

Replacement Therapies for Rare Bleeding Disorders

Lack of Availability: A Safety Issue

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ACBSA
August 26, 2004**

Rare Bleeding Disorders

Aims of Presentation

- **Highlight the issue of discrepant therapeutic standards between persons with hemophilia and those affected by the rarer bleeding disorders (RBD's)**
- **Propose several approaches to develop therapeutic options for persons with RBD's**
- **Obtain the support and collaboration of the Advisory Committee on Blood Safety in these efforts**

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Overview

- **Definition of rare disorders**
- **Background information**
- **Examples of rare clotting factor deficiencies**
- **Proposals for moving forward**
 - **Forming a coalition of organizations with mutual interest in finding solutions**
 - **Highlighting issues through presentations at meetings**
 - **Advisory Committee on Blood Safety**
 - **ISTH**
 - **Working with FDA and industry to develop mechanisms for improved access to required therapies**

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Definition

Legal definition of rare disorder in the US is a disease or condition that affects fewer than 200,000 Americans

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Background / Therapeutic Issues

- **Issues in treatment product / expertise**
 - **Availability of safe and / or effective therapy**
 - **Knowledge of appropriate replacement strategies**
- **Barriers to development of adequate replacement products**
 - **Cost of research**
 - **Cost of clinical trials**
 - **Limited market for licensed products**
 - **Regulatory burden on manufacturer and investigator**
- **Further barriers to clinical trial development**
 - **Inadequate number of study subjects for clinical trial design currently mandated by FDA**

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Background / Reimbursement Issues

- **Difficulty or inability to obtain insurance coverage for therapy**
 - **Imported for personal use**
 - **Used off-label**
- **Given the high price of medications, this issue may become increasingly important as Medicare, Medicaid, hospital budgets, etc are increasingly constrained.**
- **Importation and off-label use are not a long-term adequate solution or acceptable alternative.**

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Consequence of Lack of Specific Replacement Therapy

- **Patients with rare deficiencies**
 - Limited options for care
 - Standard of care often lower than for hemophilia
 - Potential for increased morbidity and mortality

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FVII Deficiency / Epidemiology

➤ Prevalence

- Approximately 1/500,000 population

➤ Registry data

- Approximately 650* patients identified within Registries
- North American Registry for Rare Bleeding Disorders: Acharya and DiMichele
 - Sponsored by HTRS-NA
 - Factor VII most prevalent
 - 46% (N = 135) of registry subjects (excluding FXI deficiency)
 - 35% with levels < 20%
 - limb / life-threatening hemorrhage prevalent
 - no replacement product licensed for FVII deficiency in US
- International FVII Deficiency Registry: Mariani

*515 International Registry, 135 NARBDR. Unknown if duplicate patients.

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FVII Deficiency / Potential Therapies

- **Two plasma-derived FVII concentrates manufactured and licensed in Europe**
- **Recombinant activated FVII licensed in Europe and US, but without approved indication for FVII deficiency in US**

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Other Rare Deficiencies

- For which potential specific replacement products already exist worldwide:
 - **FXIII: Fibrogammin® P (Aventis)***
 - **Fibrinogen: Haemocomplettan® (Aventis) & 4 others**
 - **FXI: Factor XI (BPL) and Hemoleven® (LFB)**
 - **PAI-1: Amicar® or Cyclokapron®***
 - **Protein C: Ceprothin® (Baxter), Xygris®**
- For which development of a specific replacement product has been precluded because the deficiencies are so rare
 - **FV, FX, FII, plasminogen, α -2 anti-plasmin**

*products available for off label or investigational use in US

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Proposals for Moving Forward

- **1. Forming a coalition of organizations with mutual interest in the care of persons with RBD's**
 - **NHF**
 - **MASAC**
 - **Blood Safety Working Group**
 - **NORD**
 - **ISTH (RBD's Working Group of the FVIII / IX SC)**
 - **WFH**

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Proposals for Moving Forward

- **2. Bringing issues to attention of community regulatory and policy-making stakeholders via meeting presentations**
 - **ISTH**
 - July 12, 2003
 - June 17, 2004
 - **Health and Human Services Advisory Committee on Blood Safety and Availability**
 - August 26, 2004

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Proposals for Moving Forward

- **3. Working with FDA and industry to develop mechanisms to allow improved access to therapies**
 - **Obtain additional licensed indications for an already US licensed product**
 - PCCs for FX and FII deficiency
 - NovoSeven® for FVII deficiency
 - Amicar ® / Clyclokapron for PAI-1 deficiency
 - **Obtain a product licensed in other countries for use in the US for which no virus-inactivated PD or recombinant alternative exists**
 - Fibrogammin® P: FXIII deficiency
 - Haemocomplettan®: Afibrinogenemia / Hypofibrinogenemia
 - Hemoleven®: FXI deficiency
 - **Stimulate new product development**
 - Plasminogen or FV concentrates

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Proposals for Moving Forward

- **3a. Proposed talking points in FDA / industry discussions relating to improved access to these therapies**
 - **FDA / EMEA harmonization of regulatory processes for biologics**
 - **Alternative mechanisms of drug importation into the US for rare bleeding disorders**
 - **Industry incentives for new indication application / new product development***
 - **Modified clinical trial design / data requirement for product licensure***

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Proposed FDA-Sponsored Workshop

- **A workshop sponsored by the FDA or co-sponsored by interested agencies may be feasible and advantageous**
 - **Bring interested parties together to discuss issues**
 - **Biopharma, regulatory agencies, consumer organizations, care providers, researchers etc.**
 - **Assist in fleshing out critical issues and identifying potential avenues along which to proceed**

**Proposals for Pre-Licensure
Studies of Replacement Products
for Rare Bleeding Disorders**

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Proposals for Pre-licensure Studies

- Due to rarity of these disorders and lack of global availability of therapeutic products, trials such as those performed in hemophilia may not be feasible

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Proposals for Pre-licensure Studies

Minimum Requirements for Pre-licensure Data Collection

- **Determination of safety**
 - AE's / SAE's
 - Viral safety data for plasma-derived products
- **Determination of efficacy**
- **Establishment of dosing guidelines**
- **Consistent and verifiable data collection**

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Proposals for Pre-licensure Studies

- **Ethical / Regulatory Compliance**
 - **Declaration of Helsinki**
 - **ICH Guidelines for Good Clinical Practice**
- **Collection of adequate data to meet existing regulatory requirements whenever possible**
- **Commitment from industry / clinical investigators to post-licensure phase IV studies**

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Proposals for Pre-licensure Studies

- **Industry-sponsored trials with modified regulatory requirements for data collection**
- **Investigator-initiated IND process**
 - **Would require process streamlining and more investigator support than currently available**
- **Use of registry data to support license application**
 - **Encourage through independent organizations such as HTRS-NA (precedent for this)**
 - **RBD registries do exist and a significant amount of data is available; however, restructuring of the databases would likely be necessary**

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Proposed Industry Incentives

1. Confer orphan drug status based upon therapeutic indication for rare disorder
 - Incentives for obtaining orphan drug status
 - 7 years exclusivity
 - Tax credit of 50% for costs of clinical trials
 - Protocol assistance from FDA
 - Waiver of FDA user fees
 - Access to orphan product research grants for clinical trials

2. Encourage off-label use of applications currently licensed product
 - Incentives to manufacturers
 - May be eligible for SBIR (small business innovative research grant)
 - May be encouraged by 6 month patent extension if drug studied in pediatric population

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Proposed Industry Incentives

- 3. Harmonize European & US regulatory agency licensure requirements for rare bleeding disorders to prevent repetitive work & increased financial burden on manufacturers**

- 4. Modify regulatory requirements for licensure of therapeutic products for RBD's**
 - Precedents exist**
 - Ceridase for Gaucher's Disease approval based upon study of 15 patients**
 - Peg-ADA approval based upon study of 8 or 9 patients**

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Summary

- **Persons with RBD's have limited, generally unsatisfactory treatment options and, consequently, an inferior standard of care when compared to the hemophilias**
- **A well-coordinated multi-organizational international effort will be required to find solutions to improve / optimal care**
- **ACBSA endorsement of the goals of this campaign would be beneficial to the global effort already in existence**