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Dear Philip, Trevor and Robin

SCREENING OF BLOOD DONATIONS AND BLOOD PRODUCTS FOR INFECTIOUS AGENTS

With the current special renewals exercise for human medicinal blood products and the introduction of screening for antibodies to hepatitis C virus, it seemed an appropriate time to review where we stand on screening of blood donations for use in blood products and screening of intermediates and final blood products.

I would be grateful if you could consider the attached paper and give me your views by the end of December. If Philip has a list of currently acceptable screening tests could he let Tony Hubbard and I have a copy for use in the special renewals exercise.

We will also be discussing this paper in-house and it is on the agenda for the Biologicals Sub-Committee meeting on 13 January 1993. Hopefully, therefore, by mid-January we will have a clear UK position on testing.

Yours sincerely

GRO-C

pp MRS GLENDA SILVESTER

cc: Dr A Hubbard
Dr M Paige
(NIBSC)

CSM/BIOLS/93/1ST MEETING

COMMERCIAL IN CONFIDENCE

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

SUB-COMMITTEE ON BIOLOGICALS

POSITION PAPER

SCREENING OF BLOOD DONATIONS AND BLOOD PRODUCTS FOR INFECTIOUS AGENTS

1. Introduction

On 1 January 1992 an EEC Council Directive (89/381/EEC) was implemented which extended medicines licensing within the EEC to medicinal products derived from human blood or human plasma. Prior to this, such products were licensed in the UK under national regulations. A special renewals exercise is now underway to ensure that all medicinal products derived from human blood or human plasma marketed in the UK comply with EEC requirements. It is, therefore, appropriate to review the current requirements for screening of blood donations and blood products for infectious agents.

2. UK History

? Screening of blood donations for syphilis.

1971: Screening of blood donations for HB_SA_g commenced.

Oct 1985: Screening of blood donations for antibodies to HIV-1 commenced.

1986: Requirements for human medicinal products derived from human blood or human plasma to be prepared from plasma donations individually tested for HB_SA_g and antibodies to HIV-1 and found negative. Testing methods to be provided including manufacturers' instructions for test kits or reagents and indicating any deviation from these instructions used in the testing laboratory. Products to be batch released.

1987: Validation of screening tests. Licence holders to provide complete information on the quality assurance tests and performance evaluation carried out on each batch of the kits of reagents used for the testing of blood donations for viral infectious agents. To include information on standards used, positive and negative controls, sensitivity and specificity of test kits, criteria by which donor units

are excluded from processing. To be provided in initial licence applications and on-going in batch protocols provided to NIBSC.

1989: UK Advisory Committee on the Virological Safety of Blood (ACVSB) recommended that subjects who had received human pituitary derived growth hormone should be excluded from donating blood.

1989-1990: Treatment with human pituitary derived growth hormone is permanent exclusion criteria for donating blood or plasma used in the manufacture of licensed blood products.

1990: Guidelines for Transfusion Service published[1].

1990: ACVSB recommended that testing of individual blood donations for antibodies to HIV-2 should be instituted from 1 June 1990.

1990: CSM recommendation that all human medicinal products derived from human blood or plasma should be manufactured from donations screened individually for antibodies to HIV-2.

(**NB**. US did not recommend screening for antibodies to HIV-2 until June 1992. Some US - derived blood products did not, therefore, comply with this recommendation. See further comment below under blood donor screening in other countries).

1991: Screening of blood donations for antibodies to hepatitis C virus (HCV) commenced.

3. EEC GUIDELINES/REQUIREMENTS

Licensing of human medicinal products derived from human blood and plasma was brought under EEC directives from 1 January 1992 with a one year transitional period for review of products with existing national licences.

The European Commission notes for guidance on 'medicinal products derived from human blood and plasma' which came into operation on 1 May 1992 require that:

'The criteria of the Council of Europe[2] and of WHO[3] shall apply to the selection of blood donors and blood donations.

Using a sensitive, specific and validated test, each donation must be tested and found:

- non-reactive for HB_sA_g, using a validated ELISA or RIA test which detects 1IU per ml of HB_sA_g or less.
- non-reactive for antibody to HIV-1 and HIV-2.

- non-reactive in tests for hepatitis C'.

In March 1992 the CPMP agreed a 'Position statement with regard to Hep CV screening of plasma used in the manufacture of medicinal products'.

This sets 1 January 1993, as the deadline by which only batches derived from screened plasma should be placed on the market. Batches of product manufactured from unscreened plasma and released onto the market before January 1, 1993, may remain on the market until 31 December 1995 at the latest, taking account of shelf-life and provided the product has not been associated with transmission of HepCV.

The CPMP guidelines also require that transfusion/collection centres inform the manufacturing/fractionation centre if, within six months of donation, there is evidence that a donation should have been excluded. (Specific criteria are stated).

The draft annex to the EC Guide to GMP on the 'manufacture of products derived from human blood and plasma' (Draft 4) requires the manufacturing or fractionation centre in these cases to carry out a complete re-assessment of the batch documentation and re-control of finished products. The need for withdrawal of the given batch should be carefully considered, taking into consideration criteria such as the disease, the number of seroconversions, the size of the pool, the time period between donation and seroconversion, and the nature of the product and its manufacturing method.

It is proposed that companies are specifically asked about the steps they take if it is found retrospectively within 6 months of a donation that it should have been excluded. Should the Licensing Authority be routinely informed of such cases or only when the decision is to recall? This could be decided for each application depending on for example, the stringency of the Company's criteria.

4. Blood Donor Screening in other Countries

A recent article in Vox Sang[4] (appended) provides a useful review of blood donor screening in other countries up to 1991.

The USA did not recommend screening of blood donations for antibodies to HIV-2 until June 1992. Some US-derived products have, therefore, continued to be manufactured from donations that have not been screen for HIV-2 despite the 1990 CSM recommendation. One company has proposed a 1 January 1993 deadline by which only batches derived from screened plasma should be placed on the market.

The US contribution to the appended Vox Sang article sets out the reasons why screening for antibodies to HIV-2 was not introduced earlier. Given the low expected incidence in US blood donations and the effective viral inactivation procedures applied to human blood products no safety hazard would be expected from this lack of screening.

It is proposed that as part of the special renewals exercise currently being undertaken for blood products, licence applicants will be informed that with immediate effect only batches derived from individual donations screened and found non-reactive for antibodies to HIV-2 should be placed on the market. Some leaway may be necessary if this creates a supply problem for an essential product but this will be kept to a minimum.

5. Evaluation of Test Kits for Blood Donor Screening

It is expected that state of the art tests will be used. In the UK, there is no statutory licensing procedure for kits for blood donor screening. Medicines Devices Directorate (MDD), Group B2C have a non-statutory involvement. Evaluation is two stage with the initial stage being undertaken by the PHLS virus reference laboratory at Colindale who look at precision, reproducibility etc. If the initial evaluation identifies the kit as a candidate for routine use, the Blood Transfusion Services undertake an evaluation under operating conditions.

The majority of UK blood products are derived from blood donations collected in the UK, Western Europe and the USA and Canada.

The FDA in the USA and the Paul Ehrlich Institute in Germany have formal licensing of kits. Kits licensed by these two countries are accepted as suitable for use in the screening of blood donations for use in human medicinal products licensed in the UK.

6. Screening of Plasma Pools

Manufacturers' are currently required to screen each plasma pool for HB_sA_g and antibodies to HIV-1 and HIV-2 by appropriate tests and only use pools that are non-reactive. NIBSC also receive samples of plasma pools for each batch of product as part of the batch release procedure and carry out their own tests.

(NIBSC are currently clarifying with manufacturers the nature of the samples they are being sent. Samples should be of the homogeneous pool which is normally the pool of supernatant from the cryoprecipitate stage.)

NIBSC and manufacturers' testing is done directly on the plasma pool. Could sensitivity be improved by pretreating the samples for any of the tests eg HB_sA_g.

The EEC has not specifically addressed whether plasma pools should be screened for antibodies to HCV. NIBSC have done some testing of pools and have found that plasma pools from US donations that have not been individually screened for antibodies to HCV are positive. They found that reactivity was lost with fairly low dilutions of the pool. Pools from UK and Swedish donations were negative.

It is proposed that from 1 January 1993, batches of product placed on the market should be manufactured from plasma pools that have been screened and found non-reactive for antibodies to hepatitis C using a sensitive, specific and validated test.

7. Screening of Final Products

EEC guidelines do not discuss screening of final products for markers of infectious agents. The European Pharmacopoeia monographs for Factor VIII and Factor IX require the products to be non-reactive for HB_SA_g. There are no other pharmacopoeial requirements for products at present. As part of UK licensing in recent years, immunoglobulin products have been required to be tested and found non-reactive for antibodies to HIV-1 and HIV-2. Validation of tests on the finished product are required since the kits have been primarily developed for and validated on plasma samples. It is proposed that the European Pharmacopoeia be approached to consider including non-reactivity for antibodies to HIV-1 and HIV-2 in immunoglobulin monographs. Some companies routinely test all their human blood products for HB_SA_g and antibodies to HIV-1 and HIV-2 but this is not universal. The UK BTS guidelines[1] require that each batch of immunoglobulin must be tested for the presence of HB_SA_g in addition to antibodies to HIV.

Should testing of all products for HB_SA_g and antibodies to HIV-1 and HIV-2 be insisted upon? Alternatively, finished product testing could be restricted to the products into which the antigen/antibody would fractionate. Overseas blood product manufacturers will usually make a range of blood products but only a few will be licensed in the UK. It would be sensible to obtain information on their testing policy for all products manufactured from the same plasma pool to ensure that the most appropriate products (not necessarily UK licensed) are screened.

The need for screening of final products for antibodies to HCV has not been addressed by the EEC. NIBSC have done some testing and found immunoglobulin products from unscreened US sources to be reactive. This has followed through from reactivity seen in plasma pools. As with plasma pools, it has been found that reactivity was lost with fairly low dilutions. It is proposed that immunoglobulin products should be screened and found non-reactive for antibody to HCV using a sensitive and specific test validated for use on the finished product.

The WHO guidelines[3] have a recommendation that each lot of immunoglobulin (whether normal or specific) shall have minimum concentration of antibody to HB_SA_g of 1IU/g of immunoglobulin. This does not currently appear as a pharmacopoeia requirement for immunoglobulins. Licence holders do seem to be applying this test to immunoglobulins. Is this requirement useful? It is included in the draft Ph Eur monographs for normal immunoglobulins (iv & im).

8. Supply Problems with Essential Products

When new screening requirements are introduced some leaway on implementation may be necessary if strict compliance would lead to a supply problem with an essential product where no alternative source is available eg rabies immunoglobulin. Any such allowances would be restricted to the minimum feasible time and would only be allowed where the benefits of clinical use outweigh any risks.

9. Conclusions

From the discussion and information in this position paper the following statement of the current position, proposals for consideration and points for consideration have been drawn up.

References

1. Guidelines for the Blood Transfusion Services in the United Kingdom 1989, HMSO, 1990.

2. Guide to the preparation, use and quality assurance of blood components, Council of Europe Press, 1992.

3. WHO Expert Committee on Biological Standardization, 39th report, WHO Technical Report Series 786, WHO, Geneva, 1989.

4. Reesink, H.W, Nydegger V.E. et al, Vox Sang, 1992, 63:59-69.

MRS GLENDA SILVESTER
November 1992

CSM/BIOLS/93/1ST MEETING

SCREENING OF BLOOD DONATIONS AND BLOOD PRODUCTS FOR INFECTIOUS AGENTS

1. SUMMARY OF CURRENT POSITION

1.1. Human medicinal products derived from human blood or human plasma are manufactured from donations individually screened and found non-reactive for HB_SA_g and antibodies to HIV-1 and HIV-2. (Except HIV-2 screening has not been introduced for some US derived products.)

1.2. From 1 January 1993, batches of product placed on the market will have to be from donations individually screened and found non-reactive for antibodies to hepatitis C virus (HCV). Batches of product manufactured from plasma that had not been screened for anti-HCV may remain on the market until 31 December 1995 at the latest, taking account of shelf-life and provided the product has not been associated with transmission of Hep CV.

1.3. Recipients of human pituitary derived growth hormone are permanently excluded from donating blood or plasma used in the manufacture of human medicinal products.

1.4. Screening tests for infectious agents are sensitive, specific and validated. Testing methods including manufacturers' instructions for test kits and reagents are provided to the Licensing Authority and NIBSC. Any deviations from the manufacturers' instructions by the testing laboratory are stated. Validation data are also provided including quality assurance tests and performance evaluation carried out on each batch of the kits or reagents. Information on standards used, positive and negative controls, sensitivity and specificity of test kits and criteria by which donor units are excluded from processing are provided.

These data are provided in the initial licence application and on-going in batch protocols provided to NIBSC.

State of the art screening tests licensed by the FDA, the Paul Ehrlich Institute or used by the UK Blood Transfusion Services are accepted.

1.5. Plasma pools are screened and found non-reactive for HB_SA_g and antibodies to HIV-1 and HIV-2.

1.6. Factor VIII and Factor IX finished products are screened and found non-reactive for HB_SA_g by a sensitive, specific test validated for use on the finished product.

1.7. Human immunoglobulin finished products are screened and found non-reactive for antibodies to HIV-1 and HIV-2 by sensitive and specific tests validated for use on the finished product.

4. ACTION

Once a clear UK position is agreed on these issues, this will be applied to the special renewal of blood products and an article will be put in the Medicines Act Information Letter (MAIL).

1.8. Human medicinal products derived from human blood or human plasma are subject to batch release.

2. PROPOSALS

2.1. From 1 January 1993, batches of product placed on the market should be manufactured from plasma pools that have been screened and found non-reactive for antibodies to hepatitis C virus using a sensitive, specific and validated test.

2.2. From 1 January 1993, batches of immunoglobulin products placed on the market should have been screened and found non-reactive for antibody to hepatitis C virus using a sensitive and specific test validated for use on the finished product.

2.3. The Licensing Authority should approach the Pharmacopoeia Secretariat to ask them to consider including non-reactivity for antibodies to HIV-1, HIV-2 and hepatitis C virus in European pharmacopoeia monographs for immunoglobulins.

2.4. Companies should provide information on all in-process and finished product screening for markers of infectious agents carried out during their fractionation process. Information should be given on all products manufactured from the pool and not just those for which UK Product Licences are sought. Screening requirements should be the same as for UK licensed products.

2.5. Companies should include in their product licence application information on the steps they would take if it is found retrospectively, within 6 months of a donation, that the donation should have been excluded from processing. The Licensing Authority to decide for each application whether it would need to be informed of such cases where no recall was made.

2.6. As part of the special renewals exercise currently being undertaken, licence applicants should be informed that with immediate effect only batches derived from individual donations screened and found non-reactive for antibodies to HIV-2 should be placed on the market.

3. POINTS FOR CONSIDERATION

3.1. Could procedures for testing of plasma pools be modified to increase their capability of detecting markers of infection?

3.2. Should all finished products derived from human blood or plasma be screened for HB_SA_g and antibodies to HIV-1 and HIV-2 or is selective testing as described at points 6, 7, 10 and 12 considered more appropriate?

3.3 Is the WHO recommendation that each lot of immunoglobulin (whether normal or specific) shall have a minimum concentration of antibody to HB_SA_g of 1IU/g of immunoglobulin considered useful?