

**Workshop on FVIII Inhibitors in PTP's
Proposal for Prospective
Pharmacovigilance**

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Workshop on FVIII Inhibitors
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Workshop on FVIII Inhibitors in PTP's

The Question: Host or Product?



Post-Licensure Pharmacosurveillance

- Will pre-licensure clinical trials have the power to ascertain true PTP inhibitor incidence?

or

- Will a post-licensure pharmacosurveillance program be required?

Why Pharmacosurveillance?

- **Post-marketing pharmacovigilance recognized by industry / regulatory organization as important to identification of ongoing safety / efficacy concerns and redefining risk / benefit ratios.¹**
- **Currently, “mandatory” spontaneous AE reporting of clinical safety / efficacy concerns is primary method of surveillance.**

¹. Talbot JCC and Nilsson BS. Br J of Clin Pharmacol, 1998.

Spontaneous AE Reporting

Important Function

- Alerts physicians / regulators / industry to
 - early strong drug-event causal associations¹
 - severe unexpected adverse events²
- *Fosters suspicions → prompts further warranted investigation²*

1. Tubert P, et al. J Clin Epidemiol, 1992

2. Alvarez-Requejo A et al. Eur J. Clin Pharmacol, 1998.

3. Goldman S. Clinical Therapeutics, 1998.

Spontaneous AE Reporting

Limitations

- Underreporting
 - < 10% SAE's; < 4% AE's are reported
 - precipitous decline in reporting after 2nd post-marketing year
- Confounders / Biases
 - reporting environment
 - quality of data
 - numerator / denominator inaccuracies
 - temporally-associated clinical and lab data
 - challenge /re-challenge information
 - outcome

Goldman S, 1998

Talbot JCC and Nilsson BS, 1998

11/03

Pharmacosurveillance Alternative

- Post licensure randomized clinical trials
 - industry-sponsored
 - larger subject accrual than pre-licensure study
 - very expensive if to GCP specs

- Post-marketing cohort studies
 - industry-sponsored
 - slow recruitment / lack of control arm

- * Long-term global pharmacosurveillance programs
 - industry-sponsored, or
 - independent of / supported by industry
 - facilitated by regulatory harmonization

Workshop on FVIII Inhibitors in PTP's

The Question: Host or Product?



Post-Licensure Pharmacosurveillance

- Assuming the need for a long-term pharmacosurveillance program, what are its necessary elements with respect to:
 - project scope
 - HTC / government agency / industry participation?
 - type of data collection?
 - surveillance period
 - clinical / laboratory data collection / analysis / reporting
 - national vs. international databases?

Workshop on FVIII Inhibitors in PTP's

The Question: Host or Product?

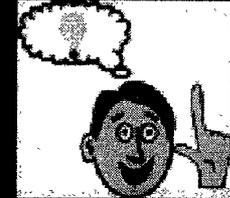


Post-Licensure Pharmaco-Surveillance (cont'd)

- Role of physician organizations? Government agencies? Industry?
- Funding?

Proposed PS Program

Participation



- **Universal data collection system for all FVIII products**

Products globally distributed

Products with limited distribution

International Database

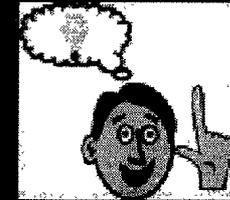
National / Multinational Database

- **Hemophilia treater-driven***

* Vermylen and Briet, Lancet 1993

Proposed PS Program

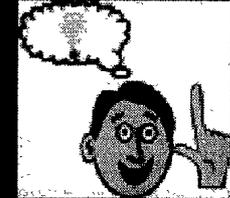
Subject Selection



- **PTP's**
 - defined by pre-licensure clinical trials
 - on all factor VIII products
 - plasma-derived
 - recombinant
 - future modified products
- **Observation period defined by cumulative factor VIII exposure days, not time**

Proposed PS Program

Data Set (1)

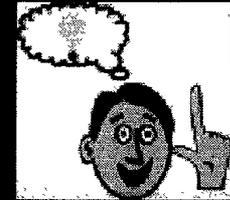


➤ Minimum Data Set

- **Defined by:** Regulatory agencies with industry input
- **Focus:** Ascertain product immunogenicity
 - incidence / prevalence of HT / LT inh
 - at risk PTP population
 - risk period
 - outcomes
- **Goal:** Ongoing reassessment of product risk / benefit ratio

Proposed PS Program

Data Set (2)



➤ Minimum Data Set

• Tools

- Adequately powered cohort size and observation period
- Reliable database for numerator / denominator ascertainment
clinician participation / adherence to protocol
industry-supported factor distribution data
- Strict definitions of
 - PTP with / without previous inhibitor
 - Inhibitor (HT / LT)
 - standardized assay (? centralized)
 - sensitivity / specificity criteria
 - inclusion of recovery / survival data?
 - Frequency of monitoring
 - Outcomes

Proposed PS Program

MDS Collection / Analysis / Reporting

Regulators / Industry



Hemophilia Center
National Databases
• existing / new

CDC

HTRS



National Data Collection / Analysis

ISTH
FVIII / IX Subcommittee
PTP Inhibitor Working Group

International Data Analysis / Collection / Reporting

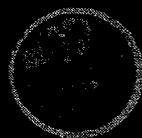
Report to Industry

Report to Regulatory
Agencies

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Proposed PS Program / Funding

MDS Collection / Analysis / Reporting



Hemophilia Center
National Databases
• existing / new

CDC
HTRS



National Data Collection / Analysis



Industry
National Org.
Gov't / Private Funds

ISTH
FVIII / IX Subcommittee
PTP Inhibitor Working Group



International Data Analysis / Collection / Reporting

Report to Industry

Report to Regulatory
Agencies

Proposed PS Program

Data Set (3)

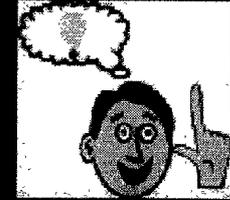


➤ Comprehensive Data Set

- **Defined by:** Clinical investigators / scientists
- **Focus:** Ascertain role of host and host / treatment interaction in PTP inhibitor formation
 - host hemophilia / immunologic genotype / phenotype
 - pertinent non-product-related inhibitor risk factors
 - type of hemorrhage / treatment specifics
 - anti-FVIII antibody characterization

Proposed PS Program

Data Set (4)



➤ Comprehensive Data Set

• Tools

- Adequately powered cohort size and observation period (case controls?)
- Comprehensive clinical database
- Prospective / retrospective sample collection / repository

Proposed PS Program

Comprehensive Data Collection / Analysis / Reporting

National Databases

Clinician
Scientist
Research
Teams

Expanded CDS / Analysis

+

Sample Repository

ISTH

Scientific Symposia

Proposed PS Program / Funding

Comprehensive Collection / Analysis / Reporting

Private / Public
Research Grants

National Databases

Clinician
Scientist
Research
Teams



Expanded CDS / Analysis



+

Sample Repository

ISTH

Scientific Symposia

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Where to Go From Here

Moving forward

- **Panel Discussion**
- **Crucial Decisions**