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European Medicines Agency (EMA)
Attention of Mr. Jean-Hugues TROUVIN,
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Position paper
of the International Plasma Fractionation Association (IPFA)
on the Draft CHMP Statement on Creutzfeldt-Jakob disease
and plasma-derived and urine-derived medicinal products.

The European Medicines Agency has issued for consultation on June 24, 2010 the Draft CHMP Statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products. This document provides a measured and factual description of the status of vCJD as a potential threat to these products, so far as this could be established at the time of publication.

IPFA has commented on the draft revision, using the template format required by EMA.
This position paper is intended to amplify these comments, and to set out the IPFA position on the important issue of product recall. This paper addresses in particular section 9.2.4. "Recall of batches where information becomes available post donation".

IPFA considers that:

1 Most modern plasma-derived products possess a very high level of vCJD safety.
- The vCJD infectivity present in plasma is generally considered to be very low (probably less than 10^2 infective doses per ml), compared to the infectivity conferred by other infectious agents such as viruses (which can be $>10^8$ infective doses per ml).
- The cumulative evidence of numerous scientific studies has demonstrated the capability of many plasma fractionation processes to remove much higher levels of vCJD infectivity than those possibly present in the product.

Therefore, the mandatory recall of *any* product linked to a vCJD donor appears to constitute an excessive application of the precautionary principle. There is an even stronger case against mandatory recall for a plasma-derived excipient where the degree of exposure is much lower.

2 The CHMP position on product recall is set out in section 9.2.4.
- In the case of a report of a confirmed case of vCJD involving a donor, or of a donor presenting with neurological symptoms, which the clinician suspects to be caused by vCJD," look-back to identify the fate of donations should be taken as far as possible".
  IPFA considers that look-back need not be extended prior to 1985.
- Section 9.2.4 also states that it would be "prudent" to recall all the batches and intermediates manufactured from a starting pool, in which a donation provided by this donor is included. We believe it would be prudent to assess the need for a potential recall of the batches and intermediates manufactured from a starting pool, in which a donation provided by this donor is included.

- In the event that this donor was a regular plasmapheresis donor, the look-back procedure is likely to implicate multiple batches of intermediates and final products, many of which will still be in-date and may be requested by the CHMP position paper to be recalled.
- A recent exercise, based on a plasmapheresis donor who developed sporadic CJD, demonstrated that a recall would have implicated approximately 120 batches of finished product and intermediates. Such a recall would have posed a serious threat to the availability of final products, and would have resulted in serious shortages of plasma products.

3 The products affected by a product recall include those that the WHO has classified as Essential Medicines

- Essential Medicines include Immunoglobulin for intravenous administration (5% and 10% solution); Immunoglobulin for intramuscular administration (16% solution) and Immunoglobulin for subcutaneous administration (15% and 16% solution), Factor VIII concentrate, Factor IX complex (coagulation factors II, VII, IX, X), anti D immunoglobulin, and anti-tetanus immunoglobulin.
- Essential Medicines are medicines that are considered to be the most efficacious, safe and cost-effective treatments for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and their potential for safe and cost-effective treatment.
- Many other plasma-derived products, although not listed as Essential Medicines by WHO are equally essential to other patient groups.

A blanket recall would therefore lead to shortages of essential plasma products, which would have major implications for many patients who rely completely on these products.

4 In the event of a blanket recall, it is unlikely to be possible to replace the recalled products at short notice for the following reasons:

- The timing of this emergency, by its nature, can not be predicted. The availability of replacement or alternative products may therefore be limited.
- Some potential alternatives or replacements, may not have a marketing authorisation in the required markets;
- Even if a replacement product with a suitable marketing authorisation is available, it is likely that stocks will be insufficient to meet the emergency requirement.

5 There may also be wide constraints on product replacement:

- No additional production capacity may be immediately available.
- The probable scarcity of suitable replacement products implies that additional plasma will need to be collected. This would be a slow process, and may be further constrained by production capacity limitations.
- There may also be risks associated with substituting a product by an alternative, even if the product type is nominally the same. An example could be the possibly increased risk of a haemophilia A patient developing inhibitors to FVIII, as a result of a change to the FVIII product used to treat him. Also, different FVIII/vWD products can vary quite widely in their efficacy in von Willebrand factor deficiency.
- The decision to inform, or to refrain from informing, those patients who have already been treated with the implicated products, would present a legal and political dilemma, with considerable ethical and logistical implications.

In short, a mandatory blanket recall would create a huge disruption to the supply of plasma products, and to the provision of safe and efficacious treatment for many patients.

Consequently, IPFA is of the opinion that:

1 In general, the real and measurable risks associated with failing to supply essential medicinal products are higher than the theoretical risk associated with plasma-derived products manufactured from a starting plasma pool to which a vCJD incubating donor has contributed. This is also implied in section 9.2.4. of the Draft CHMP Statement.

2 Nevertheless, there are some circumstances under which batches should be recalled as a reasonable application of the precautionary principle.

IPFA, therefore, recommends to EMA that:

1 Prudence should be exercised in the context of product availability as well as vCJD safety.

2 The text of chapter 9.2.4. "Recall of batches where information becomes available post donation" should be changed or adapted accordingly.

3 In any case, the risk of shortages of plasma products should always be considered in order to prevent endangering the treatment of patients.

4 An algorithm-driven approach to the decision-making process should be followed, which would involve a risk assessment of the available data on the prion clearance capability of the particular process and the availability of replacement product.

- If the product is not plasma-derived, but contains a plasma-derived excipient in low concentration, then no recall is required.
- If the plasma-derived product is at low risk because there are product-specific risk-assessment data to demonstrate a high prion clearance potential, then no recall is required.
- If the product-specific risk-assessment data do not allow definition of the plasma-derived product as at low risk, then the security of supply should inform any decision to recall.
- If the plasma-derived product has been defined as at higher risk by the risk-assessment data, and replacement product is readily available, the recall in-line with the precautionary principle might be considered.

5 The application of this risk-benefit approach to any decision to recall plasma-derived product would reduce the possibility of depriving patients of life-saving medicines because of a theoretical risk of transmitting vCJD.

We believe that this approach is consistent with applying prudence in the safety policy of medicinal products. IPFA is open to meet for further discussion.

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