The Blood Transfusion Service Board

First Annual Report To

The Minister For Health and Children

By The Irish Medicines Board

(1st January 1997 - 31st December 1997)

1. INTRODUCTION

The Report of the Tribunal of Inquiry into the Blood Transfusion Service Board, published in March 1997, made two recommendations in respect of monitoring of the Blood Transfusion Service Board (BTSB) by the Irish Medicines Board (IMB). These were firstly that the IMB should carry out at least two inspections annually of the BTSB and secondly that it should annually report to the Minister for Health and Children on the results of these inspections and of any reports of abnormal reactions to blood or blood products received by the IMB. This is the first of those annual reports.

2. THE IRISH MEDICINES BOARD

The IMB is responsible for the licensing of the manufacture, preparation, importation, distribution and sale of medicinal products. There are approximately 7,000 current product authorisations in Ireland for human and veterinary use. Each year the IMB receives more than 500 applications for product authorisations, more than one thousand applications to renew authorisations and around 5,000 applications to vary the terms of an authorisation. This requires considerable medical and scientific expertise. There are 80 manufacturers requiring to be licensed and inspected by the IMB and 130 wholesalers of medical products. It grants permission for the conduct of about 300 clinical trials per annum. It also collects information on adverse reactions to medicines which requires assessment and follow up of about 1,500 reports annually. It is the competent authority under European Union Directives and Regulations for both human and veterinary medicines and contributes actively to the assessment and regulation of medicines in Europe and to systems for harmonising these both in Europe and between the EU and other countries.

The IMB has specific responsibilities in respect of blood as follows "to establish and administer a service for the inspection of any service for the collection, screening, processing and quality control facilities and procedures in respect of human blood, blood components, blood products and plasma derivatives for the purpose of ensuring the safety and quality of blood, blood components, blood products and plasma derivatives and to advise the Minister in relation to such general or particular matters arising out of the administration of such a service as the Minister may refer to the Board" (Irish Medicines Board Act 1995). Certain of the activities of the BTSB are also licensable under the Medical Preparations, (Licensing of Manufacture) Regulations.

Thus the IMB has responsibility for inspection of blood collection, testing, processing and distribution under the Irish Medicines Board Act 1995. However, the only licensable manufacturing activities are those which relate to collection and processing activities which provide plasma, which is subsequently fractionated into medicinal products outside of Ireland. These medicinal products are then used within the Irish hospital sector. The collection and processing of blood and plasma for use in transfusion medicine are not currently licensable activities under the manufacturing regulations.
The BTSB also wholesales a number of medicinal products. This activity is licensed under the Medical Preparations (Wholesale Licences) Regulations.

3. THE BLOOD TRANSFUSION SERVICE BOARD

The BTSB is engaged in operating a service for the supply of blood, blood components, blood products and plasma derivatives to the Irish health service. It manages the national blood collection service which is based on voluntary donations. These are tested for the purposes of blood grouping and for the presence of disease producing organisms which requires associated procedures for identifying, tracking, storage and dispatch of the blood and blood products that it collects. The BTSB also makes available certain medicinal products derived from blood. These are manufactured outside of Ireland under licence arrangements approved by the IMB and are returned for use in the Irish health services.

The headquarters of the BTSB is in Dublin (the Dublin Centre), with an additional facility in Cork and a fixed clinic premises in Limerick (The Cork and Limerick premises come under the collective designation of Munster region). There are also mobile donor clinics which operate from the two centres and the Limerick premises and which travel to different parts of the country.

The BTSB is also currently involved in tissue banking services such as eye, bone, heart valves and stem cells and also provide tissue typing services. These activities do not come within the remit of the IMB.

4. THE FORM OF INSPECTIONS

The IMB inspects all of the pharmaceutical manufacturing facilities in the State, including those for both human and veterinary medicines. It also inspects outside of the European Union in connection with applications for product authorisations under European centralised procedures. These activities cover a wide range of areas from manufacture of small numbers of products not requiring sterile manufacturing conditions to facilities at the leading edge of biotechnology.

The basic processes of an inspection involve the following:

- pre-inspection preparation during which the inspector reviews previous inspection issues, the technical data relating to the facility and the processes involved. An inspection plan is prepared.

- the inspection process. This covers the areas described below. The inspection is carried out on a risk assessment basis with key relevant areas being given particular attention.

- the end-of-inspection review meeting with members of staff of the organisation being inspected.

- the subsequent inspection report which identifies areas of non-compliance with Good Manufacturing Practice (GMP). The licence holder is required to reply setting out corrective actions and a timetable for their completion.

The IMB adheres to European Commission Directives No. 91/356/EEC (Commission Directive of 13th June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use) and No. 91/412/EEC (Commission Directive of 23rd July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products).

In the conduct of its inspections, the IMB follows the requirements set out in the European Community's "Guide to Good Manufacturing Practice for Medicinal Products". These summarise the basic requirements of Good Manufacturing Practice under the following headings.

- Quality Management.
- Personnel.
- Premises and Equipment.
- Documentation.
- Production.
- Quality Control.
- Contract Manufacture and Analysis.
- Complaints and Product Recall.
- Self Inspection.

It is those headings which are used in the following sections to summarise the outcome of the inspections of the BTSB. Recommendations of the Council of Europe in relation to blood are also used.

In addition, comments are included on Haemovigilance and Pharmacovigilance.

5. MONITORING OF THE BTSB DURING 1997

The monitoring activities of the IMB took two forms, as follows:

5.1. Inspections of each of the facilities in Dublin, Cork and Limerick (see 6 below).

5.2. Meetings to address ongoing items and matters arising (see 7 below).

6. INSPECTIONS

The following inspections were performed.

6.1.	Munster (Cork)	12th -13th March 1997
6.2.	Dublin	19th and 21st March 1997
6.3.	Dublin	14th -16th April 1997
6.4.	Dublin	29th May 1997
6.5.	Munster (Limerick)	6th August 1997
6.6.	Munster (Cork)	6th - 8th October 1997
6.7.	Dublin	17th - 21st November 1997
6.8.	Dublin	3rd December 1997
6.9.	Munster (Cork)	5th December 1997

The inspections referred to under 6.1., 6.3., 6.6. and 6.7. were full inspections. The remainder addressed specific items as follows:

6.2. Follow-up of reports of the call-up of a deferred donor.
6.4. Inspection in connection with the wholesaler's licence held by the BTSB.
6.5. Inspection of the Limerick premises and its associated mobile clinic.
6.8. & 6.9. Examination of stock reconciliation.

In addition an inspection of contract testing carried out on behalf of the BTSB by the Virus Reference Laboratory was performed on 30th October 1997.

7. MEETINGS

Meetings took place between members of staff of the IMB and the BTSB on the following occasions.

7.1. 13th February 1997
7.2. 26th June 1997
7.3. 22nd July 1997
7.4. 9th September 1997
7.5. 3rd October 1997
7.6. 11th November 1997
7.7. 11th November 1997
7.8. 26th November 1997
7.9. 9th December 1997

The meetings referred to under 7.1., 7.2., 7.4. and 7.6. were part of a series of regular meetings. These dealt with a large number of items where the IMB has a role, including follow up of inspection matters, review of progress on various items, including the recommendations of the Tribunal of Inquiry, testing strategies and review of progress on new and upgraded facilities. The remaining meetings addressed specific subjects as follows:

7.3. New Dublin Centre.
7.5. New Dublin Centre.
7.7. New Dublin Centre.
7.8. Haemovigilance.
7.9. Haemovigilance.

Three further meetings were held which were attended by members of staff of the Department of Health and Children, the IMB and the BTSB as follows:

7.10.	7th April 1997	Review of recommendations of the Tribunal of Inquiry.
7.11.	6th May 1997	Further review of recommendations.
7.12.	29th October 1997	Review of progress on new facilities in Dublin and Munster.

8. LICENCES HELD BY THE BTSB

The BTSB holds a current manufacturer's licence (M225) and a current wholesaler's licence (W11/1 & 2). Copies of the licences which cover periods relevant to this report are contained in an Appendix.

9. REPORT OF INSPECTIONS

9.1. Quality Management

9.1.1. A National Quality Assurance Officer was appointed during 1997. While this was a positive step the IMB has ongoing concerns that the level of staffing in quality assurance (QA) does not permit the QA Department to adequately discharge its overview role as required under good manufacturing practice. The BTSB was formulating a three year development plan for the QA Department at year end.

9.1.2. It was considered that in its operations covered by Good Manufacturing Practice, the BTSB was operating with insufficient resources - for example, 9.1.3., 9.1.5. below. The same personnel were working on multiple projects and could not be expected to fully address those multiple tasks - for example, sections 9.2.2 and 9.5.3. below.

9.1.3. As the computer system for control of donations is vital to the operation, the IMB considers it essential that the Information Technology (IT) Department of the BTSB be adequately resourced and integrated into the quality system. The BTSB was formulating a three year plan for the IT Department at year end.

9.1.4. A number of improvements in Quality Systems were observed during 1997 at both Centres. These included the better documentation of complaints and their follow up and more formalised training in certain areas - see 9.2.1. below.

9.1.5. It is considered essential that sufficient pharmaceutical engineering and validation expertise be available within the BTSB. These are required in order to manage premises and equipment and are especially important as the BTSB embarks upon the construction of new Centres in Dublin and Cork.

9.1.6. It was considered that the decision making process in relation to all GMP related matters should be more formalised and should include consultation with all relevant Departments, including Quality Assurance in all cases. Such decisions should be formally documented and communicated.

9.2. Personnel

9.2.1. A training programme on Good Manufacturing Practice was put in place in the Munster Centre during 1997. By the end of 1997, a similar programme was planned for the Dublin Centre. A study of the operations of the Dublin Centre, including an assessment of training needs was undertaken by US consultants during 1997.

9.2.2. A training co-ordinator was appointed for the Dublin Centre during 1997. However, due to pressures of work in the other areas he had been unable to assume his new role up to the time of the inspection of 17th - 21st November 1997.

9.2.3. The Chief Executive Officer, was absent due to ill health for much of the second half of 1997. The IMB recognises the contribution which he made in implementing those elements of the strategic plan which came within the remit of the IMB. The lack of a permanent Chief Executive Officer due to his extended absence had consequences for the implementation of the strategic plan. An acting Chief Executive Officer was put in place during the latter part of 1997.

9.3. Premises and Equipment

9.3.1 An interim upgrade of the Dublin Centre was carried out. This provided more space for the processing of components, although process flows were still not ideal.

9.3.2. Plans for a new Dublin Centre at St. James' Hospital were drawn up. By year end the timetable for completion of this new Centre had slipped into 1999. The IMB was informed that this delay was unavoidable due to environmental impact studies, planning permission etc. The IMB has stressed the need for the project to be completed at the earliest possible date - see also 9.1.5. above and 9.3.4. below.

9.3.3. By year end, proposals for an interim upgrade of the Cork Centre were being drawn up. This is scheduled to be completed during July 1998. The manufacturer's licence held by the BTSB was renewed until July 1998, in line with the time table for this upgrade.

9.3.4. During the last quarter of 1997 confirmation was received that a new Centre would be constructed in Cork. The approximate time-scale for its completion is the last quarter of 1999.

9.3.5. During the inspection of the Dublin Centre on the 17th - 21st November 1997, it was considered that the clean room at the Dublin Centre was not in compliance with the requirements of Annex 1 of the EU Guide to Good Manufacturing Practice. - see also 9.5.1. below.

9.3.6. Formal systems are required for qualification and re-qualification of GMP related facilities and equipment.

9.3.7. New equipment for virology testing was installed and the testing functions were validated. The interface between this equipment and the mainframe computer remained to be validated.

9.3.8. Validation of the existing computer system used for control of donations was carried out during 1997. Significant elements of this validation were considered to be inadequate. Revalidation of the system was required in order to ensure complete traceability of all donors, donations and products. This revalidation was scheduled to be carried out during the first quarter of 1998.

9.3.9. The BTSB also began planning the installation of a new computer system for control of donations.

9.3.10. The cross match area at the Munster Centre was considered to be very crowded during the inspection of October 1997. It was intended to address this in the interim upgrade of this Centre.

9.4. Documentation

9.4.1. Some improvements in documentation and documentation control were seen during 1997.

9.4.2. The BTSB was unable to adhere to its schedules for integration of relevant documentation between the two Centres. This was stated to be due to resource limitations.

9.5. Production

9.5.1. During 1997 the BTSB continued its efforts to move all processing to closed system technology. Use of a closed system obviates the need for open processing inside a clean room.

9.5.2. Due to the Department of Health and Children's decision that plasma derived Factor VIII be replaced by Recombinant Factor VIII for all haemophiliacs, the amount of plasma collected by pheresis was significantly reduced.

9.5.3. During November 1997, the IMB was informed by the BTSB of a problem in relation to stock reconciliation which had come to light some time previously. The importance of this issue is that all units should be traceable in the event of a need to recall a unit or to institute a look-back procedure. The IMB carried out follow up inspections on 3rd December 1997 (Dublin) and 5th December 1997 (Cork). At year end, an investigation was ongoing to fully reconcile stocks of components produced, despatched, returned and discarded. The BTSB has stated that all of the units being reconciled had passed all tests of virus safety and were fit for transfusion and that none of these units has been the subject of a look-back.

At this time, the problem appears to be due to a combination of poor computer system design and operator error. Other issues, such as training and integration between departments are also relevant. The IMB is continuing to monitor the investigation and corrective actions.

9.5.4. Standardisation and validation of the procedure for disinfection of the venepuncture site was required at both Centres. This was to ensure consistency in the preparation of the site for needle insertion and blood collection.

9.5.5. During an inspection related to the stock reconciliation issue covered under 9.5.3. above, it was found that a single unit of a blood component had been issued without going through the normal release procedure. The unit was confirmed as having been negative in virology testing. Nonetheless, this incident was considered to represent a serious breakdown in procedures. An investigation and implementation of corrective actions were ongoing at the end of the year.

9.5.6. In a call up of donors to attend a mobile clinic, a deferred donor was contacted in error. Changes to the call up arrangements were introduced as a result.

9.5.7. A weakness in donor registration was identified during inspection at the Dublin Centre. This related to situations in which the donor database contained two or more donors of the same name. It was considered essential that systems be put in place and followed to permit differentiation between donors in such cases. The BTSB undertook to put corrective actions in place.

9.6. Quality Control

9.6.1. (i) As referred to in 9.3.7. above the new virology testing equipment was installed and functionally validated. A detailed assessment of a large number of test results was carried out at the Dublin Centre. This new equipment is among the most up to date available.

(ii) The previous testing equipment continued to be used for certain tests. During the inspection of 17th - 21st November at the Dublin Centre, it was considered that the routine maintenance of this latter equipment was not in compliance with the manufacturer's specification.

9.6.2. The syphilis test used is an adaptation of the testing method set out by the manufacturer of the test kit. While positive controls were included during testing, it is required that any alterations to or adaptations of a test method be validated. Towards the end of 1997, the BTSB indicated that it intended to use a different syphilis test.

9.7. Contract Manufacture and Analysis

9.7.1. The Virus Reference Laboratory (VRL) carries out confirmatory virology testing and look-back testing on behalf of the BTSB. While the basic testing was considered to be acceptable, the IMB required the installation of a formal quality system.

9.7.2. The BTSB has been requested to put in place formal technical contracts with the VRL and any other laboratory carrying out GMP related contract work.

9.7.3. The BTSB should carry out regular audits of companies which supply contract services which are GMP related.

9.8. Complaints and Product Recall

9.8.1. There were procedures in place for dealing with complaints. A number of precautionary recalls of blood components were carried out during 1997.

9.8.2. As part of the strategy to ensure full traceability of all blood components and derivatives, the BTSB and the Department of Health and Children prepared separate letters for all hospitals and health boards setting out the relative responsibilities of each party in the supply chain. The IMB was consulted in relation to the letter drafted by the BTSB.

These letters were scheduled to be despatched during the first quarter of 1998.

9.9. Self Inspection

9.9.1. Self Inspection (internal audit) is considered to be an important part of GMP. Due to staff shortages in QA it has not been possible for a full self inspection programme to be implemented. This problem was particularly acute at the Dublin Centre. (Refer to 9.1.1. above).

9.10. Other Matters

9.10.1 During 1997 the BTSB investigated the feasibility of applying viral inactivation treatment to each unit of fresh frozen plasma. By year end a definite system had been identified. Such treatment would be an adjunct to the initial virology testing of each donated unit. Such treatment is used or being investigated in a number of countries.

By year end, a proposal for carrying out this treatment had been submitted to the Department of Health and Children.

9.10.2. During 1997 the BTSB and IMB closely monitored developments in the UK in relation to leucodepletion of blood components as a possible means of minimising the risk of transmission of new variant CJD. By year end the BTSB was finalising a proposal in relation to the introduction of this new technology.

10. HAEMOVIGILANCE

Haemovigilance is defined as a "set of surveillance procedures from the collection of blood and its components to the follow-up of recipients, to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their recurrence".

During 1997, Haemovigilance was included as an agenda item for discussion at BTSB/IMB meetings. Detailed descriptions of the procedures and staff in place at the IMB for management and monitoring of pharmacovigilance data were provided. The need for a rapid alert system for notification of urgent safety issues and reporting formats for the proposed haemovigilance system was discussed.

Copies of coding and classification systems used by the IMB were provided to the BTSB during a meeting at St. James's Hospital on November 11th 1997 (7.7) for consideration of their applicability to the proposed haemovigilance monitoring system. At a further meeting, December 9th 1997 (7.9), the IMB's pharmacovigilance database was demonstrated with a view to implementation of an appropriate pilot system at St. James's Hospital.

At the end of 1997, the BTSB were making arrangements for the implementation of a national haemovigilance system.

No reports of adverse reactions associated with administration of blood or its components were notified to the IMB during 1997.

11. PHARMACOVIGILANCE

Pharmacovigilance is defined as "the process of identifying and responding to safety issues associated with use of marketed medicines". Statutory responsibility for this function rests with the IMB and the holder of the Product Authorisation. The BTSB is not currently a Product Authorisation holder for any plasma derived medicinal product.

During 1997, the IMB received three suspected adverse reactions associated with use of blood-derived medicinal products. These cases were notified directly by hospital-based doctors, using the voluntary reporting scheme.

The products involved were Haemate P, Albumin and WinRho SDF. In each of the cases notified the symptoms described (fever, headache and allergy-like symptoms) are known to occur and resolved with symptomatic treatment.

CONCLUSIONS:

The BTSB has gone through and continues to go through a period of significant change.

The IMB has ongoing concerns in relation to the lack of resources for operations covered by GMP and the need for an integrated quality management system. It is essential that there be in place sufficient numbers of appropriately qualified, trained and experienced personnel to ensure:

(i) smooth functioning of existing operations;

(ii) the implementation of necessary changes identified by the BTSB, external consultants and the IMB;

(iii) a smooth transition to the new Centres which are due for construction in Dublin and Cork;

(iv) complete prospective validation of the proposed new computer system for control of donations.

The incomplete reconciliation of all units, referred to under 9.5.3. above, is of serious concern. The investigation of this matter and the effectiveness of corrective actions put in place will be closely monitored by the IMB during 1998.

Certain deficiencies identified during 1997 are considered to be significant issues, requiring remedial action as a matter of priority. These are listed below, under the relevant headings of the EC "Guide to Good Manufacturing Practice" and refer to the corresponding sub sections in the Report of Inspections (Section 9).

Quality Management

9.1.1., 9.1.2., 9.1.3., 9.1.5.,

Personnel

9.2.1.,

Premises & Equipment

9.3.5., 9.3.7., 9.3.8.,

Production

9.5.3., 9.5.5.,

Quality Control

9.6.1.(ii).

Self Inspection

9.9.1.

IRISH MEDICINES BOARD

8th April 1998

APPENDIX

COPIES OF LICENCES

IRISH MEDICINES BOARD

IRISH MEDICINES BOARD ACT, 1995

Medical Preparations (Licensing of Manufacture) Regulations 1993 - 1996

Manufacturer's Licence

No. M 225

The Irish Medicines Board in exercise of the powers conferred on it under the Medical Preparations (Licensing of Manufacture) Regulations, 1993, *(S.I. No 40 of 1993)*, as amended, hereby grants to:-

Licence Holder
The Blood Transfusion Service Board, **40/42 Mespil Road,** **Dublin 4.**

renewal of a manufacturer's licence subject to the provisions of the said Regulations and to the general conditions specified in Schedule I hereto.

This licence authorises the holder to carry out the operations in respect of the manufacture of medical preparations of the description or general classification specified in Part I of Schedule 2 to this licence, at the premises specified in Part 2 thereof and under the supervision of the person(s) specified in Part 3 of the said Schedule. This licence is subject to any further special conditions as may be specified in Part 4 of the said Schedule.

The licence, unless sooner revoked, shall apply to the period from the 1st day of December, 1997, to the 31st day of July, 1998.

Signed on behalf of the Irish Medicines Board
this 18th day of December 1997.

Elaine Loughnan

A person authorised in that behalf by the said Board.

Bord Leighis na hEireann

Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: 353-1-676 4971 Fax: 353-1-676 7836

GENERAL CONDITIONS OF LICENCE
SCHEDULE I

The Licence Holder:-

1. shall not, without the prior approval of the Board, manufacture any medical preparation other than one which has been specified in his application for a licence to the Board or wh has subsequently been notified in writing to the Board, and which has been specified in the licence either as such or as a class of medical preparation which may be manufactured him.
2. shall provide and maintain such premises, equipment and staff as are necessary for the carrying out, in accordance with its licence and any relevant product authorization in force such stages of the manufacture of the medical preparations as are undertaken by him and he shall not carry out any such manufacture except at the premises specified in the licence such other premises as may be approved in writing from time to time by the Board.
3. shall provide and maintain such premises, equipment, facilities, and staff for the handling, storage and distribution of the medical preparations which he handles, stores or distribu under his licence as are necessary to avoid deterioration of such products and he shall not use for such purposes premises other than those specified in the licence or such other premi which may be approved in writing from time to time by the Board.
4. shall conduct all manufacturing operations in such a way as to ensure that the medical preparations conform with the standards of strength, quality and purity applicable to them whet under the relevant product authorizations, or under any pharmacopoeial standard or other specification to which they may be manufactured.
5. shall either -
   (a) provide and maintain such premises, equipment, facilities and staff as are necessary for carrying out any tests of strength, quality or purity of the medical preparations that manufactures as required by the relevant product authorization and in accordance with the requirements of good manufacturing practice for medicinal products, as may be specif by the Board, or
   (b) make arrangements with a person approved in writing by the Board for such tests to be carried out on his behalf by that person.
6. shall notify the Board in writing before making any material alteration in the premises or equipment used under his licence, or in the operations in which they are used and he sh notify the Board in writing of any change that he proposes to make in any personnel named in his licence as respectively being -
   (a) responsible for the quality control of the medical preparations being manufactured including the person named as the qualified person for the purposes of paragraph 7 of t Schedule, or
   (b) responsible for supervising the production operations, or
   (c) responsible for biological or microbiological controls used in the manufacture or testing of the medical preparations being manufactured.
7. (1) shall at all times have at his disposal the services of a person (hereinafter referred to as the qualified person), if the licence holder is not himself a qualified person who as respe qualifications and experience satisfies the provisions of Schedule II of the Medical Preparations (Licensing of Manufacture) Regulations, 1993 (as amended) to carry out the functio specified in sub-paragraph (3) below.
   (2) and shall at all times provide and maintain such staff, premises and facilities as will enable the qualified person to carry out the said functions
   (3) the functions to be carried out by the qualified person shall be as follows:-
      (a) to ensure that every batch of medical preparation to which the licence relates has been manufactured and checked in compliance with:-
         (i) the laws in force in the State in respect of such product,
         (ii) the provisions of this manufacturer's licence, and
         (iii) the provisions of the product authorization or other standard which relates to the said product.
      (b) to certify in a register, or other equivalent document appropriate for the purpose, whether each production batch of the medical preparation to which the licence relates satisf the requirements set out in sub-paragraph (a) above and to ensure that such register or other document is regularly maintained and in particular that the appropriate entries such register or other document are made as soon as practicable after each such batch has been manufactured.
   (4) Where, after giving the licence holder and the person acting as the qualified person the opportunity of making representations to him (either orally or in writing), the Board is of t opinion that the person so acting is failing to carry out the functions specified in sub-paragraph (3) above and has notified the licence holder accordingly in writing, the licen holder shall not permit that person to continue to act as the qualified person so long as the said notification has not been withdrawn by the Board.
   (5) The Board may require the licence holder temporarily to suspend the person acting as such qualified person upon the commencement of administrative or disciplinary proceedi against him for failure to fulfil his functions in accordance with sub-paragraph (3) above and the licence holder shall not permit that person to act as the qualified person pending t determination of such proceedings.
8. shall keep readily available for inspection by an officer responsible for the enforcement or execution of these Regulations durable records of the details of manufacture of each batch every medical preparation being manufactured under his licence and of the tests carried out thereon, including any register or other document referred to in paragraph 7(3) (b) above. such form that the records will be easily identifiable from the number of the batch as shown on each container in which the medical preparation is sold, supplied or exported and he sh permit such officer to take copies or make extracts from such records. Such records shall be retained for not less than five years from the date of manufacture or for the period whi ends one year after the labelled expiry date of the medical preparation whichever is the longer period.
9. shall keep such documents as will facilitate the withdrawal or recall from sale, supply or exportation of any medical preparation to which the licence relates. Such documents shall available for inspection by an officer responsible for the enforcement or execution of these regulations.
10. shall keep an adequate sample of each batch and of each active constituent used in the manufacture of such medical preparation to which the licence relates for the period which ends o year after the labelled expiry date of the preparation, and shall furnish on request by the Board a sufficient sample of each such batch for the purpose of any test, examination or analy which may be required by the Board.
11. shall, where he has been informed by the Board that any part of a batch of a medical preparation to which his licence relates has been found not to conform as regards strength, quali or purity with the specifications of the relevant product, if so directed by the Board, immediately withhold the remainder of that batch from sale, supply or exportation and, insofar may be practicable, immediately recall all supplies already sold, supplied or exported from that batch.
12. shall, where he has been informed by the Board that a medical preparation to which his licence relates has been found to give rise to unacceptable adverse reactions, if so directed by Board, immediately withhold that preparation from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies of such preparation already so supplied or exported.
13. shall ensure that any tests for determining conformity with the standards and specifications applying to any medical preparation to which the licence relates, shall, except insofar as conditions of the relevant product authorization may otherwise permit or require, be applied to samples taken from the medical preparation after all manufacturing processes have be completed, and/or at such earlier stage(s) in the manufacture as may be required or approved in writing by the Board.
14. shall comply with any provisions of a product authorization which relate to the sale or supply of a medical preparation for which he is not the holder of the authorization in respect of medical preparation to which the licence relates, and shall, by means of a label or otherwise, communicate the particulars of such provisions as they relate to mode of sale or supply restriction as to sale or supply to any person to whom the licence holder sells or supplies that medical preparation.
15. shall not dispose of any medical preparation to which his licence relates except in accordance with the laws of the State.
16. shall supply such information as may be requested by the Board for the purposes of these Regulations about the medical preparations currently being manufactured and about operations being carried out in relation to such manufacture.
17. shall, for the purpose of enabling the Board to ascertain whether there are any grounds for suspending, revoking or varying any licence or authorization granted under these Regulatio or the Medical Preparations (Licensing and Sale) Regulations, 1996, shall permit and provide all necessary facilities to enable any officer responsible for the enforcement or execut of the said Regulations to carry out such inspection, to take such samples or to take copies of any documents in relation to any business carried on by the licence holder, for the purpo of verifying any statement contained in an application for a licence or authorization.
18. shall comply with the principles and guidelines of good manufacturing practice for medicinal products for human use laid down in Commission Directive 91/356/E

UNCONTROLLED COPY

INITIALS: EL

DATE: 6th April 1998

IRISH MEDICINES BOARD

IRISH MEDICINES BOARD ACT, 1995

Medical Preparations (Wholesale Licences) Regulations, 1993 - 1996

Wholesaler's Licence No. W 11/1

The Irish Medicines Board, in exercise of the powers conferred on it under the Medical Preparations (Wholesale Licences) Regulations, 1993 *(S.I. No. 39 of 1993)*, as amended, hereby grants to:

Licence Holder	in respect of premises at
The Blood Transfusion Service Board, Pelican House, 40-42 Mespil Road, Dublin 4.	Pelican House, 40-42 Mespil Road, Dublin 4.

renewal of a wholesaler's licence, subject to the provisions of the said Regulations, in respect of the following medical preparation(s):-

Medical Preparation(s)
Any medical preparation of biological origin which is used in haematology and which is the subject of a valid product authorisation.

Responsible Person	
Person at these premises responsible for compliance with the conditions of this licence and the requirements of Good Distribution Practice	Ms. Pauline Coakley, F.I.Biomedical Sc.

The licence is subject to the conditions specified in the Schedule hereto and, unless sooner revoked, shall apply to the period from the 2nd day of January, 1997,

to the 1st day of January, 2000.

Signed on behalf of the Irish Medicines Board
this 23rd day of June, 1997

Eleanor Loughnan

A person authorised in that behalf by
the said Board.

Bord Leigheasra na hÉireann

Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: 353-1-676 4971 Fax: 353-1-676 7836

GENERAL CONDITIONS OF LICENCE

Schedule

The licence holder -

(a) shall supply a medical preparation only to (i) a person who is in possession of a wholesaler's licence as referred to in sub-article (1) of article 7 of the Medical Preparations (Wholesale Licences) Regulations, 1993 *(S.I. No. 39 of 1993) (as amended)*, or (ii) to a person carrying on a business of shopkeeping provided he has reasonable grounds for believing that the person is a person lawfully entitled to sell that medical preparation by retail sale, or to a hospital, nursing home or other such health institution.

(b) shall not sell by wholesale or keep or offer for sale by wholesale -

(i) any medical preparation other than those to which the licence relates,

(ii) any medical preparation which requires a product authorisation under the Medical Preparations (Licensing and Sale) Regulations, 1996 and which is not the subject of such an authorisation for the time being in force,

(iii) any medical preparation otherwise than in conformity with the provisions of the aforementioned product authorisation.

(c) shall provide and maintain such premises, equipment and staff, and have in operation such arrangements as are necessary to avoid deterioration of the medical preparation to which the licence relates and shall notify the Board promptly of any material change in such premises, equipment, staff or arrangements.

(d) shall undertake procedures for storage, stock turnover and maintenance of records which are in compliance with the particulars furnished in connection with the application for the licence or with such other arrangements as may be approved by the Board from time to time.

(e) shall, on being informed by the Board or the manufacturer that any batch or part of a batch of a medical preparation to which the licence relates has been found not to conform as regards the provisions of the relevant product authorisation in force under the Medical Preparations (Licensing and Sale) Regulations 1996, or as regards strength, quality or purity with the appropriate specification of that medical preparation, if so directed by the Board, immediately withdraw from sale any supplies of that batch held by him and immediately recall all supplies already sold or distributed from that batch.

(f) shall, on being informed by the Board that a medical preparation to which the licence relates has been found to give rise to unacceptable adverse reactions, if so directed by the Board, immediately withdraw any supplies held by him of that medical preparation from sale and, so far as may be practicable, immediately recall all supplies of it already sold or distributed by him.

(g) in order to facilitate the withdrawal or recall as mentioned in paragraphs (e) and (f) of this Schedule, shall keep records either in the form of purchase/sales invoices, or on computer or in any other form giving for any transaction in the medical preparations received or dispatched at least the following information:

- date of supply
- name of the medical preparation
- quantity received or supplied
- name and address of the supplier or consignee, as appropriate.

(h) shall keep available the records referred to in paragraph (g) above for inspection by an officer responsible for the enforcement or execution of these Regulations for a period of five years from the date of the transaction to which they relate.

(i) shall comply with the principles and Guidelines of good distribution practice for medical preparations referred to in Article 10 of Directive 92/25/EEC (O.J.NO.L113,30.4.1992, P1-4) and published as guidelines on Good Distribution Practice of Medicinal Products for Human Use.

(j) shall from time to time, permit such inspections and make available such information as may be required to satisfy the Board that the conditions of the licence are being complied with.

(k) shall give, without payment, an adequate sample of the medical preparation to any person authorised to take such a sample.

(l) shall furnish with the supply of a medical preparation information confirming:

- the date of supply
- the name and pharmaceutical form of medical preparation
- the quantity supplied
- the name and address of the supplier and consignor.

(m) shall retain this licence at the premises to which it relates and it shall be produced for inspection when required by a person duly authorised under Article 11(1) of the Medical Preparations (Wholesale Licences) Regulations, 1993 (as amended).

UNCONTROLLED COPY

INITIALS: EL

DATE: 6th April 1998

IRISH MEDICINES BOARD

IRISH MEDICINES BOARD ACT, 1995

Medical Preparations (Wholesale Licences) Regulations, 1993 - 1996

Wholesaler's Licence No. W 11/2

The Irish Medicines Board, in exercise of the powers conferred on it under the Medical Preparations (Wholesale Licences) Regulations, 1993 *(S.I. No. 39 of 1993)*, as amended, hereby grants to:

Licence Holder	in respect of premises at
The Blood Transfusion Service Board, Pelican House, 40-42 Mespil Road, Dublin 4.	**St. Finbarr's Hospital, Douglas Road, Cork.**

renewal of a wholesaler's licence, subject to the provisions of the said Regulations, in respect of the following medical preparation(s):-

Medical Preparation(s)
Any medical preparation of biological origin which is used in haematology and which is the subject of a valid product authorisation.

Responsible Person	
Person at these premises responsible for compliance with the conditions of this licence and the requirements of Good Distribution Practice	**Mr. David Keane, C.M.L.S., D.M.L.S., C.Q.A., C.Q.M.**

The licence is subject to the conditions specified in the Schedule hereto and, unless sooner revoked, shall apply to the period from the 2nd day of January, 1997,

to the 1st day of January, 2000 .

Signed on behalf of the Irish Medicines Board
this 23rd day of June, 1997

Elaine Loughnane

A person authorised in that behalf by
the said Board.

Bord Leigheasra na hÉireann

Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: 353-1-676 4971 Fax: 353-1-676 7836

GENERAL CONDITIONS OF LICENCE

Schedule

The licence holder -

(a) shall supply a medical preparation only to (i) a person who is in possession of a wholesaler's licence as referred to in sub-article (1) of article 7 of the Medical Preparations (Wholesale Licences) Regulations, 1993 *(S.I. No. 39 of 1993) (as amended)*, or (ii) to a person carrying on a business of shopkeeping provided he has reasonable grounds for believing that the person is a person lawfully entitled to sell that medical preparation by retail sale, or to a hospital, nursing home or other such health institution.

(b) shall not sell by wholesale or keep or offer for sale by wholesale -

(i) any medical preparation other than those to which the licence relates,

(ii) any medical preparation which requires a product authorisation under the Medical Preparations (Licensing and Sale) Regulations, 1996 and which is not the subject of such an authorisation for the time being in force,

(iii) any medical preparation otherwise than in conformity with the provisions of the aforementioned product authorisation.

(c) shall provide and maintain such premises, equipment and staff, and have in operation such arrangements as are necessary to avoid deterioration of the medical preparation to which the licence relates and shall notify the Board promptly of any material change in such premises, equipment, staff or arrangements.

(d) shall undertake procedures for storage, stock turnover and maintenance of records which are in compliance with the particulars furnished in connection with the application for the licence or with such other arrangements as may be approved by the Board from time to time.

(e) shall, on being informed by the Board or the manufacturer that any batch or part of a batch of a medical preparation to which the licence relates has been found not to conform as regards the provisions of the relevant product authorisation in force under the Medical Preparations (Licensing and Sale) Regulations 1996, or as regards strength, quality or purity with the appropriate specification of that medical preparation, if so directed by the Board, immediately withdraw from sale any supplies of that batch held by him and immediately recall all supplies already sold or distributed from that batch.

(f) shall, on being informed by the Board that a medical preparation to which the licence relates has been found to give rise to unacceptable adverse reactions, if so directed by the Board, immediately withdraw any supplies held by him of that medical preparation from sale and, so far as may be practicable, immediately recall all supplies of it already sold or distributed by him.

(g) in order to facilitate the withdrawal or recall as mentioned in paragraphs (e) and (f) of this Schedule, shall keep records either in the form of purchase/sales invoices, or on computer or in any other form giving for any transaction in the medical preparations received or dispatched at least the following information:

- date of supply
- name of the medical preparation
- quantity received or supplied
- name and address of the supplier or consignee, as appropriate.

(h) shall keep available the records referred to in paragraph (g) above for inspection by an officer responsible for the enforcement or execution of these Regulations for a period of five years from the date of the transaction to which they relate.

(i) shall comply with the principles and Guidelines of good distribution practice for medical preparations referred to in Article 10 of Directive 92/25/EEC (O.J.NO.L113,30.4.1992, P1-4) and pu' hed as guidelines on Good Distribution Practice of Medicinal Products for Human Use.

(j) shall from time to time, permit such inspections a make available such information as may be required to satisfy the Board that the conditions of the licence are being complied with.

(k) shall give, without payment, an adequate sample c : medical preparation to any person authorised to take such a sample.

(l) shall furnish with the supply of a medical preparation information confirming:

- the date of supply
- the name and pharmaceutical form of medical preparation
- the quantity supplied
- the name and address of the supplier and consignor.

(m) shall retain this licence at the premises to which it relates and it shall be produced for inspection when required by a person duly authorised under Article 11(1) of the Medical Preparations (Wholesale Licences) Regulations, 1993 (as amended).

Schedule 2

Part I

1. Classification of Products to which the Manufacturing Licence Applies

OPERATIONS COVERED	GENERAL CLASSIFICATION OF PRODUCTS TO WHICH THE OPERATIONS RELATE
Preparation of Raw Materials for Fractionation IMPORTATION OF MEDICAL PREPARATIONS FROM COUNTRIES OTHER THAN MEMBER STATES OF THE EUROPEAN ECONOMIC AREA The following Class is covered: Sterile Biological Products	Collection and Processing of Whole Human Blood and Human Plasma for use in the manufacture of medicinal products. WINRHO SD 120 mg (i) Glass vials, each containing 120 mg (600 I.U.)of freeze dried Human Immunoglobulin with antibodies against Rho(D) erythrocytes (ii) Glass vials, each containing 2.5 ml of Sodium Chloride Injection Ph.Eur. PA 521/6/1 The above product is manufactured by and imported from: Rh. Pharmaceuticals Inc., 104 Chancellor Matheson Road, Winnipeg, Manitoba R3T 2N2, Canada.

UNLESS IT IS EXPRESSLY STATED THE CLASS OF MANUFACTURE TO WHICH THIS LICENCE RELATES SHALL NOT INCLUDE:

(A) IMPORTATION OF A MEDICINAL PRODUCT FROM A COUNTRY OTHER THAN A MEMBER STATE OF THE EUROPEAN COMMUNITIES OR,

(B) THE MANUFACTURE OF STERILE PRODUCTS, OR

(C) THE MANUFACTURE OF ANY PRODUCT THE PURITY AND POTENCY OF WHICH CANNOT BE ADEQUATELY TESTED BY CHEMICAL OR PHYSICAL MEANS, OR OF ANTIBIOTICS (WHETHER OBTAINED FROM A MICROBIOLOGICAL SOURCE, OR NOT), SULPHONAMIDES, STEROIDS, AND SUBSTANCES WITH HORMONAL ACTIVITY.

Schedule 2

Part 2

2. Particulars of Premises to which the Manufacturing Licence Relates

OPERATIONS	ADDRESS OF PREMISES
1. Manufacturing (including collection and processing)	(A) 40/42 Mespil Road, Dublin 4. **AND** (B) St. Finbarr's Hospital, Douglas Road, Cork. **AND** (C) Collection of blood at Mobile Clinics operated under the control of Centres (A) and (B) above.
2. Filling	not applicable
3. Packaging (including labelling)	not applicable
4. Storage	(A) 40/42 Mespil Road, Dublin 4. **AND** (B) St. Finbarr's Hospital, Douglas Road, Cork.
5. Testing Testing of WINRHO SD only	40/42 Mespil Road, Dublin 4. **AND** St. Finbarr's Hospital, Douglas Road, Cork. **AND** NIBSC, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, EN6 3QG, England.

The manufacturing operations for which this licence is granted shall be carried out in those areas as specified above and so designated in the plan submitted and approved as part of the application made for the purpose of obtaining this licence or at any other premises in respect of which an appropriate Manufacturing Licence is held.

Schedule 2

Part 3

3. PERSONNEL who are responsible for supervising the operations covered by this licence on behalf of the licence holder	
Qualified Person(s) (see condition no. 7 in Schedule 1)	Dr. William Murphy, MB, BCh, BAO, MRCP (UK), MRCPath, MD (NUI), JCHMT, FRCP Edin 1994
Person responsible for the supervision of production operations	Mr. A. P. Finch, F.A.M.L.S, F.I.B.M.S.
Person(s) responsible for Quality Control	NATIONAL QUALITY ASSURANCE OFFICER Mr. J. Sheehy, M.Sc., Dip. Pharm. Manuf. Tech. DUBLIN: Ms. Pauline Coakley, F.A.M.L.S CORK: Dr. J. Power, M.B., M.R.C.P.I.
These responsibilities shall only be undertaken by the person named herein or by such other person as may be approved by the Board	

Schedule 2

Part 4

SPECIAL CONDITIONS

1. Full validation, in accordance with GMP requirements, shall be carried out on the existing computer systems for control of donations and components in the Dublin and Cork Centres.

2. Any new computer system installed in the Dublin and Cork Centres for control of donations and components shall be fully validated, in accordance with GMP requirements, prior to being used for its intended purpose.

3. The area used for the processing of donations at the Cork Centre shall be upgraded and replaced. A timetable for the upgrading, and replacement, was provided in a letter dated 20th November 1997. The Irish Medicines Board shall be informed of progress at the various deadlines set out in the letter of 20th November 1997.

4. In relation to the construction and validation of a new Centre at St. James' Hospital, Dublin, a detailed timetable shall be provided to the Irish Medicines Board. The Irish Medicines Board shall be informed of progress at the various deadlines set out in this timetable.