(参考) マコファルマ社回答 (英語)

MacoPharma

Robert-Bosch-Straße 11
D-63225 Langen
Bestellannahme Infusion
Telefon: +49-(0) 6103-9008-88
Telefax: +49-(0) 6103-9008-20
Zentrale Verwaltung
Telefon: +49-(0) 6103-9008-0
Telefax: +49-(0) 6103-9008-90
www.macopharma.de

Maco Pharma International GmbH · Robert-Bosch-Straße 11 · D-63225 Langen

Mr. Takahiro GOTOU
c/o Blood & Blood Products Division
Pharmaceutical & Food Safety Bureau (PFS)
Ministry of Health, Labour and Welfare (MHLW)

1-2-2, Kasumigaseki, Chiyoda-ku

Tokyo, JAPAN, 100-8916

Your Reference: Your Message of: Our Reference: Dr.W./AH Date: April 30th, 2008

Committee questions from April 24th, 2008

Dear Sirs,

following you will find answers to the questions raised by you on the Theraflex MB Plasma on April 24th, 2008.

1. **Actual conditions of blood products supply in each country, where the inactivation has been implemented**
   (*Please specify the total number of blood products supply with breakdown of inactivation processed and non-processed blood products in %. Also, describe, whether all supplied blood products must be processed mandatory or user (physician or hospital) can chose one).*

   ANSWER:

   Supply of pathogen reduced blood products by countries:
   In our letter of 31.3.2008 to you, we indicated in Table 1) the list of countries, where the Theraflex MB Plasma has been registered and used in clinical routine. Below you will find a table of the countries with the actual quantities of plasmas treated in 2007 and the percentage of the total therapeutical plasma units treated by Theraflex and/or by other methods.

Geschäftsführer:
Peter Kremmers
Amtsgericht Offenbach HRB 33620
UST-ID-Nr. DE 119 109 470

Deutsche Bank AG
BLZ: 505 700 16 · KTO. 781 777 800
BIC: DEUTDEFF505
IBAN: DE46505700180781777800

Dresdner Bank
BLZ: 500 800 00 · KTO. 926 000 00
BIC: DRESDEFF
IBAN: DE71500800000092600000

Country	Inactivation for plasma mandatory	Quantity of plasmas treated with Theraflex MB plasma	% of Theraflex to therapeutical plasma	% of inactivated plasma to therapeutical plasma
Argentina	No	2000	-	-
Belgium	Yes	70000	100	100
Brazil	No	2000	-	-
France	Yes (in future)	150000 (in 2008)	60 (in 2008)	100 (in 2008)
Greece	No	8000	5	-
Italy	No	34000	5	25
Malaysia	No	300	-	-
Russia	No	17000	1	1
Singapore	No	1000	-	-
Spain	No	105000	44	69
UK	No	9000	2	2

In Belgium and France the National Transfusion Services offer only pathogen reduced plasma products (in Belgium since 2004, in France conversion is planned by 2009).
In all other countries the physicians and hospitals are still free to use their plasma (pathogen treated or quarantine plasma) by themselves. However, the trend in Europe goes clearly to pathogen reduced plasma products and pathogen reduced platelet products.

2. **Leukocyte reduction:**
The trend of blood transfusion related side effect occurrence rate, such as GVHD, with inactivation processed with leukocyte reduction and without leukocyte reduction.

ANSWER:
Please note, that leucodepletion of all red cells and platelets is mandatory in Europe for all countries since many years.
The number of febrile transfusion reactions has decreased since significantly after Introduction of universal leucodepletion (see f.ex. *M. M. Mueller et al.*, "Clinical impact of leucocyte depletion – what is the evidence?"; Science series (2008), 3: 85-90).
To avoid GvHD, blood products are still gamma-irradiated. However, it is expected, that platelet pathogen reduction technologies, including the THERAFLEX UVC-treatment by MacoPharma, will substitute gamma-irradiation of platelet concentrates.

3. **Test:**
The existing tests and/or processes, such as leukocyte filtration and NAT, which can be omitted after inactivation implementation.

ANSWER:

In the different countries where the process is implemented the quarantine storage is omitted. This leads to be,tter logistics, reduced storage space, and immediate provision of the plasma.
Neither leukocyte filtration nor any at the time of implementation of the MB procedure used test for infection markers was stopped in any country. Nevertheless, the implementation of new tests or tests with enhanced sensitivity, like single NAT was also not done after introduction of the MB procedure.

Plasma:
In Europe the THERAFLEX MB-Plasma Procedure substitutes leucodepletion of plasma, since the membrane 0.65 µm filter is more efficient than a plasma leucodepletion filter.

Platelets:
We expect, that the THERAFLEX UVC-Platelet Procedure will substitute in the future both gamma-irradiation as well as bacterial screening.
We do not recommend any substitution of viral NAT-Testing for the moment

4. **Post marketing surveillance:**
(*Specify the actual condition of the PMS including total number in each country):*

ANSWER:
Post market surveillance is done by Blood Transfusion Services and by Hemovigilance procedures installed in all European Countries with most experience available in the U.K. and in France.
All European countries have ongoing Hemovigilance programmes for all components, which includes MB-treated plasma.
Additional, we have follow-up studies (like Phase IV Clinical Study on MB-Plasma In France) or Publications on clinical use of *Politis et al.* [Vox Sanguinis, (2007); Volume 92,Issue 4, Pages: 319-326], as already mentioned in our last letter to you dated 31.3.08, under point 4.b).

We do hope to have answered clearly to all your questions arising on April 24th, 2008.
If something is still unclear, please do not hesitate to approach us.

Sincerely yours,

MacoPharma International GmbH

Dr. Wolfram H. Walker
- Scientific Director -

Dr. Stefan Reichenberg
- Project Manager Pathogen Inactivation -

Copy: - Mr. Gus Ribeiro, General Manager, MacoPharma Asian / Pacific Region;
- Mr. Hirotaka Nagase, AMCO Inc., Tokyo / Japan;
- Mr. Kenzo Watanabe, AMCO Inc., Tokyo / Japan

BCT Japan 株式会社回答

４月８日運営委員会・安全技術調査会合同委員会後

追加質問事項２（各社共通）

１．EU主要国等、各社の不活化技術を導入しているそれぞれの国における供給の実態。輸血用血液製剤の全供給数（不活化技術を適用している製剤と適用していない製剤の合計）、そのうち不活化技術を適用している製剤の割合は何％か。また、供給はどのように行われているか（供給先、医師の希望により供給できるのか等）。

さまざまな病原体不活化技術 Pathogen Reduction Technologies（PRT）が開発されており、ヨーロッパでは現時点で通常使用されたり、さまざまな評価段階であったりしています。

－3 種類の血漿処理のできる PRT 処理方法が現在市場で販売されています。
Solvent Detergent 処理（1990 年代初期からいろいろな国で既に使用中）
Methylene Blue（2001 年以降市場に出て、フランス、スペイン、イタリア、英国で通常使用）
Intercept Blood System（2006 年以降 CE マーク取得：通常使用についてはは未確認）
Milasol PRT System は、2008 年に血漿処理で CE マークを取得予定です。

－2 種類の血小板処理のできる PRT 法が現在販売されています。
Intercept Blood System（2002 年の CE マーク取得以降、主にフランス、スペイン、ベルギー、ノルウェーとスウェーデンの血液センターで限定的に使用中）
Mirasol PRT System（2007 年後半に CE マーク取得済み。現在アイルランド、スペイン、イタリアと中東諸国のいくつかの血液センターで通常使用に向けた評価試験を実施中）

全体として、ヨーロッパでは輸血に使用されるすべての血小板製剤の 5%に PRT 処理が施されており、これらの製剤への PRT の使用は明らかに増加傾向があると我々は考えます。とりわけ血小板製剤について高い関心および使用を予定している国々には、フランス、ベルギー、アイルランド、スペイン及び中東諸国があります。

PRT 処理済みの製剤の供給および配送に関しては、PRT 処理方法の違いにより物流方法も異なります。Mirasol PRT での血小板と血漿の処理は短時間（処理時間は 15 分以内）で、しかも簡単に処理ができることから、血液センターの通常の血液成分製剤の製造