FAQ MB Situation in France
January 2013
• **MB-Plasma withdrawal in France**

1. **Q. What official reasons did AFSSAPS* give for their decision to withdraw THERAFLEX MB-Plasma from the list of approved labile blood products in France?**

   **A. 2 reasons:**
   1) more frequent allergic reactions with methylene blue (MB) treated plasma than with other types of treated plasma (solvent detergent (SD) plasma or Intercept (IA) plasma)
   2) a greater variability in the concentration of fibrinogen in MB treated plasma compared to the other types of treated plasma.

   * AFSSAPS: Agence française de sécurité sanitaire des produits de santé - French Drug and Medical Device Regulatory Agency has been replaced since May 2012 by ANSM: L’Agence nationale de sécurité du médicament et des produits de santé - National Agency for the safety of drugs and health products)

2. **Q. When was this decision made?**

   **A. AFSSAPS’s decision was communicated through an official press release on their website on October 12, 2011 and in the “Official Journal of the French Republic” on November 3, 2011: “withdrawal of MB-Plasma from the list of approved products, from March 1st, 2012”**

3. **Q. From which date was MB-Plasma withdrawn and no longer available in France?**

   **A. March 1st, 2012**

4. **Q. What types of secured plasma are authorised in France for therapeutic transfusions after March 1st 2012?**

   **A. Only aphaeresis plasma**
   3 treated plasma types:
   - Solvent Detergent treatment (SD plasma, EFS Bordeaux production site)
   - INTERCEPT Plasma (IA plasma, Cerus)
   - Quarantine plasma (Q plasma, EFS)
5. Q. What action has Macopharma taken against AFSSAPS’s decision for withdrawing MB-Plasma in France?

A. Macopharma has instituted proceedings against AFSSAPS’s decision before the French Administrative Supreme Court because of a serious manifest error of evaluation (Erreur manifeste d'appréciation). The law suit is that AFSSAPS/ANSM took a poor decision due to an incorrect analysis and interpretation of the available data.
**Allergies**

1. Q. What data were used to justify the claim that there were more frequent allergic reactions with MB-Plasma than with other types of treated plasma?

A. More frequent severe allergic events (SAE) observed between 2005 and 2009/2010 with MB-Plasma when compared with other treated plasma types (Q plasma and SD plasma) as outlined in the 2010 haemovigilance report.

<table>
<thead>
<tr>
<th>Pour les réactions d'imputabilité 1 à 3, les fréquences sont de :</th>
<th>Pour les réactions d'imputabilité 2 et 3, les fréquences sont de :</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 pour 19.269 unités de PFC-Se (2005-2009)</td>
<td>1 pour 42.393 PFC-Se (2005-2009)</td>
</tr>
<tr>
<td>1 pour 25.597 unités de PFC-SD (2005-2010)</td>
<td>1 pour 35.349 PVA-SD (2005-2010)</td>
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PFC - Plasma frais congelé : Fresh frozen plasma (FFP)
PFC-BM - Plasma viro-atténué Bleu de methylene : Methylene blue viro- inactivated plasma
PVA-SD - Plasma viro-atténué Solvant détergent : Solvent detargent viro-inactivated plasma
PFC-Se - Plasma frais congelé sécurisé par quarantaine : Quarantine FFP

2. Q. Why does Macopharma think that the 2010 haemovigilance report seems to indicate that there were more SAE’s observed?

A.

a/ AFSSAPS did not assess “comparable data” due to the incomparable periods of time concerned:
- In 2005, MB plasma was not transfused in France.
- In 2008, implementation of MB plasma in France: MB plasma was used only for 5 months, i.e. from August 2008.
- In 2009, MB plasma was used for 12 months
Therefore it is unsurprising that the number of SAE’s recorded in 2009 showed an increase as this represents 12 months of use versus 5 months in 2008.

b/ Various factors and events sensitised users to MB-Plasma in both 2008 and 2009 resulting in them recording more SAE’s

- **Users more vigilant in observing and recording allergic reactions**
  - The Commission Nationale d’Hémovigilance (CNHv) from AFSSAPS created a specific working group (groupe de travail – GT) to investigate
allergic reactions called “GT Allergie” which met for the first time on 30 June 2008. It should be remembered that the issue & transfusion of MB-Plasma started in August 2008.

- Users started to actively look for signs of allergic reactions when MB-Plasma was transfused to patients
  - In 2009 Afssaps’ communicated recommendations for the use of MB-Plasma - “do not transfuse MB-Plasma to MB allergic patients”.
  - In May 2009, CNHv put in place a new exploration procedure of serious allergic reactions (grades 3 and 4) when MB-plasma was transfused to patients

3. Q. What is Macopharma’s position regarding the conclusion that there are more frequent allergic reactions with MB-Plasma than with other types of treated plasma?

A. Macopharma has analysed the data provided in the 2010 haemovigilance report and considers that the statistical evaluation was not done correctly. Time frames included data for SD plasma and Q plasma from 2005 to mid-2008 when MB-Plasma was not in the market. In addition, the reporting habits changed because of the reasons described in Q2 in the Allergies section above.

Supportive Information:

  - The weaknesses in the data and analyses show that it is not possible to distinguish a relationship between the plasma inactivation systems and the allergic or total adverse event frequencies.
  - No rigorous comparative studies exist at present demonstrating a significant difference of allergic adverse event rates between THERAFLEX MB-Plasma and other inactivation systems used in France.

4. Q. Does the AFSSAPS Haemovigilance Report 2011 confirm that there are more frequent allergic reactions with MB-Plasma than with other types of treated plasma?

A. No. In contrast, 2011 data are in favour of MB-plasma. MB-plasma recipients in 2011 had the lowest serious adverse reactions incidence rate (1/206 578 units)
Furthermore, the AFSSAPS 2011 Haemovigilance Report confirms that there are no statistical differences in severe allergic adverse reactions between the different plasma inactivation systems (SD vs. IA vs. MB).

5. Q. Have other MB-Plasma users observed more frequent allergic reactions with MB-Plasma than with other types of treated plasma?

A. There are no published reports of any other user in the world observing more frequent allergic reactions linked to MB-Plasma. In contrast, there are reports from Greece and Austria stating lower adverse event rates for MB-Plasma compared to Quarantine plasma which was recently confirmed by a recent publication from France and the UK maintains their use of MB-Plasma.

Supportive Information:

**FRANCE**
- **Oral presentation:** A regional haemovigilance retrospective study of four types of therapeutic plasma in a ten-year survey period in France, V. Bost, H. Odent-Malaure, P. Chavarin, H. Benamara, P. Fabrigli & O. Garraud.
  - All types of FFP (Fresh Frozen Plasma) were associated with extremely very low occurrences of AEs.
  - The main strength of this study is to bring evidence that FFP is safe in general (AEs linked to FFP transfusion are infrequent, especially the severe ones; most reported were either unlikely minor)
  - This survey further shows that PI for plasma (SD, MB, IA) bring some reduction in AE compared to Q plasma
  - This study indeed confirms that all four types of FFP – including MB that delivery has been stopped on the claim of allergies in patients – are safe on the basis of individual link per product to AEs in patients.
  - There is no discrimination into the different AEs, especially the allergy cases are not separately analysed.

**GREECE**
  - The incidence of Adverse Reactions (ARs) is statistically significantly higher in quarantine FFP than in MB-FFP in Greece (2001-2011).
Only three mild allergic ARs associated with transfusion of MB-FFP (imputability level 2-3) were observed.

High frequencies of allergic-anaphylactic and other ARs were observed in association with quarantine FFP.

This study demonstrates the safety and quality of MB-FFP.

**Oral presentation:** ADVERSE REACTIONS ASSOCIATED WITH METHYLENE BLUE INACTIVATED FRESH FROZEN PLASMA (MB-FFP).

(Politis C). IPFA/PEI 19th Workshop on Surveillance and Screening of Blood Borne Pathogens; Budapest 2012

The incidence of ARs is statistically significantly higher in quarantine FFP than in MB-FFP in Greece (2001-2011).

The incidence of ARs is statistically significantly higher in France that expected, compared to the other countries (European Retrospective Haemovigilance Study 2007-2010).

In contrast to France, based on their respective haemovigilance data, in Belgium, Greece, UK, Spain and Austria no unusual allergic event rates have been observed leading to continuous usage of MB-plasma.

**Poster presentation:** HAEMOVIGILANCE FOR THE USE OF METHYLENE BLUE INACTIVATED FRESH FROZEN PLASMA VERSUS QUARANTINE PLASMA OVER THE PERIOD 2007-2011 IN GREECE.

(Politis C). Transfusion, AABB 2012

ARs associated with MB-FFP transfusion are rare; however significantly higher frequencies of allergic and anaphylactic as well as FNHTR were observed in association with Q-FFP.

No viral ARs associated with either type of FFP were found.

This study demonstrates the safety and good quality of MB-FFP during a long treatment experience.

**AUSTRIA**

**Oral presentation:** REDUCED NUMBER OF ADVERSE EVENTS WITH METHYLENE-BLUE TREATED PLASMA COMPARED WITH QUARANTINE STORED PLASMA: A SINGLE CENTER’S THREE YEAR EXPERIENCE.


Based on our data (2009-2011), we cannot confirm the French concern about a higher rate of AE in general, and also not for allergic Adverse Event (AE).

In contrast to their findings, we found a significant lower AE rate for MB treated plasma compared with Quarantine plasma, and also the character of the AE was, in all cases, of minor relevance.
UK

- **Annual SHOT (Serious Hazards of Transfusion) Report 2011**
  - The French haemovigilance group, Agence Francaise de Securite Sanitaire des Produits de Santé (AFSSAPS), have phased out production of MB-FFP because of reports of severe allergic reactions.
  - At present there are no changes to UK policy.
  - SHOT data do not show significant differences in allergic reactions to MB-FFP from standard FFP.

- **Joint UKBTS / HPA Professional Advisory Committee* / Serious Hazards of Transfusion (SHOT) November 2012: Position Statement Methylene Blue-Treated Plasma**
  - The analysis of UK reactions to MB-FFP from SHOT data shows no significant increase in overall reactions or severe allergic reactions when compared to standard FFP.
  - Other EU countries with experience of using MB-FFP have not published concerns of increased allergic reactions to MB-FFP.
  - The UK haemovigilance data have not demonstrated a statistically significant increase in the rate of reactions to MB FFP compared to standard FFP.

*Joint United Kingdom Blood Transfusion Services and Health Protection Agency Professional Advisory Committee

6. **Q. What is the conclusion about MB-Plasma in the recently published Letter to the Editor by P.M. Mertes et al, (Mertes et al. Methylene blue-treated plasma: An increased allergy risk? J Allergy Clin Immunol 2012; 130(3):808-12) supported by the French National Haemovigilance Committee and by the Haemovigilance Unit of AFSSAPS**

   A. It is suggested that the use of MB-Plasma possibly increases the risk of hypersensitivity reactions compared to SD plasma and Quarantine plasma following analysis of the use of the three plasma types from 2005-2009.

7. **Q. What is Macopharma’s position regarding the conclusion of the Letter to the Editor?**

   A. Macopharma believes that incorrect or insufficient data and assumptions were used to make the conclusion. MB-Plasma was not used in France until August 2008 and so no comparison can be made between the three plasma types from 2005 to mid-2008. Additionally, the data about allergic reactions from the 2010 Afssaps Haemovigilance Report was not included. We have re-run the analysis including this data and we observed no statistical differences between the different treated plasmas used in France.
8. Q. What is a user’s position regarding the conclusion of the Letter to the Editor?

A.

- **UPDATED HEMOVIGILANCE DATA DO NOT SHOW AN INCREASED RISK OF ALLERGIC REACTIONS FOR METHYLENE BLUE-TREATED PLASMA**
  (Seltsam A, Müller TH). J Allergy Clin Immunol 2012 (accepted for publication)
  - Our extended analysis provides additional information to the discussion on severe allergic reactions following FFP-MB transfusion. By including the 2010 haemovigilance data we could not confirm a significantly higher incidence of severe allergic reactions for this plasma type in comparison to other FFP types;
  - There is clinical and experimental evidence for adverse reactions due to sensitization to MB. However, the currently available haemovigilance data do not support the hypothesis of additional allergic mechanisms specifically related to the MB/light pathogen inactivation process.

9. Q. What Haemovigilance studies are Macopharma performing on MB-Plasma?

A. Studies in the pipeline:

1) **European Retrospective Study (I)**
   - Retrospective analysis of European haemovigilance data excluding France
   - Publication in 2013

2) **French Retrospective Adverse Reactions Analysis (+CRO*)**
   - Retrospective analysis of the French haemovigilance data
   - The statistical analysis is expected in Q1 2013

3) **European Retrospective Study (II)**
   - Retrospective analysis of European haemovigilance data including France
   - Data to be presented in 2013 (ISBT)

4) **European Prospective Study (+CRO*)**
   - European prospective haemovigilance study (without France)
   - Data to be collected in 2013-2014

* CRO: Clinical Research Organisation
• **Fibrinogen variability**

1. **Q.** What data was used by ANSM to justify the claim that there is a greater variability in the concentration of fibrinogen in MB-Plasma compared to the other types of plasma?

   A. Reports from some EFS centres based on their Quality Control data suggest, however, the variation appears to be inter-site (between different centres) and not intra-site (within one site). This indicates to a site-specific processing problem and not to a general deficiency of the THERAFLEX MB-Plasma process.

2. **Q.** Why does Macopharma think that EFS has reported variability in the concentration of fibrinogen in MB-Plasma compared to the other types of treated plasma noted in France?

   A. Macopharma investigated the issue and concluded that the variability observed does not appear to be due to the treatment process but due to incorrect handling of samples before measurement of fibrinogen by certain EFS sites.

3. **Q.** What are the new requirements for fibrinogen and Factor VIII stated for Intercept plasma in France in the Official Journal?

   A. 1) Minimum Fibrinogen concentration = 2 g/l in 70% of treated plasma units (reduced from 80% of treated plasma units)
   2) Lower limit for Factor VIII content = 0.5 IU/ml (reduced from 0.7 IU/ml)

4. **Q.** Was there a difference between the fibrinogen variation in MB-Plasma and IA Plasma in France?

   A. During the last French transfusion congress (SFTS congress, Lyon, May 2011) Doctor Rachel Petermann* (AFSSAPS) presented the quality control data of different therapeutic plasmas approved in France. The mean fibrinogen value for MB plasma was 2.3g/l ± 1 and 2.2g/l ± 0.8 for IA plasma. Based on Afsaps desire to have a mean value greater than 2g/l, it was calculated that 71.8% of MB plasma units were above this mean with only 60.9% for IA plasma thus not meeting the fibrinogen requirement.
Suivi de la qualité des plasmas thérapeutiques sécurisés par une méthode physico-chimique dans le cadre du contrôle de qualité externe des produits sanguins labiles

R. PETERMANN, F. AUVRAY, S. NEVES, Y. DEMAS, N. GOUJON, S. GROS, L. MOUILLOT, A. NICOLAS
AFSSAPS, SAINT-DENIS, FRANCE

- Therefore, from the data shown above, the variation in fibrinogen content in MB-Plasma is not statistically different from Intercept plasma.

5. Q. What other evidence is there that fibrinogen and Factor VIII content is maintained after MB-Plasma treatment?

Supporting Information

  - Regardless of the plasma donation procedure (whole blood (WB) or aphaeresis), these results showed a moderate reduction of recovery on both factors studied (FVIII 11-22%; Fibrinogen 8-15%).
  - When the treatment was performed before freezing/thawing, the recoveries obtained in WB plasma were higher than in aphaeresis plasma arms. (Recovery before freezing WB: FVIII 89%; Fibrinogen 89-92%; Apheresis FVIII 78-80%; Fibrinogen 85-87%).
    NB. This point could be related to the anticoagulant composition or ratio.
  - All produced plasmas met the criteria of the European guidelines.
Liver transplantation


A. To compare the total volume of MB-Plasma, SD plasma and Q plasma transfused in the operating room during the liver transplantation procedure to evaluate their efficacy.

2. Q. What is the conclusion of the study?

A. The authors claimed non-equivalent final transfused volumes in disfavour of MB-Plasma, suggesting that a greater volume of MB-plasma needs to be used when compared to Q plasma and SD-plasma for a similar clinical efficacy.

3. Q. What is Macopharma’s position regarding the conclusion?

A. The study outcome is misleading. The argument structure is unrealistic because the volume of each manufactured final therapeutic plasma unit between the three plasma types is not equivalent:
   - MB plasma volume: 221 ± 15 ml
   - SD plasma volume: 200 ml
   - Q plasma volume: 224 ± 15 ml

Clinicians prescribe plasma units for transfusion, not volumes. If the volumes are not equal from the offset, then this needs to be corrected for especially in a study when a comparison based on final volume will be made. Despite knowing that this initial difference in plasma bag volumes exists, the authors did not take into account any weighting or correction factor. Indeed, when they compared the number of units used, there was no difference between SD plasma and MB plasma.

4. Q. What are Macopharma’s other observations about the study?

A. 
   1) The difference in blood loss (Hb (g)) between the three plasma types during the surgical intervention is not statistically significant Coagulation variables correction is not statistically and significantly different.
   2) The study has many methodological biases:
- Patients with more severe illnesses were treated with MB-Plasma (despite the study being randomized).
- Laboratory coagulation variables (fibrinogen plasma concentration, prothrombin time, and Factor V level), before treatment, were lower in the MB-Plasma treatment patients.
- The use of MB-FFP led to a 24% higher median volume of plasma transfused when compared to the consumption of the two other (combined) FFP groups.

This combination of S/D-FFP and Quarantine (Q) groups was not stated in the Material and Methods section, a reason to do so is not given. Instead, one objective of the trial was to know if the plasma volume transfused was equivalent when using treated plasma (MB-FFP and S/D-FFP) compared to untreated plasma (Q-FFP) and this comparison was not made.

5. Q. What can be deducted about the adverse events?

A. Adverse events between the three plasma types were not significantly different. Nevertheless, the risk of experiencing adverse events was double when patients were transfused with Q-FFP than with MB-FFP.