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Immuno Ltd

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Bill - 4-4-86

Ref: RN/jar

1 April, 1986

Mrs Perry,
please acknowledge
& return to
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13/4/86

COMMERCIAL IN CONFIDENCE

Mr. D. A. Kennedy,
Scientific & Technical Branch,
Department of Health and Social Security,
14, Russell Square,
LONDON. WC1B 5EP.

Dear Mr. Kennedy,

We are now able to reply in detail to your letter dated 12 March concerning the HBsAg and HTLVIII Ab status of Diagnostic reagents.

In general we welcome your proposals which are in line with our own policies. We do feel however that the appointed date for their introduction is rather premature. We would suggest a phased introduction for HTLVIII testing with recommendations that reagents whenever possible should conform to these standards in the interim and the "appointed date" for enforcement should be later in 1986.

Whilst we appreciate that concern has been expressed over tests on final product for antibody to HTLVIII, there is we believe some merit in these tests. This opinion has also been expressed in Medicines Division, where for certain therapeutic blood products intended for actual administration to patients a negative status on final product is acceptable until 31/12/86 and only from 1/1/87 is compliance with donor testing requirements for antibody to HTLVIII being sought. In addition, the National Institute for Biological Standards and Control in Hampstead are also testing for antibody to HTLVIII in final containers of therapeutic products.

As far as our own products are concerned, comment is most appropriately made according to product group, i.e., Biochemistry, Blood Group Serology and Coagulation diagnostic reagents.

In all cases our products have routinely been tested for absence of HBsAg for some years and specified as such in pack inserts and labelling. Our comments relating to products are therefore solely restricted to HTLVIII antibody testing.

Biochemistry

Human based products are either standards or control sera. All products currently on sale are HTLVIII Antibody negative when tested on final container. All donations now being used for production are donor tested. Labelling requirements will be applied as soon as practicable.

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Blood Grouping Reagents

All human based antisera exept two are currently heat treated. These other two products are currently donor screened. This heat treatment has been routinely carried out primarily to inactivate complement rather than provide HTLVIII inactivation. However, in vitro tests on trial batches spiked with live HTLVIII virus has shown our own heat treatment to be capable of inactivating six log steps.

In addition four of our heat treated products are currently additionally donor screened.

As far as red cell products are concerned these have been HTLVIII antibody negative since June, 1985.

As to future supplies these will all be heat treated as before but introduction of donor screening on all products must await use of current stocks. All receipts of source material since June 1985 have however been donor screened.

Currently products are not labelled as heat treated or donor screened but this will be introduced. In this context your proposals under section 2.6 may cause undue concern as heat treatment has been used as a standard procedure prior to the current concern over HTLVIII status.

Coagulation

As you are aware from our recent letter, steam treatment (STIM-D) has now been introduced for those products manufactured from haemophiliac donors who show a high frequency of HTLVIII antibody positivity. These STIM-D products currently comply with your labelling proposals and are marked HTLVIII Antibody positive. This is an area which is currently not covered in your proposals namely virally inactivated HTLVIII Ab positive products. Here it is the reduction in potential for infection rather antibody status which is relevant. For these products (STIMD) it has been decided to test each batch for absence of HTLVIII virus activity as a further reassurance.

This antigen test which takes six weeks to perform uses the reverse transcriptase assay as described by Gallo, following tissue culture with HTLVIII susceptible marker cells.

We believe our STIM-D products are the only diagnostic reagents to be routinely tested for HTLVIII virus activity and in this context the relevance of HTLVIII antibody status is debatable.

As far as other deficient plasmas are concerned i.e. those prepared from donors with deficiencies of factors other than VIII or IX these are now only supplied from donors who are non reactive in tests for antibody to HTLVIII.

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The current batches of our remaining coagulation products - reference and control plasmas are currently all HTLVIII antibody negative when tested on final container. However, restrictions on donors apart from HTLVIII Ab testing have been routinely applied for many years which are likely to reduce any potential infection risks. For these products, only European donors are used who meet the requirements for collection of plasma for the manufacture of therapeutic products. Part of these requirements has recently included questions designed to eliminate high risk donors in accordance with FDA guidelines.

The main reasons for these reference and control plasmas currently not being donor screened are concerned with logistics. A prerequisite of good quality control is standardisation of which not least is the importance of the maintenance of the same batch of control preparation for a long period. In fact several of our customers phone to check on expiry dates of products to ensure continuity of controls for as long as is possible.

Accordingly, many of these products which are currently not donor screened are made in very large batches with a shelf life of 2 years. In addition the calibration data which accompanies this type of product takes 4 - 6 months to establish by an external quality assurance institute (Instand - The German Institute for Standardisation and Documentation in the Clinical Laboratory) and therefore lead times are considerable. New batches prepared from donor screened material are in production and will be introduced as soon as possible together with the necessary labelling requirements.

Conclusion

As we hope we have demonstrated we have already established a real commitment to the introduction of measures similar to those you have proposed. This commitment extends back to before our initial discussions with your department in the first half of 1985. However, as indicated above the proposed appointed date of 1st May 1986 is we feel too early for dogmatic introduction. The major area of concern, that of HTLVIII antibody positive reagents has we believe been effectively countered by steam treatment and the remaining products are well on the way to compliance with our objectives. This action coupled with existing careful donor selection, the extension of HTLVIII antibody screening for those products with long production times, the warnings in our pack inserts and general user awareness has meant considerable progress has been made since we first identified these areas of concern.

The date of introduction of donor screening for all relevant products under the terms of your proposals is difficult to estimate exactly but should be complete in the second half of the year.

As indicated at the beginning of this letter, we would propose phased introduction for some products possibly by a similar wording to that in section 3.2.

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In response to your request for comment on specific points we wonder whether point 2.4 is relevant. Following the introduction of steam treatment and the tests to ensure absence of detectable viral activity described above, there may not be any demand for haemophiliac derived products which cannot be met by virally inactivated reagents.

As far as labelling requirements are concerned, these have already been touched upon but further comment seems appropriate. In principle we believe that the first consideration must be in ensuring that the products reach our objectives in terms of donor screening. Labelling requirements should not hold back the introduction of donor screened products and if necessary labelling could be accomplished by temporary stickers. Following your discussions with ABPI representatives, we believe such an approach would be an acceptable temporary measure.

In section 2.6 you warn that heat treatment of products may adversely affect some assay procedures. We feel this section could be extended to ensure that the heat treatment process used has been validated and data is available to show the inactivation characteristics of the method. This should ensure that effective heat treatment is being used.

In the midst of this genuine concern we feel the currently available evidence should not be ignored. Human based reagents and controls are an integral part of modern clinical laboratory practice for which alternative synthetic products are not suitable or available. Laboratory staff should now be well aware of intrinsic hazards and in accordance with warnings accompanying products be taking suitable precautions. This coupled with reports such as those from Dr. Peter Jones' tests on HTLVIII Ab status of staff working with haemophiliacs and the recent B.M.J. editorial (15th March) emphasize the fact that HTLVIII transmission is very difficult except for certain specific routes. Having said this we re-emphasize our commitment to reducing this apparently minimal risk even further.

We hope you will find these comments useful in the final drafting of your Health Notice.

Should you need any further information please contact either our Managing Director, Mr. P. J. Coombes, or myself. Alternatively, if necessary we would be pleased to come and discuss this further with you at Russell Square.

Yours sincerely,
for IMMUNO LTD.,

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R. Nicholson, M.Sc.,
Marketing Manager