quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin.

October 1997

Virus tests performed at various cell levels:

A. Tests for retroviruses or endogenous viruses

	MCB	WCB	EOP
Infectivity	+	-	+
ELMI	+	-	+
other virus-specific tests	as appropriate		

B. Tests for non-endogenous or adventitious viruses

<i>in-vitro</i> assays	+	(+)	+
<i>in-vivo</i> assays	+	(+)	+
MAP, RAB, HAP	+	-	-
other virus-specific tests	+	-	-

Product assessment

European routes

- Centralised Procedure
 - mandatory for high technology products eg McAb purified concentrates, recombinant concentrates
 - may be used for other plasma products
- Mutual Recognition Procedure
 - may be used for acquiring authorisation for “older” technology products
- National Procedure
 - authorisation in single country

Trends in approvals for Plasma Protein Products (Germany)

Centralised procedures

~ 10 Products

MRP

~ 5 Immunoglobulins
~ 15 Clotting factors

National approvals

~ 40 Immunoglobulins
~ 50 Factor VIII
~ 80 other Clotting factors
~ 45 Albumin and S/D Plasma
(~4000 cellul. products/FFP)

Clinical trial requirements with new FVIII products - EMEA

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
12 haemophilia A patients (factor VIII $\leq 1\%$) without inhibitors and not actively bleeding.	1. Pharmacokinetics 2. Safety	Incremental recovery, half-life, AUC, clearance and mean residence time. Patients should be re-tested after 3-6 months. Blood pressure, heart rate, temperature, respiratory rate and adverse events.
5 haemophilia A patients undergoing at least 10 surgical procedures.	1. Clinical efficacy 2. Safety	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor VIII consumption. Adverse events.
PTP study 50 PTPs (>12 years) (factor VIII $\leq 2\%$ and CD4 $>400/\mu\text{L}$).	1. Clinical efficacy 2. Immunogenicity 3. Safety	Factor VIII consumption, physician's assessment of response in treatment of major bleeds. Inhibitor titre in Bethesda Units, using the modified assay, at baseline and every 3 months, at least 50 exposure days or 6 months' treatment. Adverse events.
Treatment of PUPs.	All treatment of PUPs should be documented.	
Open multicentre trial in 20 children with haemophilia A (<6 years) to be started after results of 50 exposures in 20 PTPs (>12 years) have become available.	1. Clinical efficacy 2. Immunogenicity 3. Safety	Factor VIII consumption, physician's assessment of response in treatment of major bleeds. Inhibitor testing every 3 months or if there is any suspicion of inhibitor development. Continue until at least 50 exposure days or 6 months' treatment. Adverse events
Post-marketing study.	1. Clinical efficacy 2. Immunogenicity 3. Safety	Protocol should be provided.

← PD

Rec →

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
12 haemophilia A patients (factor VIII $\leq 1\%$) without inhibitors and not actively bleeding.	1. Pharmacokinetics 2. Safety	Incremental recovery, half-life, AUC, clearance and mean residence time. Patients should be re-tested after 3-6 months. Blood pressure, heart rate, temperature, respiratory rate and adverse events.
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Post-marketing study.	1. Clinical efficacy 2. Immunogenicity 3. Safety	Protocol should be provided.

Clinical trial requirements for modified FVIII products - EMEA

PD

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
12 haemophilia A patients (factor VIII $\leq 1\%$) without inhibitors and not actively bleeding.	1. Pharmacokinetics 2. Safety	Comparative trial: incremental recovery, half-life, AUC, clearance and mean residence time. Patients should be tested again after 3-6 months. Blood pressure, heart rate, temperature, respiratory rate and adverse events..
Any haemophilia A patients undergoing surgical procedures.	1. Clinical efficacy 2. Safety	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor VIII consumption. Adverse events.
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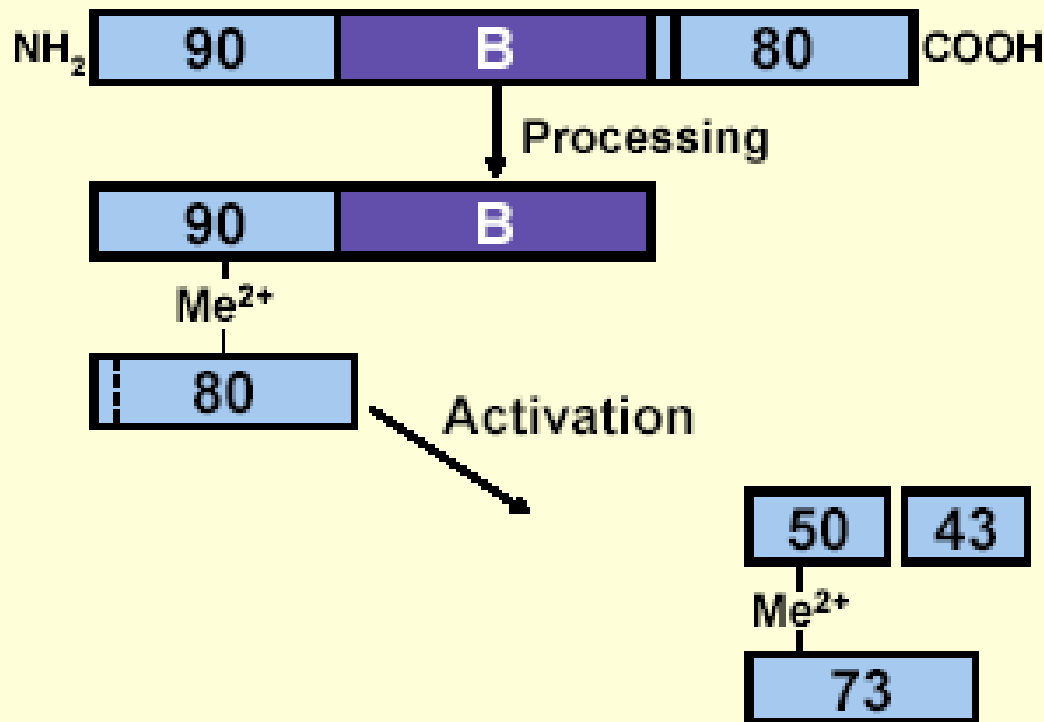
Plasma and recombinant haemophilia products

Some different features of the EU and FDA approaches

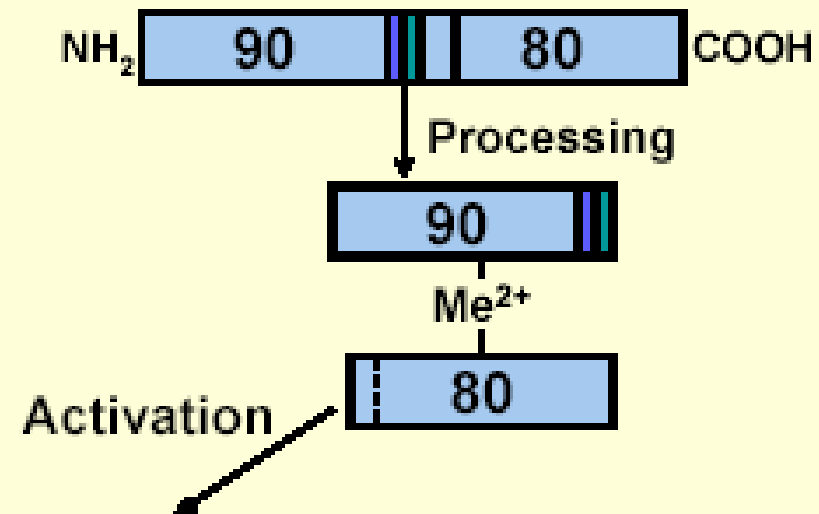
- FDA classifies recombinant products as “well-characterised proteins” justifying a lighter regulatory touch eg single BLA license, no BR.
 - ? Justified in light of eg Refacto problems
- EMEA requires recombinant products to go through the centralised procedure – higher level of evaluation through expert rapporteur.
- Plasma concentrates in EU mostly go through MRA route; requires member countries to accept each other’s decisions/review.
 - ? Incongruous in terms of risk profile

Molecular structure of rFVIIIs

Full Length FVIII



ReFacto



Comparative effectiveness of full-length and B-domain deleted factor VIII for prophylaxis – a meta-analysis

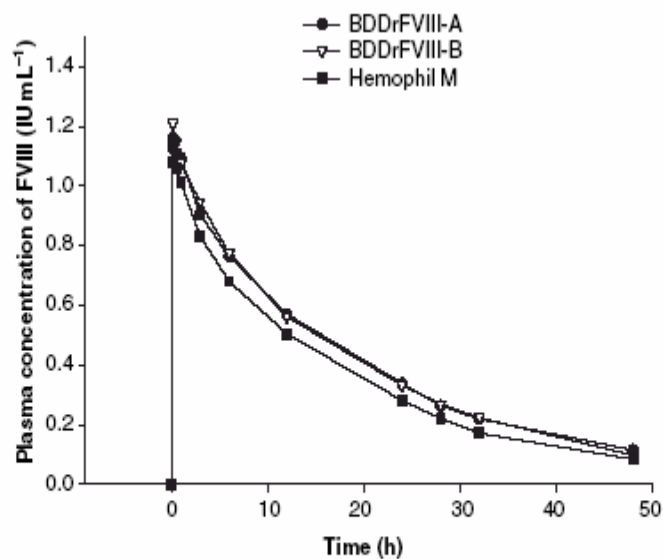
R. A. GRUPPO,* D. BROWN,† M. M. WILKES‡ and R. J. NAVICKIS‡

*The Division of Hematology/Oncology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; †The Department of Hematology/Oncology, Children's Memorial Hospital, Chicago, IL, USA; and ‡Hygeia Associates, Grass Valley, CA, USA

*The pooled cumulative weekly prophylactic dose of BDD-rFVIII (81.3 ± 13.8 IU/ kg)/week) was greater by 36% ($P = 0.11$) than that of FL-FVIII (60.0 ± 5.9 IU/ kg)/week . **The pooled incidence of bleeding in BDD-rFVIII recipients [16.8 bleeds per patient year; confidence interval (CI), 9.5–24.2 bleeds per patient year] was more than 2.5-fold larger ($P < 0.0005$) than that in patients receiving FL-FVIII (6.6 bleeds per patient year; CI, 4.7.... 8.5 bleeds per patient year). In a multivariate analysis, the incidence rate ratio was 2.10 (CI, 1.98.... 2.24), indicating that breakthrough bleeding under prophylaxis was more than twice as likely with BDD-rFVIII than FL-FVIII at half-life for BDD-rFVIII (11.3 h; CI, 9.9.... 12.7 h) was shorter by approximately 3 h compared with FL-FVIII. Although the results of the meta-analysis need to be interpreted with caution, the pooled data suggest that breakthrough bleeding under prophylaxis may occur more frequently in patients receiving BDD-rFVIII than FL-FVIII and may at least partly reflect a more abbreviated half-life of BDD-rFVIII.***

B-domain deleted recombinant factor VIII preparations are bioequivalent to a monoclonal antibody purified plasma-derived factor VIII concentrate: a randomized, three-way crossover study

C. M. KESSLER,* J. C. GILL,† G. C. WHITE II,‡ A. SHAPIRO,§ S. ARKIN,¶¹ D. A. ROTH,** X. MENG†† and J. M. LUSHER‡‡



“While PK data remain the most important surrogate endpoints for clinical efficacy, direct assessment of intraindividual variability should be considered when comparing the efficacy of different FVIII products.”

Fig. 1. Mean plasma concentration of factor VIII vs. time profiles of BDDrFVIII-A, BDDrFVIII-B, and Hemophil M ($n = 18$) after injection of 50 IU kg⁻¹.



Letter (1)Ten lots of ultrafiltered clarified tissue culture fluid (UFTCF) material that exceeded the bioburden limit of not more than [DELETED] were released for further processing without determining an assignable cause for the increased microbial load.....Investigations into microbial excursion results for the water for injection (WFI loops in the [DELETED] facility buildings [DELETED]are incomplete in that there is no documentation of the recommendations for further investigations, corrective actions, and follow-up..... Failure to clean, maintain, and sanitize equipment and utensils at appropriate to prevent malfunctions or contamination that would alter the safety, strength, quality, or purity of the drug product [21 CFR 21 1.67(a)] used for the production for injection, is not monitored for steam quality. Steam produced by to sterilize the transfer line and bulk tanks immediately prior to filling tank.

**Does product-type
influence
inhibitor-risk?**

Cumulative Risk of Inhibitors with multiple pdVIII and single pdVIII and rVIII products

• Schwartzinger	multiple pdVIII	62	25%
• Rasi	multiple pdVIII	60	22%
• Ehrenforth	multiple pdVII	63	33%
• Lorenzo	multiple pdVIII	57	20%
• Addiego	multiple pdVIII	89	28%
• Peerlink	single pdVIII	67	7%
• Guerois	single pdVIII	56	12.4%
• Schimpf	single pdVIII	22	0%
• Yee	single pdVIII	37	2.7%
• Lusher	single rVIII	95	24.8%
• Bray	single rVIII	79	38.4%
• Rothschild	single rVIII	50	38.7

Wight & Paisley Haemophilia 9, 418-352003,

Hay 2005

Effect of treatment on FVIII inhibitor incidence

French PUPs treated with a single FVIII product (1986-2002)

N = 149 PUPs	Median ED
n = 63 pdFVIII with vWF (FVIII-LFB™)	120
n = 86 rFVIII (n = 62 Recombinate; n = 24 Kogenate)	86

**Cumulative incidence of inhibitor at 100 CED:
rFVIII 36% and pdFVIII 10%**
Univariate analysis $p < 0.005$
Multivariate analysis $p < 0.009^*$

*adjusted for intron 22, ethnic origin and age at first exposure

CED, cumulative EDs

PTP studies

Summary

Product	N	<i>De novo</i> inhibitors	Incidence of inhibitors (ITT)	
			(%)	95% CI
Kogenate ¹	86	0	2 (2.3)	0.28, 8.15
Kogenate FS ²	71	0	1 (1.4)	0.04, 7.6
Recombinate ³	69	0	2 (2.9)	0.35, 10.1
ReFacto ^{1,4,5}	113	0	1 (0.9)	0.02, 4.83
Advate ¹	103	1	1 (1.0)	0.02, 5.4

The FDA have proposed an intention-to-treat (ITT) analysis and an upper 95% CI of 6.5%

CI, confidence intervals; ITT, intention to treat population

¹Lee & Roth 2005; ²Abshire et al 2000;

³White et al 1997; ⁴Lusher & Roth 2005; ⁵Lusher et al 2003

Hay
2005

PTP studies FDA proposals

- It is probably impractical to completely exclude patients with a past history of inhibitors
- Yet patients who may have an anamnestic response should be excluded
 - intention-to-treat (ITT) analysis would include all inhibitors, even those that may not be “new”
 - ITT analysis with a 95% CI upper bound of 6.5% would have excluded Kogenate, Kogenate FS and Recombinate from the marketplace!
 - much much larger studies would also be required

Bayesian ITT analysis

Posterior probability of inhibitor development based on published PTP studies

Product	ITT Observed inhibitor incidence (%)	Upper threshold of the true population incidence of inhibitors (%)			
		1	2	3	6.8
Kogenate	2.3	0.16	0.44	0.68	0.98
Kogenate FS	2.3	0.39	0.68	0.83	0.99
Recombinate	2.9	0.11	0.34	0.56	0.94
ReFacto	0.9	0.57	0.85	0.95	0.999
Advate	1.0	0.53	0.82	0.93	0.999
^a Octavi SDPlus	5.7	0.00006	0.006	0.05	0.73

**Bayesian ITT analysis readily distinguishes
Octavi SDPlus from other concentrates at
all predicted levels of inhibitor incidence**

Conclusions

It remains to be established whether there are true general differences in antigenicity between pdFVIII and rFVIII

Small numbers and multiple other confounding variables complicate such comparisons

Newer trial / statistical approaches may be required both to answer this question and to license future products

Regulation and coagulation products

Conclusions

- Haemophilia products are among the most regulated drugs, enhancing safety, but restricting access
- Regulators would consider that both pd and rec products have a place in the therapeutic armamentarium, and view the contraction of the plasma industry with some concern
- Safety from known pathogens is an issue of the past for both types of products, but vigilance for emerging threats is necessary for BOTH pd and rec products
- The relationship of inhibitor risk to product type is still under investigation, emphasising the need to keep access to both types of products

Acknowledgments

I would like to thank Dr Charles Hay of the University of Manchester for generous gifts of slides and advice.