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From J Sloggem
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You asked for a "what if" position paper, if it was decided to withdraw plasma derived products from the market, if a donation had been used, which later was found to have come from someone not meeting the donor exclusion criteria re CJD, or having been diagnosed has having CJD. Please see below.

CREUTZELD JAKOB DISEASE AND PLASMA DERIVED BLOOD PRODUCTS.

POSSIBLE CONSEQUENCES OF WITHDRAWAL OF MEDICINES CONTAINING PLASMA DERIVED PRODUCTS

1. Plasma derived blood products may be used for their physiological activity, and be the recognised active ingredient in a pharmaceutical product. These include coagulation factors - Factor VIII, Factor IX, Factor VII, Factor XIII, fibrinogen, prothrombin complex and anti-thrombin III. There may be others which are used on a much more restricted basis [eg alpha-1-proteinase inhibitor].

2. Albumin may be used as a plasma expander, but it is also used as a stabiliser in other biological products. These products include classical biologicals like vaccines and hormones, but in additional the products of biotechnology. Hence rDNA made Factors VIII are stabilised with albumin. There are no licensed rDNA Factor IX products. Some GM-CSF type also have albumin included in their formulation.

3. If albumin is not included as an active, but as an excipient it would not be possible to identify the products that contained a particular source/ manufacturer of the albumin used from MCA computerised records. Hence if there were a recall of components of fractions made from a "CJD positive pool" there would be no easy way of getting a list of affected products, which could then be investigated by MCA re particular manufacturers, to see if the implicated batches of albumin had been used in product formulation.

4. In the absence of batch release for products made by rDNA technology, neither NIBSC nor other Control Authorities would not have any batch records which could be inspected. Manufacturers would have to be alerted generally to the issue either by the blood component supplier concerned , or possibly the MCA/EMEA. The latter is more likely to receive uncontrolled ill informed publicity. These are the administrative problems which might arise if withdrawals were made.

5. The recall or quarantining of vaccines, may not only affect unused bulks which could represent many thousands or millions of doses, but filled and issued product. Vaccines and other biological products would be recalled from the distribution train. With the increased tendency to have multi-antigen vaccines, any recall is likely to affect not only the component formulated with the albumin, but the other components, which might as single components not be directly affected by the "CJD albumin". That clearly would be a major news item. If the recall were limited to supplies in the professional distribution chain, patients might later query why product in their possession was not withdrawn, and replace with "safe" product.

6. Where one blood product manufacturer is affected by a CJD donor, one cannot assume that there will alternative supplies readily available. As happened in the 1994, when Baxter withdrew product, closely followed by the American Red Cross - two manufacturers were affected in close succession Presumably it is possible in the USA for a single "CJD donor" to have given donations over a period to different blood/plasma collection organisations, supplying different commercial/public fractionator, leading to just such a situation..

7. In France in 1994 there 10 "CJD donation" events. 5 were familial CJD; 1 HGH associated; and the others presumably were sporadic. 77% of the Factor IX produced during that year was withdrawn. 71% of 5 gram iv immunoglobulin was withdrawn. About 20% of the albumin 20% was withdrawn.

8. In the report of the FDA ad hoc group meeting on CJD and blood in June 1995, it is stated that the "CJD donation" meant that the American Red Cross withdrew 10% of available product. That organisation supplies 50% of the American market it was stated. On the basis that the Americans had discovered 4 "CJD donors" in 1994, and the French 13, and that CJD reporting is internationally increased, presumably due to increased awareness, it is likely that a higher percentage of material may be candidates for withdrawal in future.

9. The implications of a "CJD donor " being discovered on the size of any withdrawal is difficult to judge, since it is based on many unknowns. The major factors would be the number of donations given per year, and the number of years over which donations had been given, and whether the resulting plasma pools had gone into products with a presumed quicker turnover eg co-agulation and immunoglobulin products; or whether fractions eg albumin had gone into longer lasting bulks eg frozen vaccine concentrates.

10. If the donor was hyperimmune, and plasmapheresed regularly, it is likely that all current batches of that product eg anti-D immunoglobulin would be candidates for recall. It is possible that it would take 2-6 months to make and test replacement stock from scratch. It is possible that batch failures could increase the problem of re-supply. It could even longer if decontamination of plant and equipment is required. Especially if that process has to be validated.

11. If there is only one licensed supplier of a hyper-immune globulin, that may raise the issue of obtaining supplies from unlicensed sources for possibly 2-6 months or more. If the failure of supply was from a commercial manufacturer, it could affect several countries at once, requiring replacement supplies all at the same time. That would lead to shortage of supply, which would become public. It is possible that American based manufacturers would feel obliged to give their home market priority when allocating any fresh supplies.

12. Even if the UK were not minded to recall product, if that manufacturer was called upon to recall product in other countries, that would mean that the UK would need to consider the implications of not withdrawing product, and being out step with regulatory action elsewhere. The media might criticise the less strict action taken by the MCA/DoH.

13. Irrespective of licensing authorities view the **manufacturer** might decide to withdraw product, creating a shortage. Adverse publicity might follow as in 12 above.

14. BPL have indicated in general terms that a plasma pool could represent 2 Mega units of Factor VIII, and IX; 250 Kg of albumin and 50 Kg of immunoglobulins. If one makes the assumption that the "CJD donor" has given 5 donations which are independently blended into different pools, then the amount with increase by x5.

15. If there are 1 in 10^6 "CJD sufferers" in the population that means that potentially there are likely to 50 in the UK per annum. The number of blood donors are about 2.4 million ie 2.4 "CJD donors" in the UK. What number that would represent in the eligible donor population age 18-65? Given an age bias, most donors are in the age range 25-44, but those aged 44-65 is about 30% of the panel, so the incidence might be higher in the blood donor population. That makes no special allowance for familial or iatrogenic cases, which might be considered increase the figure, if a worst case scenario is being drawn up.. Currently donors on average donate 1.2-1.3 donations per year in the UK. The position with commercial suppliers would be very different with donation [ex plasmapherisis] being as frequent as every 2 weeks. That suggests commercial suppliers are more vulnerable to a single "CJD donation".

16. If product is withdrawn and that precipitates a supply crisis, that raises the issue of product being re-issued, possibly with labels or patient information leaflets explaining the theoretical risk of CJD transmission via blood/blood products , which would have to be balanced against the therapeutic benefit. Such a move would call into question the credibility of the licensing system. Equally if a parallel is drawn with HIV and HCV transmission via blood products, it could be held that MCA should have learnt from the previous experience and withdrawn very thing. However non-A non-B [ie HCV] transmission was recognised as being transmitted by blood and blood products.It became an issue when a test was available, and whether it should be adopted, even when its reliability was unproven. With HIV presumably it would be considered that haemophiliacs should have been made aware of the risk as it emerged, or at-risk product should have been withdrawn, even if it not possible to substitute a known "safe" one. Nothing was known of the properties of the HIV virus to take steps to safeguard the blood product supply. With CJD exclusion criteria are in force, but if they are vitiated no withdrawal action is to be taken. If the public perception with CJD was that no action was inappropriate, then MCA/DoH might be accused of not learning from previous blood product transmission incidents.

17. There could be implications for clinical trials using biological products. I believe there is CTX for a wound healing product, which uses platelets. These being a cellular element of blood might be considered to more of a potential CJD transmission risk. Alferon-N is not licensed in the UK, but it contains interferon produced from cultured leucocytes. It would be interesting to know that the FDA would do if the leucocytes were from a "CJD donor".

18. It is possible that the FDA will have to change its stance on product withdrawals/ re-issues because of the practicalities concerned. Suppliers might not wish to re-issue product, because of the legal implications.

.19. In summary it is not possible to estimate the amount of material or the number of batches that would be effected. If it was a commercial supplier, especially sourcing from the USA, with a higher percentage of plasmapheresis donors, the amount of material affected is likely to be higher than for a UK manufacturer. Commercial sources may also supply components for formulating other biologicals used in the UK. MCA may not in practice be able to stop the plasma components or vaccine manufacturer from withdrawing the affected products.

Childhood vaccines could be affected. Shortages could raise the problem of re-issue, which apparently can be countenanced in the USA.

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