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**REPORT OF
EXPERT MEETING ON FACTOR VIII PRODUCTS AND
INHIBITOR DEVELOPMENT**

28 February 2006 –2 March 2006

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GLOSSARY

ADR	Adverse Drug Reaction
BPWP	Blood Products Working Party
BU	Bethesda Units
CDC	Centres for Disease Control and Prevention (US)
CHMP	Committee for Human Medicinal Products
CV	Coefficient of Variation
ED	Exposure Days
ELISA	Enzyme Linked ImmunoSorbent Assay
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
FIX	Blood Clotting Factor IX
FVIII	Blood Clotting Factor VIII
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ISTH	International Society of Thrombosis and Haemostasis
ITT	Immune tolerance therapy
IU	International Units
LA	Lupus Anticoagulants
MTP	Minimally Treated Patients
NHD	National Haemophilia Database
NIBSC	National Institute for Biological Standards and Control
PEDNET	European paediatric organisation for haemophilia management
PhVWP	Pharmacovigilance Working Party
PK	Pharmacokinetic
PUP	Previously Untreated Patient
PTP	Previously Treated Patient
RMP	Risk Management Plan
SD	Standard Deviation
SPC	Summary of Product Characteristics
TGF- β	Tissue Growth Factor β
vCJD	Variante Creutzfeldt-Jakob Disease
VWF	Von Willebrand Factor
WHO	World Health Organisation

SUMMARY

An EMEA expert meeting on FVIII products and inhibitor development was held on 28 February to 2 March 2006 to provide a forum to discuss the international standardisation and harmonisation of requirements for clinical studies on FVIII inhibitor development in haemophilia A patients. The long-term objective is to collect comparable clinical data on the immunogenicity of recombinant and plasma-derived FVIII products in future.

The expert meeting was divided into an open session, where haemophilia treaters, competent authorities from EU, US, Japan and Canada, representatives from the International Society for Thrombosis and Haemostasis (ISTH), the World Health Organisation (WHO), patient organisations and industry discussed clinical study requirements, and a restricted session, where EU competent authorities discussed the outcome of the meeting.

A number of issues were discussed relating to: current data on FVIII products and inhibitor development, FVIII inhibitor measurement, clinical relevance of FVIII inhibitor occurrence, clinical study design, registries, risk management, post-marketing studies and pharmacovigilance.

This report summarises the discussions held at the open sessions. Conclusions drawn from these discussions in the restricted session and at the Blood Products Working Party (BPWP) meetings in June and September 2006 are listed at the end of the report.

The outcome of these discussions will be taken into account in the revision of the Notes for Guidance on clinical investigation of human plasma-derived and recombinant FVIII and FIX products and the corresponding core Summaries of Product Characteristics (SPCs). In addition, on recommendation of the experts, the Committee for Human Medicinal Products (CHMP) has contacted the ISTH SSC Subcommittee for FVIII and FIX in June 2006 regarding two topics: the FVIII inhibitor assay and the development of common data sets for registries. The activities of the ISTH SSC Subcommittee in these two areas are complementary to the work of the CHMP/BPWP/Pharmacovigilance Working Party (PhVWP) and national competent authorities.

INTRODUCTION

The occurrence of an antibody against FVIII is a major clinical complication in haemophilia A treatment. The risk of inhibitor development is increased in patients with severe haemophilia A compared to moderate and mild disease. The occurrence of inhibitors in PUPs should be seen as an immune reaction to a foreign protein linked to patient specific factors such as to underlying clotting factor gene defect, genetic immunity disposition and pre-existing immunity, while the development of inhibitors in multi-transfused and stable PTPs may reflect neo-antigenicity of the product. In the early 1990's two clusters of inhibitors observed in PTPs treated with specific plasma-derived products showed that such neo-antigenicity is a real concern (Rosendaal et al. 1993; Peerlinck et al., 1993 and 1997). Since it is not known whether recombinant FVIII products carry an enhanced immunogenic risk and whether there are differences between recombinant products in their relative immunogenicity, CHMP initiated in 2003 a review of recombinant FVIII products and inhibitor development. (The EMEA/CHMP is responsible for recombinant FVIII products.)

This review, co-ordinated by the PhVWP in liaison with the BPWP, did not allow definitive conclusions on the incidence of inhibitor formation with recombinant FVIII products (EMEA public statement, 2005) based on the data collected in 2003 and 2004: Considering post-marketing spontaneous reports and all completed or ongoing post-marketing safety studies, it was not possible to finalise the comparison for all recombinant products due to differences in study design, case definitions, treatment regimes (e.g. for bleeding episodes), patient characteristics, methodology of the FVIII inhibitor assays and differences in the duration/follow-up of studies.

The CHMP recommendations arising from the EMEA review are:

- Pharmacovigilance planning is recommended for all recombinant FVIII products.
- There is a need to establish standardised requirements for pre- and post-marketing studies to ensure comparable safety data on inhibitor development in PUPs and PTPs treated with rFVIII products. Harmonisation at an international level is desirable to achieve this aim.
- The value of patient registries as a source of data on incidence of inhibitors should be further explored.

The purpose of the expert meeting on FVIII products and inhibitor development was to address these recommendations with the aim of collecting comparable clinical data on the immunogenicity of recombinant and plasma-derived FVIII products in future.

OPEN SESSION ON 28 FEBRUARY AND 01 MARCH 2006

SESSION 1

M. Haase, the chairperson of the BPWP, welcomed the participants and presented the rationale for convening the meeting.

SESSION 2 FVIII PRODUCTS AND INHIBITOR DEVELOPMENT – UPDATE

The scope of this session, chaired by P.M. Mannucci, was to introduce the subject of inhibitor development in haemophilia A patients. A general presentation on FVIII immunogenicity, followed by an update of the EMEA review of recombinant FVIII products, and a summary of the outcome of the 2005 French workshop on plasma-derived and recombinant FVIII were given.

Presentations

As a general introduction, P.M. Mannucci discussed the clinical importance of the occurrence of FVIII inhibitors in patients with severe haemophilia A. He stressed in particular the importance of inhibitor occurrence in PUPs, affecting 20-35% of these patients.

J.M. Saint-Remy highlighted the mechanisms of the FVIII immunogenicity. He discussed several patient-related and product-related factors predisposing to inhibitor formation. These include genetic disposition, pre-existing immunity, age at first treatment and ethnic origin of the patients, as well as FVIII mutation, glycosylation pattern, stabilisation and C2 aggregation of the FVIII preparation and its content of other plasma proteins (VWF, fibrinogen, fibronectin, TGF- β) as well as the route of administration.

B. Keller-Stanislawski presented the EMEA review on recombinant FVIII products and inhibitor development performed in 2003, 2004 and 2006, which assessed the data from clinical trials, post-marketing studies and spontaneous reports including the design of the studies and inhibitor assays. She identified several gaps in the comparison of different products: discrepancies in duration of the follow-up of the patients, dosing regimens and definitions of severe haemophilia, MTPs and PTPs, other patient characteristics, methods of inhibitor testing and the use of central versus local laboratories. The frequency of inhibitor development in PTPs and PUPs found in clinical trials prior to marketing authorisation is considered comparable for all products assessed. However, the post authorisation inhibitor incidence in PTPs cannot precisely be estimated from post-marketing spontaneous reports. Furthermore, risk management plans are considered essential for all recombinant FVIII products.

C. Ratignier reported on the outcome from the 2005 French workshop on “Development and management of inhibitors after treatment of haemophilia patients by recombinant or plasma-derived FVIII or IX:

Data indicating that the immunogenicity of plasma-derived FVIII and recombinant FVIII products may be different remain weak from a preclinical point of view. Transgenic animal models are needed to study the effect of the VWF component.

At the French workshop, available publications on FVIII inhibitor occurrence, which fulfilled defined inclusion criteria for evaluation, were assessed. As in the EMEA review on recombinant FVIII products, several issues made a comparative analysis of the studies difficult: The baseline FVIII level was variable or not well defined, the study designs and follow up times were variable, the number of patients in the studies was often low, and the risk factors for inhibitor development were only partly defined or not defined at all. The French workshop recommended a risk based approach for choice of FVIII product: If the risk of infection is considered as the most important issue, a recombinant FVIII product may be chosen for first line treatment. However, if the risk of inhibitors is considered as the most important issue, a plasma-derived FVIII product may be selected.

A retrospective study on the influence of the type of FVIII concentrate on the incidence of FVIII inhibitors in previously untreated patients with severe haemophilia A has been published by J. Goudemand et al. after the French workshop. C. Ratignier reported on the results of this study in her presentation.

Discussion and Conclusions

The discussion was opened by two brief presentations.

P. Mannucci presented the protocol of SIPPET (Study on Inhibitors in Plasma-Product Exposed Toddlers). The aim of this international, prospective, controlled (open-label) and randomized clinical trial is to compare the immunogenicity of plasma-derived-VWF-FVIII products with that of recombinant FVIII products, by determining the frequency of inhibitor development in PUPs and MTPs less than 6 years of age. Prophylaxis or on-demand regimens will be chosen by the clinician according to local guidelines and patient preferences. The screening assessment is to be done at the central laboratory, and the patients will be followed-up until 50 EDs or 6 months after the inhibitor occurrence (for discussion see session 5.1).

A. Kallas gave a presentation on the role of VWF in plasma-derived FVIII preparations in the development of FVIII-specific antibodies in a FVIII-deficient mouse model. The ability of FVIII antibodies to interfere with functional FVIII activity (Bethesda assay) was lower in the VWF-treated mice.

Experts agreed there is a clear need for further clinical studies and data on inhibitor formation. Reliable information on the incidence of inhibitor development in PTPs cannot be obtained from post-marketing spontaneous reports. There is the need to standardise the requirements, definitions and methods in pre-and post-marketing as well as in observational studies with PTPs and PUPs. In view of the low patient numbers the need for international collaboration was stressed.

No robust conclusions could be made on the relative risk of inhibitors regarding plasma-derived or recombinant products for the time being even though some signals may be seen.

SESSION 3 METHODOLOGY

The scope of this session, chaired by K. Mertens, was to discuss the current status of the FVIII inhibitor assay including information regarding its optimisation and standardisation as well as new scientific approaches on the detection of inhibitor development. This topic was addressed in seven presentations. In an open discussion a number of specific questions were answered.

Presentations

K. Mertens gave an introductory presentation on inhibitory and non-inhibitory antibodies against FVIII asking what may cause differences. Seventy five percent of detectable FVIII antibodies do not inhibit FVIII activity and are therefore not quantified by the currently used Bethesda assay and its Nijmegen modification. K. Mertens reported on his own results obtained with inhibitory and non-inhibitory anti-FVIII light chain antibodies cloned by phage display technology. A single point mutation in the epitope of one inhibitory antibody resulted in the loss of its inhibitory function. While the specificity of the antibody was not affected by the point mutation, its affinity was reduced by 100 fold. It was concluded that affinity maturation of antibodies might cause a switch from non-inhibitory to inhibitory antibodies or vice versa. The absence of a detectable inhibitor in the Bethesda assay does not exclude an immature antibody directed to a functional FVIII epitope with affinity in nanomolar levels possessing a potential inhibitory effect. Furthermore, the dissociation of the FVIII/FVIII antibody complex may influence residual FVIII activity and could have an impact on the haemostatic effect.

S. Raut presented unpublished data on the step-by-step standardisation of the FVIII inhibitor assay obtained in an exercise during a workshop at the National Institute for Biological Standards and Control (NIBSC). The data showed a stepwise improvement of the performance of the FVIII inhibitor assay with reduction of CVs from 53-80% to 14-20%. An International Collaborative Study to

Standardise anti-FVIII Inhibitor Assays showed a high variability of test results. Critical for the standardisation of the FVIII inhibitor assay are the antibody dilutions, the incubation stage, the choice and standardisation of FVIII activity assay (chromogenic CVs < one-stage CVs) and the need for an international inhibitor standard. NIBSC/ISTH/WHO are currently working on the establishment of a WHO international FVIII inhibitor standard (panel of monoclonal and polyclonal antibodies) and progress will be reported at the ISTH SSC Subcommittee for FVIII and FIX meeting in June 2006.

P. Meijer reported on the outcome of the ECAT Foundation collaborative study, which underlines the NIBSC findings concerning the need for standardisation of the FVIII inhibitor assay. 135 clinical laboratories participated in this study, 69% used the Bethesda assay, 22% the Nijmegen modification of the Bethesda assay and 9% other assays. Interlaboratory CVs ranged from 28% (Nijmegen assay) to 41 % (Bethesda assay). There was a broad range of cut-off values (0-2 IU). The specificity of the assays was acceptable, while the sensitivity was rather poor. This is of interest for the detection of low titre inhibitors, which may or may not be of clinical relevance. In conclusion, further improvement of the specificity, sensitivity, inter- and intra-lab CV is necessary. Laboratories need to strengthen standardisation as shown by conflicting information on assay type and conditions used.

C. Miller reported that the Centres for Disease Control and Prevention (CDC) is setting up a centralized FVIII inhibitor testing program as part of a surveillance project. The testing program includes the Nijmegen modification of the Bethesda assay and the assessment of the impact of various parameters, e.g. collection and transport of blood sample, and sample treatment for removal/inactivation of previously infused FVIII. Furthermore, the project investigates the clinical importance of non-neutralizing antibodies, the possibility to use ELISA methods to screen for FVIII inhibitors, and to compare the influence of chromogenic versus one stage FVIII activity assay on inhibitor test results.

J. Goudemand addressed clinical conditions known to influence FVIII inhibitor measurement. Among these, the time interval since the last infusion of FVIII product is of importance because the infused residual FVIII may mask an inhibitor in the assay. Therefore, anti-FVIII antibodies should be tested pre-infusion when the FVIII level is at its lowest. In addition, especially in children secondary effects due to viral infection (e.g. Lupus anticoagulant) may have a major impact on the inhibitor measurement. Furthermore, occurrence of new FVIII inhibitors was reported in HCV positive haemophilia A patients undergoing treatment with interferon as well as in HIV positive haemophilia A patients having an immune reconstitution inflammatory syndrome associated with anti retroviral therapy.

B. Verbruggen, addressing variables influencing the performance of the Nijmegen modification of the Bethesda assay, concluded in line with previous speakers that further standardisation, e.g. the improvement of sensitivity and the validation of the assay are needed. Specificity and sensitivity are individually influenced by various parameters (pH stability; type of FVIII deficient plasma; vWF content of control sample; FVIII content of normal plasma; chromogenic or one-stage FVIII activity assay). The level of cut-off values is influenced by factors such as the vWF content of the control plasma and the choice of the FVIII activity assay (chromogenic or one-stage assay). This especially affects low titre or borderline inhibitor detection.

J.M. Saint-Remy presented new methods, which can detect the full range of FVIII antibodies in the patient plasma. These include memory B cell epitope mapping and T cell epitope identification. However, only 25% of the currently detected FVIII antibodies are suspected of having an inhibitory effect with clinical correlation. Therefore, the experts agreed, that these immunological methods to detect FVIII antibodies might be of greater use to assess the specific antigenicity of a new or modified FVIII product, rather than representing tools for clinical monitoring of FVIII inhibitor development.

Discussion and Conclusions

The questions below were addressed in the discussion in session 3 and the following consensus reached:

- *What are the critical experimental parameters/conditions for the standardisation of the Bethesda assay for the detection of type I and type II inhibitors?*

The use of the Nijmegen modification of the Bethesda assay is recommended for pre-authorisation studies and also for post-marketing surveillance. The Nijmegen modification requires further optimisation/standardisation and validation for performance improvement. The following parameters were identified as critical for valid inhibitor results: The buffering of the normal plasma and its FVIII content; the type of control plasma (chemically or immune depleted or severe congenital FVIII deficient) and its VWF content; the incubation time; the type of FVIII activity assay (chromogenic or one-stage assay) and its reagents (e.g. phospholipids). The measurement of low-titre inhibitors is recognised as a difficult task. The results of inhibitor measurements should always be interpreted in relation to clinical observations. It was agreed to refer this consensus to the ISTH SSC Subcommittee meeting for FVIII and FIX products in June 2006 for further considerations and input.

Development of standards / reference materials was considered as necessary. ISTH / NIBSC are currently working with the WHO on the implementation of a standard and progress will be reported at the ISTH SSC Subcommittee meeting for FVIII and FIX products in June 2006.

The optimisation of the FVIII inhibitor assay should also address the detection of type II FVIII inhibitors. Type II FVIII inhibitors are mostly linked to acquired haemophilia A, while type I FVIII inhibitor reactivities mainly occur following treatment of severe haemophilia A. However, a modified FVIII plasma-derived product (double virus inactivated) induced type II FVIII inhibitors in PTPs with severe haemophilia A in the past.

- *Are modified tests / in-house methods acceptable and if yes, under which conditions?*

The Nijmegen modification of the Bethesda assay is acknowledged as a gold standard.

- *Is there value in FVIII inhibitor measurements being carried out in specialised central laboratories? Should testing laboratories be encouraged to participate in proficiency studies?*

It is recommended to perform the inhibitor assay in a centralised laboratory for pre-licensing studies. The participation of laboratories in proficiency and collaborative studies is essential.

- *How should FVIII inhibitors be defined in terms of borderline/low titre/high titre inhibitors; type I/type II inhibitors; intermittent inhibitors? With regard to the various thresholds applied in different studies (≥ 0.6 BU, 1.0 BU or ≥ 1.0 BU), how should the threshold be defined? Will a single sample / single positive test result qualify for an inhibitor diagnosis?*

It was emphasised that the diagnosis of an inhibitor should primarily be based on clinical observations and be confirmed by FVIII inhibitor testing in the laboratory. A close collaboration between clinical and laboratory staff is important.

Consensus was reached on the threshold of ≥ 0.6 BU for the diagnosis of an inhibitor and of >5 BU for a high titre inhibitor. A confirmatory test on a second, separately drawn sample should always be performed. This second sample should be taken prior to any change of treatment and shortly after the previous positive test (within a month).

- *What are the clinical conditions that influence the results of inhibitor measurement (e.g. significant amount of FVIII in the sample due to timing between last FVIII administration and sampling for FVIII inhibitor measurement)? How to define the clinical parameters / conditions under which inhibitor testing will bring reliable results?*

Reference is made to the discussion of residual FVIII plasma levels and lupus anticoagulants in session 4.

Inhibitors have been detected in patients with chronic viral infections (e.g. HIV, HCV) during anti-viral therapy.

- *What is the added value of FVIII antibody measurement by ELISA?*

The added value of FVIII antibody measurement by ELISA is not yet defined, but is an interesting area of research.

SESSION 4 CLINICAL RELEVANCE OF FVIII INHIBITOR OCCURRENCE

The purpose of session 4, chaired by J. Ingerslev, was to discuss the clinical relevance of FVIII inhibitor occurrence. Three main questions were addressed by experts, dealing with the interpretation of inhibitor results, clinical signs of inhibitor occurrence, and the case of low titre FVIII inhibitors.

In order to answer these questions, a round table discussion was convened with the participation of five experts - G. Auerswald, R. Lassila, C. Lee, P.M. Mannucci and M. van den Berg.

Discussion and Conclusions

- *How to interpret inhibitor results, which are obtained under clinical conditions that may interfere with the FVIII inhibitor measurement?*

P. Mannucci pointed out that clinical conditions could interfere with the FVIII inhibitor measurement but not with the clinical signs of inhibitor occurrence.

This question was addressed under three aspects: content of FVIII in the sample for testing, lupus anticoagulant, and use of heparinised ports. Summaries of these discussions, as well as the consensus reached with all participants, are presented below.

FVIII content in the sample for testing

Presence of FVIII in plasma samples, due to a recent infusion of FVIII or to endogenous FVIII in the plasma of non-severe haemophilia patients, can interfere with the results of the test for FVIII inhibitor measurement. For routine inhibitor testing, preferably no clotting product should have been given in the previous 3 days. The inhibitor test should be performed when the plasma FVIII level has reached a pre-substitution nadir rather than at a specific time point.

The inhibitor assay should be validated for the impact of residual FVIII on the test results. In test samples the residual FVIII level should be low. Heating of the sample in order to inactivate residual FVIII content could circumvent the possible interference, while keeping immunoglobulins intact. (For example, H. Verbruggen uses a one-hour pre-treatment at 58°C; in the French Expert Group Report, a pre-treatment of 30 min at 56°C is recommended if the plasma contains FVIII). The heating pre-treatment needs to be validated. This point should also be referred to ISTH SSC Subcommittee for FVIII and FIX products for review.

Lupus anticoagulant (LA)

LAs are a heterogeneous group of immunoglobulins directed against negatively charged phospholipids in complex with proteins (β_2 -glycoprotein I (β_2 -GPI), prothrombin and others). Although LA and anti-FVIII inhibitors are dissimilar in terms of specificity and clinical presentation, they are somewhat related; as both of them prolong the phospholipid-dependent coagulation tests. Differentiation of LA from anti-FVIII inhibitors is crucial, because of different therapeutic consequences (i.e. antithrombotic agents in the former or haemostatic agents in the latter). LA is apparently rare in adults, but so is the occurrence of inhibitors in PTPs. Therefore, immediate signs of a positive inhibitor test in a PTP might be due to LA. Small children suspected of having an inhibitor should be also tested for LA, which especially in children are associated with viral infections and are difficult to differentiate from FVIII inhibitors.

Heparinised ports

In general, it is recommended for FVIII inhibitor testing to take blood from a vein and not from a port, as flushed heparin has an impact on FVIII inhibitor measurement.

- *What are the clinical signs for the occurrence of FVIII inhibitors to be monitored in clinical studies (e.g. increased bleeding tendency, high consumption, lack of response or efficacy, decreased recovery, shortened half life)?*

PTPs

It is much easier to detect changes from the patient's usual condition in PTPs as compared to PUPs. All the following parameters are relevant: increased bleeding tendency, high consumption, lack of response or efficacy, decreased recovery, shortened half life. High consumption was a clinical sign in the cluster of inhibitor cases (type II) in PTPs seen in Germany with modified plasma-derived FVIII product (double virus inactivated).

Infants and young children

It is much more difficult to diagnose inhibitor development from clinical signs in infants and young children.

Pharmacokinetics: It is not feasible to perform extensive pharmacokinetic investigations in infants and young children. If an inhibitor is suspected, it is recommended to look at the recovery. If the recovery appears greatly reduced and/or no FVIII is detected, an inhibitor is suspected.

It should be kept in mind that the normal pharmacokinetic range may be age-related, with children exhibiting different kinetics (shorter half-life and lower recovery) compared to adults.

High consumption: This parameter is not a reliable indicator for FVIII inhibitors in infants and young children as there is no "usual condition" to compare with. Furthermore, there are many differences in lifestyle of children (careful or accident-prone), which may lead to dose modifications.

Increased bleeding tendency: This parameter is unreliable as a clinical sign. Bruising can be observed, but it is difficult to assess objectively.

Lack of response or efficacy: Poor response to treatment, including prophylaxis, is useful as a clinical sign of inhibitor occurrence. High titre inhibitors may be signified by an increased bleeding tendency (e.g. joint bleeds), while treated under a FVIII prophylaxis regimen. Effectiveness of treatment of a fresh joint bleed is measurable. Low titre inhibitors will probably not be detected under FVIII prophylaxis regimens.

Nevertheless, there are inhibitor patients who do not bleed. Therefore, there is a need for careful monitoring of all parameters. The need for close collaboration between the clinical laboratories and the physicians has been clearly emphasised during the meeting: linking of the results of FVIII inhibitor tests to clinical signs of each patient appears crucial to determine the best therapeutic approach.

- *Some patients with low titre FVIII inhibitors show an increased FVIII consumption. Should the clinical relevance of borderline/low titre and intermittent FVIII inhibitors be further investigated and how should clinical studies and their follow-up be designed to obtain meaningful data?*

Generally there is a lack of knowledge of the clinical relevance of transient and low titre inhibitors. It is not known whether these might become clinically relevant in a PTP later in life. This indicates the importance of prolonged follow-up of patients. However, such long-term data are much more difficult to collect, but data are essential for pharmacovigilance assessment and registries. Another confounder of data relates to the fact that FVIII inhibitor testing is most often carried out in local laboratories only rather than a central laboratory. It was noted that the CDC is developing central laboratory testing for surveillance (see session 3) in the USA.

In this context, consensus on the following points was reached:

- Monitoring of inhibitor development should be started at the onset of treatment in order to obtain solid baseline data.
- Regular laboratory measurements of inhibitors should be implemented in clinical studies. In addition, clinical signs suggesting inhibitor development (see previous question) should be defined and used to trigger investigations between the regular laboratory visits.

- Routine testing for inhibitors should be carried out on a regular basis. In particular, testing should be frequent in the early phases of substitution. However, it was acknowledged that frequent sampling might prove difficult in young children.
- In order to disclose product related immunogenicity, all inhibitors should be documented.
- Linking clinical and laboratory findings is very important.

SESSION 5 CLINICAL DATA – STUDY DESIGN

This session was divided into 5 sub-sessions in order to address all identified issues related to clinical trials and study design in relation to the risk of inhibitor development.

5.1 REGULATORY REQUIREMENTS ON CLINICAL STUDY DESIGN EU/USA

Session 5.1, chaired by J. Ingerslev, addressed the regulatory requirements on clinical study design in EU and USA.

Presentations

A. Hilger presented the EU requirements as outlined in the current CHMP note for guidance on clinical investigation of plasma-derived and recombinant FVIII products. Prior to marketing authorisation, a pharmacokinetic trial should be performed in at least 12 immunocompetent subjects suffering from severe haemophilia. Efficacy, safety and immunogenicity data are required from 50 PTPs (≥ 150 ED, aged > 12 years) with residual FVIII levels $\leq 2\%$. Immunogenicity data should be based on follow-up over a period of ≥ 50 ED or 6 months. The inhibitor titre should be monitored at baseline and every 3 months using the Nijmegen modification of the Bethesda assay. There is no formal requirement for a PUP study. However, treatment of PUPs should be documented and should not be initiated before data on 50 ED from 20 PTPs included in the clinical trials are available. As outlined in the concept paper for the revision of the guideline, the EU requirements will be revised in line with the outcome of this workshop. Proposals for revision also include dosage regimen, risk management plan, definition of patient characteristics, the paediatric population, and improved design of post marketing studies.

J. Lozier presented the outcome of the 2003 FDA workshop on FVIII inhibitors and the current considerations for clinical study design in USA. At the workshop, the FDA encouraged manufacturers of recombinant products to put data from product development and clinical trials into the public domain. In addition, FDA intended to advance the discussion of inhibitor definition, risk, measurement and regulatory concerns in a public forum. The current FDA approach is to request efficacy and safety in PTPs (defined as >150 ED) rather than in PUPs, and a PK comparative study vs. equivalent recombinant product. Eighty PTPs should be studied for 50 ED to be able to permit the detection of one inhibitor while ruling out by statistical analysis a true inhibitor rate of $>5.6\%$. Paediatric studies are preferred over PUP studies and are required as a phase IV commitment although the protocol should be approved prior to licensure.

Unresolved issues for the FDA were highlighted such as the inhibitor threshold of <1.0 BU, post-marketing surveillance, alternative statistical approaches (Bayesian) and inhibitors in PUP studies.

Discussion and Conclusions

The approach for regulatory requirements for pre-licensing studies clearly differs between Europe and the USA. In Europe it is considered impractical to perform pre-licensing studies with sufficient statistical power to reliably exclude abnormal immunogenicity of a new product. Therefore a pre-licensing study carefully assessing inhibitor occurrence in a limited PTP number is combined with mandatory post-licensing studies and pharmacovigilance. In the USA, the acceptability criteria of “ruling out of a true inhibitor rate of $>5.6\%$ ” for a new product has been chosen based on observations

made in Canada during the switch from plasma derived concentrates to one recombinant FVIII product.

Several participants highlighted the need for harmonization of the requirements between EU and USA taking account of the limited size of the patient population available.

The experts addressed two questions: the first on the most relevant patient population to be studied for inhibitor development and the second on the use of MTPs.

- *The current CHMP guidance recommends that PTPs rather than PUPs should be used to study product related immunogenicity. Since children may respond differently from adults, children under the age of 6 should also be studied regardless of prior treatment. There is no requirement for specifically studying PUPs. However, the core SPC recommends inclusion of information on the incidence of inhibitors in PUPs and PTPs as addressed in the core SPC section 4.8 Undesirable effects.*

Is the general philosophy of this approach still valid?

In daily practice, the clinically most significant and relevant inhibitors occur in PUPs. An important issue in the treatment of PUPs is the choice between plasma-derived FVIII or recombinant FVIII product and the weighing of the potential risks of transmission of infectious agents vs. the risk of inhibitor development. Therefore, some of the haemophilia treaters participating in the meeting strongly recommended the investigation of inhibitor development in PUPs treated with plasma-derived FVIII compared to recombinant FVIII product as the highest priority. To study this aspect in an evidence-based approach, a randomised controlled clinical trial was suggested (for possible trial design see session 2). Experts recognised that in principle a randomised controlled trial is the most reliable study design, but highlighted difficulties to use this design (small patient population, which product to use, dose regimen design (prophylaxis vs. on demand)). It was noted that in some EU countries randomised controlled trials comparing plasma-derived FVIII to recombinant FVIII products are not feasible as only recombinant FVIII products are used.

At the time of marketing authorisation, the most important question is whether a new plasma-derived FVIII or recombinant FVIII product reveals an abnormal immunogenic profile compared to products already on the market. Since PTPs are considered at low risk for inhibitor development, they should be included in immunogenicity investigations of products because excessive inhibitor formation in PTPs would indicate increased immunogenicity of a product.

Previous experience with the occurrence of two clusters of inhibitors in PTPs treated with two modified plasma-derived FVIII products showed no abnormal product immunogenicity during the clinical pre-licensing phase, while the first inhibitors occurred post approval (detected 18 months after market introduction for one of the products; most patients had more than 100 ED). Based on this experience and considering the small patient population, it was concluded that full immunogenicity data could not be collected pre-authorisation. It was proposed to require limited data prior to authorisation and to strictly follow-up patients post-authorisation.

In conclusion, some agreement was reached that inhibitor development in PTPs remains the main focus in pre-authorisation studies. The opinion of experts on the utility of clinical studies in the paediatric population (e.g. PUPs or PTPs, plasma-derived vs. recombinant FVIII) seemed to be divided.

- *Should minimally treated patients (MTPs) be reported together with PUPs?*

As the population of MTPs is not well defined, participants unanimously agreed not to combine data on MTPs with data on PUPs.

5.2 DEFINITIONS - PATIENTS CHARACTERISTICS

Session 5.2, chaired by J. Ingerslev, addressed definitions and patients characteristics. Two presentations were followed by a round table discussion, in order to provide consensus statements to the three proposed questions.

Presentations

M. van den Berg presented the re-evaluation of PUP recombinant FVIII studies and the Canal Study. Any diagnosis of inhibitor should be made on clinical findings confirmed with two separately drawn, positive samples. Recovery data and other PK tests were considered necessary for a full diagnosis of inhibitors. Both studies presented by M. van den Berg revealed comparable results indicating that intensive treatment in case of surgery and large bleedings is associated with inhibitor occurrence, while early onset of prophylactic treatment seems to have benefit. Recommendation for further investigation on this potential beneficial effect was proposed.

J. Ingerslev presented, on behalf of J. Oldenburg, a review on risk factors, providing examples of high-risk scenarios for inhibitor development. Two types of risk factors, genetic and environmental, could be considered to determine the risk profile. Predisposing genetic factors are type of FVIII mutation, family history of inhibitors, severity of haemophilia A, race and ethnicity, and polymorphisms and mutations in immune response genes. The environmental factors that may influence the likelihood of inhibitor formation are the age of first exposure to FVIII, immunological challenges, invasive clinical procedures, treatment regimes with FVIII (dosages, intervals); socioeconomic aspects, abnormal FVIII molecules and infant diet.

Discussion and Conclusions

Experts and regulators (J. Astermark, C. Hay, C. Lee, D. Mentzer, W. Schramm, M. van den Berg) participated in the round table discussion:

Three questions were addressed dealing with the definition of severe haemophilia, PUP, MTP and PTP, and the relevant patient characteristics for the evaluation of FVIII inhibitors.

- *Definitions for severe haemophilia A used in different clinical studies vary between FVIII baseline level of < 1% and < 2%. How should severe haemophilia A be defined? The ISTH SSC Subcommittee defined severe haemophilia A with a FVIII baseline level of <1%. Should the SSC classification be adopted in clinical pharmacovigilance studies?*

Industry representatives pointed out that there is no problem in defining severe haemophilia A as a baseline level <1% for pre-licensing studies. Nevertheless, for post-marketing studies a baseline level of 2% has been chosen in the past in order to meet laboratory difficulties. One industry proposal was to collect all data for FVIII baseline level of < 1% and < 2% in a post-marketing setting, and provide for statistical analysis with distinct results for FVIII baseline level of < 1% and < 2%. Assessment of the gene mutation is recommended whenever possible.

The final agreement was to adopt the definition for severe haemophilia A of the ISTH SSC Subcommittee, namely a FVIII baseline level of <1%.

- *How should PUP, MTP and PTP be defined on the basis of the total number of exposure days? Is there a value in the introduction of additional categories, e.g. heavily treated PTP? Should the number of exposure days be reported with the product under which the FVIII inhibitor developed?*

As agreed during the previous session, the categorization of patients as MTPs is not seen as a useful concept. Therefore, the discussion focused on the definitions of PUPs, and PTPs.

Regarding the definition of PUPs various positions were considered. Agreement was reached that PUPs are patients who have never been exposed to clotting factor products. Nevertheless, previous exposure to other blood components should not be regarded as treatment in this

respect. Agreement was reached that pre-authorisation inhibitor development should be studied in PTPs that are at low risk, e.g. more than 150 ED.

In addition, a different approach to categorise patients in low-risk, intermediate-risk and high-risk groups rather than PUP, MTP and PTP was discussed. The cumulative risk for development of an inhibitor within the first 150 ED is 20-30%. Fifty per cent of those patients that eventually develop inhibitors, develop these within the first 20 ED, 95% within the first 50 ED and >99% within the first 150 ED. It was proposed that patients with more than 150 cumulative ED are grouped as low-risk patients, while patients with less than 20 cumulative ED are regarded as high-risk patients. Nevertheless, for the intermediate risk group, the definition in cumulative ED seems to be more difficult to draw, since patients are still at high risk up to the first 50 ED. The number of ED could be utilised in categorization parameter rather than the classification as PUP or PTP. In terms of pharmacovigilance all patients, including those with moderate and mild haemophilia, should be included in any surveillance.

Regulators needed clear definitions of patients, whatever their basis, number of exposure days, or risk categorization. To provide relevant and reliable data, these definitions should be clearly established and practicable. For pharmacovigilance, it appears important to define categories based on risk, especially for spontaneous reporting. Therefore, further reflection on categorization of patients - low, intermediate and high-risk groups - would be critically considered during the revision of the guidance.

- *Which patient characteristics are relevant for the evaluation of FVIII inhibitors? Is it of value to collect information on ethnicity, type of FVIII gene mutation, general health status, intensity of treatment/consumption, circumstantial factors - e.g. surgery, age at start of first treatment in severe haemophilia A? Are special parameters required for children?*

The experts agreed that all mentioned patients' characteristics should be recorded: severity of haemophilia A, age, age at time of first exposure to FVIII, race and ethnicity, type of FVIII gene mutation, general health status (infections - HIV, hepatitis and other infections), vaccination, family history of inhibitors, and surgery. Reason for treatment, regimens and intensity of treatment (prophylaxis or on demand, in case of surgery continuous infusion or bolus injection, dosages and intervals), ED (total and on product) should also be recorded.

5.3 MODE OF TREATMENT- CONTINUOUS ADMINISTRATION AND PRODUCT SWITCH

Session 5.3, chaired by J. Ingerslev, addressed the influence of the mode of treatment - continuous administration and product switch - on inhibitor development. Two presentations were given, followed by a round table discussion, in order to provide consensus statements to the three proposed questions.

Presentations

J. van der Bom presented the ideal study design for inhibitors in haemophilia A from an epidemiological point of view. While risk factors for inhibitor development in PUPs (e.g. type of gene mutation, ethnicity) are established, there is little knowledge about the risk factors for inhibitor development in PTPs. Intensity of treatment (continuous infusion, prophylaxis) and switch of product have been investigated as possible risk factors for PTPs. J. van der Bom questioned the feasibility and ethics of a randomised controlled trial to study the occurrence of inhibitor development under continuous infusion in comparison with daily bolus injections due to the high patient number required (2282 PTPs and 96 PUPs). Because of the limited number of haemophilia A patients, case control and cohort studies requiring a smaller sample size are more realistic. Attention should be moved from the determination of incidence to the investigation of risk factors, which cannot be studied in randomized controlled trials. Most knowledge is based on observation and the ideal situation from the epidemiological perspective would be when every patient would carry an electronic logbook for data on treatment and side effects to be entered into a central research data base bi-annually. In addition,

due to the very limited number of patients, it is important for haemophilia treaters to join forces and collaborate across borders.

G. Auerswald presented epidemiology data of inhibitor formation in Bonn and Bremen before 1990 and between January 1990 and July 2001 in patients under immune tolerance therapy (ITT) treated with plasma-derived FVIII concentrates solely and patients treated with recombinant FVIII products. Prior to 1990 the success rate of ITT with plasma-derived FVIII products was 87% (44 /51 cases) at these centres. From 1990 to 2001 the success rate was 82% with plasma-derived high purity FVIII products (23/28 cases) and 43% with recombinant FVIII products (6/14). 13 patients, who failed ITT and were initially treated with highly purified plasma-derived or recombinant FVIII products, were switched to plasma-derived intermediate purity VWF containing products and immune tolerance was achieved in 10 of 13 patients. The inhibitor reappeared in 2 patients after changing back to high purity FVIII product but disappeared under treatment with a VWF-containing intermediate purity plasma-derived FVIII concentrate. In conclusion, FVIII concentrates containing VWF may possess a reduced immunogenic potential.

Discussion and Conclusions

Experts and regulators (G. Auerswald, B. Ljungberg, I. Scharrer, J. van der Bom, M. van den Berg) participated in the round table discussion: Three questions were addressed by the group, dealing with potential impacts of administration practice, continuous infusion and product switch on the development of inhibitors.

- *Does administration practices (like prophylaxis and on-demand treatment) influence the development of inhibitors?*

The data from the Canal study presented by M. van den Berg in session 5.2 indicated that there is a correlation between prophylaxis / on-demand treatment and the occurrence of FVIII inhibitors: there were significantly less inhibitors in patients under prophylaxis regimen. Some of the participants raised the issue that these results could be confounded by the fact that prophylaxis starts later in life, when a lower risk of inhibitor development exists. In the Canal study, a time dependent analysis was performed in order to take into account this confounding factor.

Available data in literature seem to support the notion that prophylaxis might be protective with regards to inhibitor development.

Nevertheless, because a limited amount of data are available on this topic, the respective impacts of on-demand / prophylaxis regimens on the development of FVIII inhibitor need to be further investigated.

- *Does administration by continuous infusion influence the development of inhibitors and is there a need for specific data related to administration by continuous infusion?*

I. Scharrer started the discussion by reporting on a retrospective trial on inhibitor occurrence after continuous infusion in Germany. Two hundred continuous infusions were performed in 128 patients, of which 14 developed an inhibitor (3 PUPs, 9 PTPs; 5 patients with severe, 1 with moderate and 8 with mild haemophilia). Four of these 14 patients (29%) had a missense mutation, which is striking since J. Oldenburg and colleagues found only 4% missense mutations in more than 100 inhibitor patients. The other 114 patients who did not develop an inhibitor were suffering from severe (78), moderate (8) and mild (8) haemophilia A and from haemophilia B (7). Taken together these data indicate that continuous infusion in patients with mild haemophilia A should be carefully evaluated.

Participants agreed that there is a need of control data and further investigations to fully answer this question, particularly in mild haemophilia. Participants raised the issue of confounding factors, such as intensity of treatment and ED. The number of ED is lower in patients with mild haemophilia and most of these patients are constantly at risk of developing an inhibitor during high-intensity treatment.

- *The change from one product to another might booster or silence an existing FVIII inhibitor. Currently there is insufficient follow-up on these cases. How should the follow-up after a switch to another recombinant FVIII or plasma-derived FVIII product be standardized?*

I. Scharrer reported on the review of the risk for inhibitor development in PTPs when switching from plasma-derived to recombinant FVIII. In a series of 5 clinical trials with a total of 307 patients, one patient was found with a de novo, transient low titre inhibitor.

For pharmacovigilance reporting, it appears important to obtain information about possible product switches before and after inhibitor detection.

The participants agreed that possible ill effects of product switching could be extracted from registry data. The need for a European or international registry was emphasized.

Nevertheless, no consensus on whether increased inhibitor testing should be implemented after a product switch was reached. Testing recommendations are different depending on the countries: in United Kingdom, every 6 months is recommended, while in France, after a product switch, inhibitor testing is recommended after 10-20 exposure days, and thereafter according to the patient status: in PTPs, inhibitor testing is performed upon each visit (one or two per year), while in PUPs with severe haemophilia, inhibitor testing is regularly performed every 5-10 until 50 ED, then every 3 months until 100 ED, then every 6-12 months.

5.4 DURATION AND FOLLOW UP, SAMPLE SIZE

Session 5.4, chaired by J. Ingerslev, addressed the duration, follow-up and sample size of clinical studies on inhibitor development. One presentation was followed by a round table discussion.

Presentation

J. Goudemand presented an overview of all available literature data on the scope of the session. While the occurrence of inhibitors is a relatively frequent and early event in PUPs, it is rare in PTPs. Therefore, duration and follow-up in clinical studies should be differently defined for PUPs and PTPs and should be long enough to detect the possible occurrence of inhibitors. In published studies, duration was monitored in exposure days and/or exposure months. Depending on the reasons for use (intensive treatment/ prophylaxis/ on demand), the same number of exposure days was accumulated in very different time periods and it is very likely that the patients were not exposed to the same inhibitor risk. J. Goudemand concluded that in PUP studies, all inhibitor risk factors as well as the exposure days or period of exposure should be documented until at least 50 cumulative ED. In PTPs inhibitor risk factors are probably more therapy-related than patient-related (intensity of previous exposure (>50, > 100, >150 ED), intensity of treatment, prophylaxis, mode of administration, product switch) and should be documented in a defined way. According to current practice in France, Italy and UK, the recommendation for the duration of inhibitor screening is a combination of ED and period of administration. J. Goudemand recommended monitoring clinically relevant inhibitors depending on titre and therapeutic consequences.

Discussion and Conclusions

Experts and regulators (J. Goudemand, C. Lee, R. Seitz, J. van der Bom) participated in the round table discussion. Three questions were addressed dealing with duration, follow-up and sample size required in clinical studies in order to enable proper assumptions on the FVIII inhibitor occurrence.

- *Duration and follow-up are important parameters to compare the FVIII inhibitor incidence in clinical studies. As published in literature, the FVIII inhibitor incidence observed over 2 or 4 years differs. How long should the duration and follow-up period be and how should it be defined, based on exposure days or years? Which clinical and laboratory parameters should be monitored and in which intervals (e.g. prophylaxis, treatment on-demand, consumption, number of bleedings, FVIII plasma level, inhibitor measurement) ?*

The requirements for follow-up of PUPs and PTPs as well as the requirements for pre-authorisation and post-marketing studies should be clearly distinguished.

The risk factors for inhibitor development in PUPs are well understood and experts agreed that PUPs should be monitored for at least 50 ED in clinical trials independently of the exposure period. On the other hand there is limited knowledge about risk factors for inhibitor development in PTPs. Experts suggested a longer follow-up period for PTPs. Considering that patients have the freedom of choice of product and treatment, they should be monitored as long as they are treated with one given product, e.g. through registries.

As previously mentioned in session 5.1, due to the small patient population, it is difficult to obtain firm evidence concerning immunogenicity of a product in pre-marketing clinical studies. According to the current CHMP note for guidance on clinical investigation of plasma-derived and recombinant FVIII products, pre-licensing immunogenicity data should be obtained in 50 PTPs to show that the product under evaluation does not exhibit any signs of abnormal immunogenicity compared to other products on the market. In this context, a follow-up of at least 50 ED seems to be relevant.

On the other hand, post-marketing studies can allow more freedom to request long-term data, notably regarding inhibitor development.

- *Should the number of exposure days to the product under which the FVIII inhibitor developed be given?*

All the participants agreed to collect the number of exposure days to the product under which the FVIII inhibitor developed.

- *Concerning statistical evidence for a risk of inhibitor formation how should the sample size and observation period in clinical studies be defined to enable proper assumptions on the FVIII inhibitor incidence in PUPs and PTPs?*

During the meeting, the FDA approach of pre-defining a cut-off for inhibitors was discussed. For the participants, it appears quite difficult to pre-define such a cut-off, based on pre-licensing data, which appear insufficient (see J. van der Bom presentation in Session 5.3). Any inhibitor case seen should be carefully analysed.

From the presentation of J. van der Bom, it appears that randomised controlled trials to investigate inhibitor incidence are difficult to perform due to the high patient number required. Case control studies in PTPs could be a possible approach in order to get reliable and relevant data on inhibitor risk factors.

SESSION 6 REGISTRIES

Session 6 was chaired by C. Lee. The aim of this session was to discuss experiences gained with patient registries. For this purpose, 5 presentations were given followed by a plenary discussion.

C. Lee opened the session by highlighting the importance of epidemiological data on FVIII inhibitor formation. C. Lee mentioned that excellent data from national registries are already available in some countries. The survey of the existing registries provided by the EMEA was tabled for information. According to the survey, there are national registries in at least 10 Member States and registries are under construction in three Member States. The European paediatric organisation for haemophilia management (PEDNET) also includes a paediatric registry (www.pednet.nl). The International Society on Thrombosis and Haemostasis (ISTH) also has a database for FVIII Deficiency.

Presentations

The question of the potential benefits from introduction of a haemophilia patient registry and the link/exchange of data subsets between registries that could be provided was elaborated in the following presentations.

M. Soucie gave a presentation on the United States Pilot Study of Inhibitors in Haemophilia. The study is based on the Universal Data Collection (UDC) program, which monitors blood safety among recipients of blood products. Even though the UDC is not designed to study inhibitors, some related data are collected including demographics, bleeding frequency, inhibitor test results and all product brands used. In a preliminary study, 2.75 new inhibitor cases per 1000 person years were verified. No robust conclusion on the immunogenicity of different products could be made due to lack of statistical power. M. Soucie explained that, in the pilot post-marketing study, a data coordinator is employed to collect the factor exposure data and ensure the annual blood testing. Methodologies to collect required treatment and bleeding information are being explored. Inhibitor testing is performed in a centralised laboratory. Inhibitor testing is to be done annually and prior to any planned product switch. In addition complete gene sequencing in a central lab is planned. Inhibitor history, infusion logs and product details are collected using specific data collection forms, electronic data entry from the sites and by patient.

M. Soucie mentioned that, when fully implemented this approach will provide the benefits of large population monitoring that yields the most power for studying rare events, permits product choice and avoids random assignment to treatments, and facilitates the quality control of the study. He also elaborated on the need for international collaboration in this field to increase study power and diversity of products monitored.

C. Hay presented the results from the UK National Haemophilia Database (NHD), which was established in 1968. The database collects data to provide national statistics to promote improved healthcare for patients with bleeding disorders. The new diagnoses, deaths and patient demographics are reported. Annual treatment data, including products used, are available from the whole UK. Inhibitors and other adverse events are reported. A vCJD database has been recently developed. The system has a real-time adverse event reporting and quarterly on-line reminders for adverse events. C. Hay showed that the use of recombinant products has been increasing while the use of plasma-derived products has been decreasing from the late nineties. In haemophilia A patients, about 13% have less than 1BU inhibitors, less than 9 % have 1-5 BU inhibitors and only about 1 % have severe haemophilia with more than 5 BU inhibitors. In 1991-2001 28 % of patients changed products. The incidence of inhibitors is highest in the age group from 0 to 9 years of age (22 % in 1990-2003), and decreases remarkably with increasing age (0.5 % in patients aged from 10 to 19 years). The incidence increases again during the fifth and sixth decades. Data on the relative risk by product is not complete and the data between PTPs and PUPs are not directly comparable. The exposure data is available only for younger patients and the risk can be expressed only in terms of treatment years. C. Hay concluded that there seems to be no clear difference between the recombinant products and an improved dataset will be more informative in this regard.

B. Haschberger gave an overview on the building of a national register in Germany. According to the German Transfusion Act, the number of patients with haemophilia, with inhibitors, and the amount of product consumption figures are collected to obtain data concerning the supply situation. Since 1999 the data have been requested in paper questionnaires from the haemophilia treating physicians. The new German register is intended to provide an extended database to enable scientific evaluation to optimise the treatment of the haemophilia patients and to reduce unnecessary exposure and costs. It is also considered important to aggregate international data and harmonise definitions with other national registries. However, several challenges were faced. The German Transfusion Act foresees only the collection of summarised data, but a registry needs individual patient data. Due to the very high impact of data protection in Germany, it was important that the data would be securely anonymised and no list of patients would be generated. The registry will ensure that the data protection mechanism will enable long term follow-up, and diagnostic and therapy data will be included, as well as other extensions like adverse effects and infections. User-friendly software was considered essential for the motivation of the treating physicians. B. Haschberger stated that the German Haemophilia Register, which is planned to start by the end of 2006, is a joint activity of Paul Ehrlich Institute, German Ministry, the German scientific society GTH (Gesellschaft für Thrombose- und Hämostaseforschung), and the patient organisations DHG (Deutsche Hämophilie Gesellschaft) and IGH (Interessengemeinschaft Hämophiler).

H. K. Hartl, chairperson of the European Haemophilia Consortium (EHC) (44 National member organisations) gave the patients' perspective on registries. He pointed out that the number of national

registries in Europe and worldwide is low, even though the registries are vital in many aspects. The difference of registries vs. epidemiological surveys is often neglected and comparisons between the data not possible. In February 2006, the Western European national member organisations (NMO) Advocacy Initiative (a World Federation of Haemophilia (WFH) – EHC joint activity) considered the lack of national patient registries as number four in the list of threats for patients. The patients' organisations have been active in increasing the awareness of the disease at the political level and in promoting the concept of enhanced cooperation between people with haemophilia, the medical profession and health policy makers.

Discussion and Conclusions

W. Schramm opened the discussion by presenting preliminary data from an annual questionnaire from 1980 to 2005 on inhibitor prevalence in Germany.

The following question was addressed in the discussion of this session:

- *Which benefits would the introduction of a haemophilia patient registry and the link/exchange of data subsets provide?*

Based on the presentations and discussions the following conclusions can be drawn:

There is a clear need for registries. This comprehensive database on factor exposure enables scientific evaluation to optimise the treatment of haemophilia patients and identification of areas for research.

International collaboration will be desirable in this area to increase study power and diversity of products monitored. The starting point could be a network of national registries. Common criteria for data collection are essential to ensure that data are compatible between national registries in order to allow pooling of anonymised data. It was proposed by experts to refer this topic for further consideration by the ISTH SSC Subcommittee on FVIII and FIX, who has already established a working party to develop a consensus minimum international data set for registries.

The main challenges identified were resource issues, compliance issues with the data protection act in the EU, the definition of the data to be collected and combined, and the motivation of the treating physicians to collaborate. Public funding for registries was advocated. All physicians should be encouraged to participate at the national level by explaining the benefits of the registries.

SESSION 7 RISK MANAGEMENT, POST-MARKETING STUDIES AND PHARMACOVIGILANCE FOR FVIII PRODUCTS

The aim of this session chaired by C. Kreft Jais was to present the risk management plan procedure recently introduced in EU and to give the opportunity for the Industry to present its view on pharmacovigilance and risk management aspects for FVIII products.

Presentations

S. Blackburn presented the recent EU guideline on the Risk Management System and explained in which situations applicants should consider a Risk Management Plan. Briefly, the description of the risk management system is submitted in the form of a risk management plan. This plan consists of two parts: (I) the safety specifications and the pharmacovigilance plan; (II) the evaluation of the need for risk minimisation activities and, in addition, a risk minimisation plan, in case of the need for additional (i.e. non-routine) risk minimization activities.

J. Feingold and T. Steinbach presented Wyeth's approach on pharmacovigilance and risk management for FVIII inhibitors. Wyeth clearly advocates the use of registries and recommends a global comprehensive registry with participation of all MAHs, uniform data collection, and standardized laboratory assays.

G. Lemm presented the view of Bayer on clinical trials and post marketing surveillance. It is proposed to include large post-marketing studies with the general objective to evaluate long-term safety and efficacy, and with the specific objective to assess inhibitor risk and perform signal detection on a routine basis with a comprehensive follow-up program.

H. Ehrlich and B. Ewenstein presented Baxter's views on risk management and lessons learnt from registries. A post-marketing surveillance clinical program is considered of utmost importance to contribute to a reliable assessment of inhibitors. Baxter considers that prospective clinical trials in PTPs remain the best indicator of product-related immunogenicity. Baxter considers also that studies in immunologically naive patient populations are confounded by sample size and genetic /non-genetic risk factors. The need of standardisation of key variables (e.g. inhibitor assay, inhibitor definition, duration of observation, immune tolerance treatment methodology) is essential.

F. Bridey presented joint position statements of the International Plasma Fractionation Association (IPFA) members for pre- and post-marketing studies. The importance of defining the best conditions for clinical study design was highlighted to avoid statistical bias, to define the population (severity <1%), to monitor the mode of treatment, and define laboratory parameters. The example of a retrospective study in 104 exhaustive PUPs treated with one plasma-derived FVIII product, a pre-marketing study in PTPs and a post marketing study in PTPs was given.

C. Waller presented the Plasma Protein Therapeutic Association's (PPTA) view on RMP and pharmacovigilance for FVIII products. PPTA member companies do not anticipate any difficulties in implementing the EU guideline on risk management and are committed to work with the authorities on additional approaches for accurate determination of FVIII inhibitor frequencies. PTPs remain the patient population for the investigation of product related immunogenicity and pharmacovigilance is seen as the mainstay of post-licensing risk management. Non-interventional prospective data collection is supported for which a standardised protocol could be implemented in all countries. The FVIII inhibitor assay needs to be further standardised and ideally should be performed in some coordinated laboratories.

Discussion and Conclusions

A risk management plan should be considered for a new product or when a modification to an already approved product is introduced, taking the known genetic and environmental risk factors of inhibitor development into account as well as the severity of this rare serious adverse event.

The pharmacovigilance plan needs to clearly address the assessment of known risks (e.g. risk profile) and its standardized evaluation and the reporting of adverse reactions (ADRs; definition of inhibitors based on laboratory results, clinical signs and recovery and half-life). It needs to be highlighted that every inhibitor detected should be reported in the clinical trial setting and in pharmacovigilance surveillance. In this respect, the role of health care professionals is of utmost importance in order to help health authorities in assessment of pharmacovigilance.

The type I inhibitor is the clinically most dominant inhibitor in haemophilia A and the primary focus of haemophilia treaters. Nevertheless, there should also be alertness for type II inhibitors with their different kinetics. Type II inhibitors were induced under treatment with one modified double-virus inactivated plasma-derived FVIII product (SD + heat treatment at 63°C), which disappeared when patients were taken off the product (see also 5.1).

For a clear observation of rare ADRs, it was reiterated that registries would be an important tool to follow-up patients throughout the life-long course of disease and treatment.

CLOSURE OF OPEN SESSION

B. Ljungberg chaired this part of the meeting, in which the chairpersons from the single sessions gave final remarks.

In conclusion, inhibitor development in PTPs remains the focus of observation for pre-authorisation studies of new and modified recombinant and plasma-derived FVIII products. Standardized protocols for enrolment into the trials as well as for the conduct and evaluation of these studies are needed.

These protocols should contain defined risk factors and be based on ED rather than a specific time period (see previous experience in 5.1).

The need for a risk management plan for FVIII products was clearly identified by all stakeholders in order to enable the detection of inhibitors. The need for registries, large observational studies, and reporting of adverse events are important aspects in the pharmacovigilance setting.

However, from the discussion with the Experts, it was difficult to reach definite conclusions on the recommended design of post-marketing studies and, therefore, this would be further considered by CHMP's Blood Products Working Party and Pharmacovigilance Working Party.

RESTRICTED SESSION ON 2 MARCH 2006,

BPWP MEETINGS IN JUNE AND SEPTEMBER 2006,

RECOMMENDATION FOR THE REVISION OF THE

**NOTES FOR GUIDANCE ON CLINICAL INVESTIGATION OF RECOMBINANT
AND PLASMA-DERIVED FVIII PRODUCTS**

Summary of Restricted Session and BPWP meetings

At the restricted session on 2 March 2006 and the BPWP meetings in June and September 2006, European regulatory experts discussed the views and consensus expressed by experts during the open session on 28 February and 1 March 2006 as follows:

In line with common clinical practice, the diagnosis of a FVIII inhibitor in a haemophilia A patient should primarily be based on clinical observations and be confirmed by FVIII inhibitor testing in the laboratory. The collaboration between clinical and laboratory staff is of most importance. For valid FVIII inhibitor results it is very desirable that also clinical laboratories working under field conditions participate in proficiency studies.

PTPs are defined as patients with more than 150 ED and PUPs as patients with no previous exposure to clotting factors. The suggested categorisation of patients in low-, intermediate- and high-risk groups will be further discussed during the revision of the guidelines on clinical investigation of plasma-derived and recombinant FVIII and FIX products.

From a regulatory point of view, health authorities must obtain sufficient assurance, before granting a marketing authorisation, that a new or modified product does not exhibit excessive immunogenicity. PTPs, who are clinically stable under regular replacement therapy, should be immunotolerant to FVIII, and an enhanced incidence of inhibitors would be unexpected and would be a signal of increased immunogenicity. Therefore for pre-licensing studies, PTPs appear to be the most relevant study population and should remain the target for the pre-marketing clinical studies. Standardised protocols for the enrolment into the trials, for the conduct of the inhibitor assays, especially for the non-interventional studies, and for the evaluation of the trial results are strongly requested.

The need for studying paediatric patients should take into account the Paediatric Regulation. Furthermore, the specific need for paediatric studies for new plasma-derived, new recombinant and modified products (e.g. pegylated) should be considered separately. PUPs are rare patients and BPWP members felt that data in PUPs should be collected when PUPs receive innovative products.

The risk profile is important for the evaluation of data and should be reflected as far as possible by the population studied. For pre-authorisation studies, preferably all known risk factors should be included in the investigation of the product and considered for the evaluation of data, e.g. genetics, age at onset of treatment, immunological situation strongly in correlation with age. According to the current status of scientific knowledge, this should be part of the protocols. For randomized trials there may be the need to match risk factors in study groups. To what extent these aspects may be appropriate for the post-marketing situation, will be further considered during the revision of the guidelines.

With regard to the small haemophilia A patient population, it is considered difficult to obtain firm evidence concerning immunogenicity of a new or modified FVIII product in pre-marketing clinical studies. Moreover, it appears difficult to set a predefined limit for the inhibitor incidence in PTPs solely on the basis of statistical considerations, without knowing the true incidence with plasma-derived and recombinant products on the market.

Considering these points, it is concluded, that the full immunogenicity evaluation of a given product could not be performed in the pre-marketing stage and it is important to foresee particularly efficient mechanisms of monitoring and pharmacovigilance for the post-licensing period. A complete

evaluation of product immunogenicity requires long-term data, which could only be obtained from post-authorisation setting, via post-marketing studies or registries. Post-marketing studies allow requesting of long-term data. An adequate design and standardization of post-marketing studies is of great importance, in order to collect relevant and reliable data to enable proper assumptions on FVIII inhibitor occurrence related to products. All these requirements should be reinforced in the revised guidance. Nevertheless, with an observational design, it will be difficult to stay on one given product, or one type of treatment, over an extended period.

It may not be evident to health care professionals when there has been a change to a specific product on the market through a modification in the manufacturing process. Therefore, in this context, it is of importance that MAHs commit to undertake appropriate inhibitor monitoring also after manufacturing changes. These requirements should be clearly highlighted in a risk management plan.

Also in post-marketing studies, the number of patients will be limited. Therefore, the establishment of national registries with harmonised data sets is strongly supported. In June 2006, as recommended during the expert meeting, CHMP contacted the ISTH SSC Subcommittee on FVIII and FIX products for collaboration on common data sets and also on FVIII inhibitor assay.

BPWP members noted that a new generation of recombinant FVIII products with longer half-life is in development and new experience on FVIII inhibitor development might be gained.

An additional point, which has been raised, concerns the meaningful information on inhibitors, which should be mentioned in the relevant sections of the SPC of a given product. Revision of the core SPC should clearly define what type of data should appear, in order to be as informative as possible for clinicians and patients with regards to the development of inhibitors.

Further Observations and Conclusions, as well as Recommendations for the Revision of the Notes for Guidance and core SPCs

In line with the consensus reached during the open session of the expert meeting, regulatory experts agreed with the following requirements and recommendations for the pre- and post-authorisation monitoring of inhibitor development in haemophilia A patients:

FVIII inhibitor assay

- The Nijmegen modification of the Bethesda assay is recommended for pre-authorisation studies and for post-marketing surveillance. Validated testing should be performed in a centralised laboratory for pre-licensing studies.
- Optimisation of the Nijmegen modification of the Bethesda assay should address the detection of type I, and also type II inhibitors.
- The participation of laboratories involved in clinical studies in proficiency and collaborative studies is essential.
- A threshold of ≥ 0.6 BU for the diagnosis of a low titre inhibitor was defined as well as a titre of ≥ 5 BU for a high titre inhibitor.
- A confirmatory test on a second, separately drawn sample should always be performed in a qualified laboratory. This second sample should be taken prior to any change of treatment and shortly after the previous positive test (within a month).
- For routine inhibitor testing, the inhibitor test should be performed when the plasma FVIII level has reached a pre-substitution nadir rather than at a specific time point. The inhibitor assay should be validated for the impact of residual FVIII on the test results.

Clinical conditions interfering with the FVIII inhibitor assay

- Presence of exogenous or endogenous FVIII: The interference of residual FVIII activity with the FVIII inhibitor assay can be circumvented by heating the sample in a validated step (e.g. one hour pre-treatment at 58°C).
- Lupus anticoagulant (LA): Differentiation of LA from FVIII inhibitors may be crucial, because of the different therapeutic interventions required. Two or more positive test results, particularly from assays with different designs, are more informative and more likely to differentiate LA from anti-FVIII inhibitors.

- **Heparinised ports:** In general, it is recommended for FVIII inhibitor testing to take blood from a vein and not from a port, as flushed heparin has an impact on FVIII inhibitor measurement.
- **Chronic viral infections:** Inhibitors have been detected in patients with chronic viral infections (e.g. HIV, HCV) during anti-viral therapy.

Clinical signs of inhibitor occurrence to be monitored

- **PTP:** Increased bleeding tendency, high consumption, lack of response or efficacy, decreased recovery, shortened half-life are indicative for an inhibitor in PTPs.
- **Infants and young children:** Poor response to treatment, including prophylaxis, is a useful clinical sign of inhibitor occurrence. High titre inhibitors may be indicated by an increased bleeding tendency (e.g. joint bleeds), while treated under a FVIII prophylaxis regimen. Effectiveness of treatment of a fresh joint bleed is measurable. Low titre inhibitors will probably not be detected under FVIII prophylaxis regimens. It is recommended to look at incremental recovery in a sample after infusion. Greatly reduced or no FVIII activity are indicative of an inhibitor. High consumption and increased bleeding are less reliable indicators in infants and young children.
- Careful consideration of all parameters is required, because some inhibitor patients do not bleed.

Clinical relevance of low titre inhibitors

Transient and low titre inhibitors might become a clinically relevant inhibitor in a PTP later in life. This indicates the importance of prolonged follow-up of patients. Such long-term data are much more difficult to collect, but are essential for pharmacovigilance assessment and registries. An additional difficulty in the interpretation of data is that FVIII inhibitor routine testing will often only be carried out in local laboratories rather than a central laboratory.

General recommendation for monitoring inhibitors

- Monitoring of inhibitor development should be started at the onset of treatment with a new or modified product in order to obtain solid baseline data.
- Regular laboratory measurements for inhibitors should be implemented in clinical studies. In addition, clinical signs suggesting inhibitor development should be defined and used to trigger investigations between the regular laboratory visits.
- Routine testing for inhibitors should be carried out on a regular basis. In particular, testing should be frequent in the early stages of replacement therapy. However, frequent sampling may prove difficult in young children.
- In order to identify product-related immunogenicity, all inhibitors should be documented and reported.
- Linking clinical and laboratory findings is very important.

Study population

- Product-related inhibitor development should be studied in PTPs pre-licensing.
- MTPs should not be included together with PUPs.

Definitions

Severe haemophilia A: FVIII baseline level of <1%. For pre-licensing studies, this definition (<1%) should be applied for PTP. In post-licensing studies, also patients with up to 2% baseline level may be included in the protocol for severe haemophilia A, when a separate statistical evaluation for <1% and <2% is provided.

PUP: Patients who never had exposure to clotting products, previous exposure to blood components is not excluded.

PTP: Patients at low risk, e.g. more than 150 ED.

MTP: not clearly defined and not useful concept.

Patient characteristics to be reported

Age

Age at time of first exposure to FVIII

General health status (infections (HIV, Hepatitis and other infections), vaccination)

Reason for treatment (e.g. bleeding, surgery)

Regimens and intensity of treatment (prophylaxis or on demand, in case of surgery continuous infusion or bolus injection, dosages and intervals)

ED (total, and to product under which treatment inhibitor developed)

Genetic risk factors:

Severity of haemophilia A

Gene mutation

Family history of inhibitors

Ethnicity

Mode of treatment

Prophylaxis vs. on demand treatment and continuous infusion

More data should be generated by post-marketing studies and pharmacovigilance reporting on inhibitors, in which information on prophylaxis vs. on demand treatment regimes and continuous infusion are being gathered.

Product switch

For pharmacovigilance reporting, it is important to get information about product switches before and after inhibitor detection. Respective data should be provided. The effects of product switching could also be investigated from registry data. The need for a harmonised data set in order to enable European or international evaluation is emphasized.

Also after changes to a specific product because of modifications in the manufacturing process, appropriate inhibitor monitoring should be undertaken. These requirements should be clearly highlighted in a risk management plan.

Duration and follow-up

Patients should be followed up for at least 50 ED, independently of the exposure period, in clinical studies performed prior to marketing authorisation. Long-term data can be obtained from post-authorisation setting, via post-marketing studies or registries (see below).

Sample size

Considering the small patient population, case control studies in PTPs could be a possible approach to get reliable and relevant data on risk factors for inhibitor incidence. In principle, any inhibitor case seen should be recorded.

Registries

A network of national registries with common criteria for data collection is desirable to ensure that data are compatible between national registries in order to allow pooling of anonymised data. This topic has been referred for further consideration to the ISTH SSC Subcommittee on FVIII and FIX.

Risk management, post-marketing studies and pharmacovigilance for FVIII products

The need for risk management plan, registries, large observational studies, and reporting of adverse events are important aspects in the pharmacovigilance setting for FVIII products.

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