IRISH MEDICINES BOARD

Irish Medicines Board

Second Annual Report to

The Minister For Health and Children

on the Blood Transfusion Service Board

(Period Covered: 1st January - 31st December 1998)

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EXECUTIVE SUMMARY

This is the second report to the Minister for Health & Children by the IMB in relation to the BTSB. This report has been produced in response to the recommendations of the Finlay Tribunal. It is based on inspections of the BTSB facilities nationwide and on information provided at joint meetings.

The BTSB is undergoing a period of major change with new processes and new facilities being developed which are welcomed. This report, however, focuses on ongoing activities during 1998 and monitors their conformity with current standards of Good Manufacturing Practices (GMPs). Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. Hence, GMP non-compliance may result in variability in product quality characteristics which in turn may give rise to safety concerns regarding the products. The report identifies the specific instances of GMP non compliance organised as in the first report in accordance with the relevant EU Directive on GMP.

The BTSB has not yet achieved an acceptable level of GMP compliance and no significant improvement in GMP compliance is evident relative to 1997. In addition, the IMB is very concerned that the status and resources of the QA function at the BTSB be addressed and that the lengthy delays in validation, as seen with the Blood Bank Control System (BBCS), should not recur. It is essential that the ultimate responsibility for all GMP activities, including engineering work, rest within the BTSB.

During 1998, requirements for a haemovigilance system were further discussed with proposals for establishment of the system prepared and developed. In addition, a pilot haemovigilance project was undertaken at a major teaching hospital. Towards the end of 1998, the BTSB appointed a haemovigilance administrator who has reviewed the SHOT system and arranged a training programme for haemovigilance officers. The IMB was also kept informed of the ongoing medical training programme in the BTSB.

In conclusion, the IMB recognises that the BTSB is in a state of flux with very many positive new developments underway which will help assure the safety of the blood supply. It is critical that those are accompanied by improved GMP compliance and establishment of an effective haemovigilance system. The IMB will continue to insist on conformance with the highest standards and will, where appropriate, work with the BTSB to help it achieve these.

The structure and format of this 1998 report is essentially the same as that for 1997 and for completeness, these two reports should be read in conjunction.

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 second 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 1200 applications for product authorisations, more than one thousand applications to renew authorisations and around 7,000 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 medicinal 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 aforementioned activities of the BTSB also require a licence from the IMB under the Medical Preparations (Licensing of Manufacture) Regulations, 1993 - 1996.

Specifically, these are 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 acts as a wholesaler for a number of medicinal products. This activity is licensed under the Medical Preparations (Wholesale Licences) Regulations, 1993-1996.

In terms of blood products and plasma derivatives, the IMB medical and pharmaceutical staff have many years experience in the assessment of the safety, quality and efficacy aspects of these products. Specific IMB inspectors have received extensive training in relation to current requirements for blood and blood components and in relation to facilities for their collection, testing and processing. These inspectors also have considerable relevant inspection experience.

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. The activities of the BTSB include donor selection and screening, anti-body testing, screening for the detection of infective agents, blood processing, and storage and distribution of blood and blood products. 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 base for a mobile collection team in Limerick (the Cork and Limerick operations come under the collective designation of Munster region). There are also mobile donor clinics which operate from the Dublin and Cork Centres 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 provides tissue typing services. These BTSB 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 in which medicinal products for both human and veterinary use are provided. It also inspects outside of the European Union in connection with applications for marketing 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.

In relation to medicines for human use, the IMB adheres to European Commission Directive 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).

In the conduct of its inspections, the IMB, principally, 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 chapter headings.

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

Taken in their totality, these chapters provide the basis for a Quality Assurance system which can be applied to the operations of the BTSB as well as those of conventional manufacturers. It is these headings which are used in the following sections to summarise the outcome of the inspections of the BTSB. The Council of Europe "Guide to the Preparation, Use and Quality Assurance of Blood Components" provide specific recommendations in relation to blood collection, testing and processing and these are also used.

In addition, comments are included in this report on Haemovigilance and Pharmacovigilance.

Annex 1 gives a list of relevant guidelines and recommendations referenced by the IMB in its assessment of the operations of the BTSB.

5. MONITORING OF THE BTSB DURING 1998

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

5.1 Inspections of each of the facilities in Dublin and Cork (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)	14 - 16 April 1998
6.2	Dublin	15, 16 & 18 June 1998
6.3	Munster (Cork)	8 September 1998
6.4	Mobile Clinic (UCD)	4 November 1998
6.5	Munster (Cork - including Mobile Clinic (UCC))	11 - 13 November 1998
6.6	Dublin	23 - 27 November 1998

The inspections referred to under 6.1, 6.2, 6.5 and 6.6 were full inspections. The remainder addressed specific items as follows:

6.3 Inspection of new components laboratory at Cork Centre.
6.4 Inspection of mobile clinic at UCD.

7. MEETINGS

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

7.1	8 January 1998
7.2	24 April 1998
7.3	27 August 1998
7.4	6 October 1998
7.5	3 November 1998
7.6	10 November 1998 (Department of Health & Children also present)

The meetings referred to under 7.1, 7.2, 7.3 and 7.5 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. During 1998 terms of reference covering the purpose and scope of these meetings were agreed. The remaining meetings addressed specific subjects as follows:

7.4 Meeting regarding the validation status of computer systems used for controlling the status of donations and components.

7.6 IMB's concern about the validation status of the existing IT system.

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 Annex 2.

Following completion of the upgrade to the Components Area at the Cork Centre in September 1998, the manufacturer's licence was renewed until October 1999. This date coincides with the target completion date for the new Dublin Centre and the completion of the installation and validation of a new computer system.

9. REPORT OF INSPECTIONS

NOTE: At the beginning of each of sections 9.1 - 9.9 below a summary of the GMP requirement is given in italics. This is followed by the actual status at the end of 1998. At the end of each section a compliance summary is given in bold type.

9.1 Quality Management

GMP Requirement

To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of quality assurance. All parts of the Quality Assurance system should be adequately resourced with competent personnel and suitable and sufficient, premises, equipment, and facilities.

Actual Status

9.1.1 The status and resources available to Quality Assurance (QA) at the BTSB were not considered to be sufficient to meet requirements of Good Manufacturing Practice (GMP).

STATUS: It is considered that the QA department should have a comprehensive overview role in relation to all GMP impacting activities. The current situation is that the quality assurance department has not always been represented at an appropriate level when key GMP decisions have been made.

RESOURCES: Existing quality assurance resources were considered to be unreasonably stretched leading to difficulties in a number of areas, including:-

- ability to oversee the close out of incident reports and complaints in a timely manner;
- review of standard operating procedures, qualification and validation protocols and their associated reports. This includes the new Dublin facility and computer systems;
- documentation control;
- ability to adhere to quality assurance programmes for components in accordance with Council of Europe recommendations;
- ability to adhere to a self-inspection programme.

9.1.2 The BTSB continued to use the services of an outside contractor for much of its engineering work. It is essential that the ultimate responsibility for all GMP activities, including engineering work, rest within the BTSB. This approach does not preclude the use of outside contractors. However, an in-house engineering department is also required to review contracts with and reports from contractors in order to ensure that these are adequate and comprehensive.

9.1.3 The lack of progress in relation to the maintenance, upgrading and validation of the existing computer system for control of the status of all donations was the subject of intensive contacts between the two organisations, particularly during the last quarter of 1998 - see 9.3.5 below.

9.1.4 At both Centres, the Chief Technologist had overall responsibility for production and elements of quality control. This is at variance with the requirements of the EC Guide to GMP. The BTSB was requested to review these reporting relationships and to revert to the IMB. - See also 9.6, Requirement, below.

9.1.5 The achievement by the Cork Centre of ISO 9000 certification, granted by the National Standards Authority of Ireland, during 1998 is welcomed. This is a general, internationally recognised, quality standard. However, it does not cover GMP or blood collection and processing issues in the detail required by EU medicines regulatory authorities.

Compliance Summary

Throughout 1998 the Irish Medicines Board was concerned at the lack of progress in providing resources in a number of key quality impacting areas.

9.2 Personnel

GMP Requirement

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training relevant to their needs.

Actual Status

9.2.1 At the Dublin Centre, the Training Co-ordinator took up his post during 1998.
The majority of staff went through a basic GMP training programme and documentation of training was improved.

By the end of the year a comprehensive GMP training programme was not yet in place. The training plan for 1998 was not approved and thus, had not been fully implemented.

Examples of this incomplete programme at the Dublin Centre included:

(i) Adequate training was not provided prospectively in relation to the new processes and the associated Standard Operating Procedures (SOPs).

(ii) Retrospective training with regard to existing SOPs was not yet in place.

(iii) Retraining with regard to corrective actions arising from incidents, complaints or recalls was not performed in all cases.

(iv) Training records were not always specific to each SOP for each individual.
For example, the despatch training records.

(v) The effectiveness of the GMP training was not monitored.

It was recommended that Heads of Departments, QA and the training co-ordinator should liaise to ensure that all necessary training is provided for within a defined time frame.

9.2.2 At the Cork Centre, the basic GMP training programme was completed during 1998. However, a training co-ordinator was not available to oversee training programmes for internal staff and for external contract staff.

Other issues which arose at the Cork Centre included:

(i) Retraining with regard to corrective actions arising from incidents, complaints or recalls was not performed in all cases.

(ii) The effectiveness of the GMP training was not monitored.

9.2.3 It was considered that there were insufficient resources available to the Information Technology (IT) department to deal comprehensively with computer systems impacting GMP, including Year 2000 compliance issues - see 9.3.5 below.

A new Information Technology (IT) Manager took up his post during the second half of 1998. Because of personnel changes in the IT department a revised plan for the department was not implemented during 1998. However, it was noted that additional contract staff were approved for the latter portion of 1998.

9.2.4 The new Chief Executive Officer of the BTSB took up his post during July 1998.

9.2.5 The BTSB sought to recruit a validation officer during 1998 with a particular view to qualification and validation of the new Dublin Centre. No appointment was made. Towards the end of 1998 the BTSB was examining the feasibility of contracting out the qualification and validation to a consultancy company.
- see also 9.4.5 below.

9.2.6 A new Donor Services Manager, with responsibility for all aspects of donor recruitment and organisation, took up his post during 1998.

Compliance Summary

By the end of 1998 the IMB considered that the approach to GMP training was still not sufficiently comprehensive nor adequately resourced. While additional contract staff had been approved in the IT area it was of concern that a massive workload was faced as the year 2000 approached. Certain new key appointments were made during 1998 and these are welcomed.

9.3 Premises and Equipment

GMP Requirement

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.

Actual Status

9.3.1 An interim upgrade of the Cork Centre was completed during September 1998. This included a new Components Area. This new Area is of a good standard of finish and environmental conditions and was considered to be acceptable at inspection.

Significant issues remained in relation to other parts of the Cork Centre. For example,

(a) Due to its being prone to flooding, the basement area was not considered to be a suitable location for a number of GMP critical items. These included:

(i) Records and archive samples;

(ii) Virology QC samples;

(iii) Crossmatch records. These are highly significant considering that there is no computer record system for crossmatch;

(iv) All virology and grouping raw data.

(b) The Microbiology and Grouping laboratories did not have sufficient area to allow personnel to review test results in an orderly fashion.

(c) There was no QC laboratory to allow for QC of;

(i) Blood components
(ii) Reagents
(iii) Critical materials - for example, blood bags

(d) There was no area for testing and validation of equipment prior to its introduction to the production or testing environments.

(e) There was insufficient space in the stores area to allow for quarantine segregation of incoming critical materials.

See 9.3.2 below.

9.3.2 During the last quarter of 1997 confirmation was received from the BTSB that a new Centre would be constructed in Cork (see section 9.3.4 of the 1997 report).

During a BTSB/IMB meeting on the 3rd November 1998 the BTSB indicated that the requirement to continue testing of donations at two sites was being reviewed. The further necessary refurbishment of the facility at Cork was being reviewed in that light. In the report of the inspection of 11-13 November 1998 at the Cork Centre, the IMB requested details of proposals for the Centre from the BTSB.

9.3.3 Work continued on construction of the new Dublin Centre at St. James's Hospital. The IMB has emphasised to the BTSB the need to prepare well in advance for qualification of new equipment and requalification of existing equipment which will be transferred from the Mespil Road premises.

9.3.4 The cleanroom at the Dublin Centre ceased to be used for open processing of products which fell within the remit of the Irish Medicines Board.

9.3.5 There were two major computer validation projects ongoing during 1998. These were:

(i) Existing Blood Bank Control System (BBCS).

The BBCS system was initially procured in the later 1980s. Installation commenced in the early 1990s.

This system became fully operational in 1995 without carrying out a validation of the computer systems - a necessary GMP requirement. Following queries raised by the IMB in 1995, validation of the system has been ongoing for some time. Particular difficulties relating to validation were the extensive customisation of the BBCS and the availability of only one programmer at the BTSB who is thoroughly familiar with the software.

In the middle of 1998 the BTSB, without consultation with the IMB, took a strategic decision to concentrate its available resources on the installation and validation of the new computer system which is referred to in (ii) below. The principal reason was that the BBCS is not year 2000 compliant.

In view of ongoing concerns in relation to the integrity of the BBCS system, the stopping of work on its validation was not considered to be acceptable to the IMB.

Intensive discussions took place between the two organisations, particularly during the last quarter of 1998.

The issues included the following:

(i) The IMB required that the validation be based on a risk assessment of the BBCS.

(ii) What was sought was a combination of validation of critical functions plus manual controls which would provide a high degree of assurance that only acceptable donations could be despatched to patients - see (iv) below.

This combined approach had been referred to in IMB letters to the BTSB during December 1997.

(iii) A written statement, signed jointly by the CEO, National Medical Director and Management Services Officer of the BTSB, was received by the IMB in relation to their view of the safety of the blood supply. Their overall conclusion was that the current supply was safe but that the best option was to replace the BBCS.

(iv) Documentation of the validation status of the BBCS and the additional manual controls was provided by the BTSB during October 1998. It was the view of the IMB that where critical functions had not been validated, the need for and type of manual controls had not been assessed in detail in each such case.

Towards the end of 1998 agreement was reached on the approach with regard to validation of the BBCS and it was further agreed that by the end of May 1999 a final validation report would be available for review.

During the November 1998 inspections it was found that a component which had been placed on hold on the system for a medical reason had been released for use by a non-medical person. In addition, irradiated red cells had been released with an inappropriately long expiry date. Some corrective actions and retraining was carried out in relation to both of these issues.

Another important issue with the BBCS was the need to have the data on this system in a form which will be readily transferable to the new system referred to under (ii) below. Again, this task places a heavy demand on the programmer who is conversant with the BBCS.

(ii) <u>Progesa System (New)</u>

This is a Year 2000 compliant system which has been installed in a number of blood banks across Europe and elsewhere. The replacement of the BBCS with the Progesa System represents a comprehensive response to the problems of the existing BBCS. A project team was formed by the BTSB and initial installation and validation work was carried out at the Cork Centre. A Project Manager with experience of computer validation in the pharmaceutical industry was appointed.

The BTSB's aim is to have the Progesa system fully operational before the 9th September 1999, a date which is potentially problematic for systems such as the BBCS which are not year 2000 compliant. The timetable for installation was an aggressive one and by the end of 1998 the BTSB indicated that it was on target to meet the September 1999 timetable.

The IMB has also requested the BTSB to consider how the Progesa system can be moved in a controlled manner to the new Dublin Centre when this facility comes on stream during the last quarter of 1999.

The IMB will review the validation of this system during 1999.

9.3.6 Aside from the comments set out in 9.1.2 above on engineering resources, the following specific issues also arose in relation to maintenance and calibration:

(i) The schedule for preventative maintenance of equipment and the actual maintenance performed were not always in compliance with the manufacturer's instructions for the piece of equipment.

(ii) Approval (sign off) of equipment as being fit for return to use after breakdown or other non-routine events was not carried out.

(iii) One instance of non-calibration of timers on plasma freezers was noted.

9.3.7 It was considered that the location for one mobile donor clinic at one of the Higher Education sites was not suitable. The location was a busy and noisy corridor which was a thoroughfare for students.

<u>Compliance Summary</u>

Throughout 1998 there were significant concerns in relation to the validation status of the BBCS. The installation and validation of the Progesa system is a key project. The IMB welcomes the major investments in new premises which have been undertaken by the BTSB and the first element of which came on stream in Cork during 1998. However, the programme for overall replacement of the Cork Centre is now behind schedule.

The IMB is very concerned at the fact that validation of the BBCS has not been completed, but welcomes the commitment of the BTSB to now complete its validation. The IMB also welcomes the plans to complete validation of the new PROGESA system prior to its implementation.

The IMB has emphasised to the BTSB that it is essential to ensure the safety of major new equipment and/or processes via prior completion and approval of a validation programme.

9.4 Documentation

Requirement

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, procedures and records must be free from errors and available in writing.

Actual Status

9.4.1 Installation and operational qualification were carried out on the new Components Area at the Cork Centre. While there were some areas in which the qualification reports required to be more clear and/or complete, the overall package was considered to be an acceptable approach to qualification.

9.4.2 At the Dublin Centre, an SOP describing the use of the COBE pheresis equipment was not issued until 4 months after the equipment was introduced into use. This is unacceptable.

9.4.3 At the Dublin Centre, various aspects of the product masterfile had been updated during the second half of 1998. Some specifications and indications had changed. However, the updated aspects of the product masterfile had not been forwarded to the relevant hospitals by the time of the November inspection.

9.4.4 Process equipment used in the manufacture or testing of blood components did not have logbooks providing a comprehensive history of each piece of equipment. Calibration, preventative maintenance, breakdown and non-routine events and cleaning were not recorded in a uniform manner.

9.4.5 A Validation Master Plan for the new Dublin Centre was drafted during 1998. The IMB is concerned that this should be fully approved and issued at an early date in order that the framework for qualification and validation of the new Centre is clearly understood.

Compliance Summary

The majority of existing documentation was found to be acceptable with the important exceptions noted above and elsewhere in this report. The delay in finalising a Validation Master Plan was of concern because of the need to have such a plan available well in advance for all qualification and validation elements which arise in relation to transfer to the new Dublin Centre during 1999.

9.5 Production

Requirement

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing licence.

Actual Status

9.5.1 A review of the complaints and non-conformances files showed there to be a number of ongoing problems in the cross-match department at the Cork Centre. These related to compliance with operating procedures, the lack of any IT system and the number of different functions carried out by the crossmatch department: i.e.;

(1) manufacture of components
(2) compatibility tests
(3) clerical activities

There was evidence of transcription errors between documents.

A double verification of transcription elements of the work must be put in place until such time as a validated IT system is available for use.

The upgrade of the components area in Cork and the subsequent relocation of crossmatch department to the old components area provided additional office space. However, there were no administration personnel available for the Crossmatch Department.

9.5.2 A stock reconciliation problem was referred to in section 9.5.3 of the 1997 report. Work on locating units which were unaccounted for continued during 1998. The main issue here is the need to be able to trace all units in the event of any future look back.

At the Dublin Centre, a firm of consultants was engaged in order to examine all invoices and delivery dockets issued since the BBCS system became operational in 1995. Any apparent discrepancy was listed with a view to visiting the customer concerned to check if it had received any of the units not accounted for.

At the Cork Centre a similar exercise to that described above was carried out by staff.

At the time of the November 1998 inspections the BTSB stated that, despite the extensive review of records and the visits to customers, it was probable that a number of units would not be definitively traced. The BTSB thinks that the majority of these probably expired in inventory and were discarded. However, where no objective evidence exists this cannot be concluded definitively.

The firm of consultants employed at the Dublin Centre also produced a report of its work during 1998 and this included a number of recommendations for improvements in stock control and order picking. These mirrored a number of similar recommendations made by the IMB at the end of 1997. It was of concern to the IMB that not all of the Consultants' recommendations, or those of the IMB, had been implemented at the time of the November 1998 inspections. These concerns were expressed in the inspection reports and clarification has been requested.

9.5.3 It was noted that a complete reconciliation of donor registration forms (BT1s), versus donations versus sample tubes was not carried out at the end of one of the mobile clinics inspected.

9.5.4 There were instances of the use of call out by one person and tick off by a second for verification of updated computer records, analysis results and labelling. This method of double check/verification is not acceptable to the IMB in a GMP environment.

The BTSB was requested to ensure that each checker physically verifies the item which he/she is verifying.

9.5.5 Projects aimed at further improving the safety of the blood supply continued during 1998. In relation to processing of donations these were:

(1) Viral inactivation treatment of plasma for therapeutic use

Pilot work on Methylene Blue treatment of plasma by a manufacturer located outside of Ireland was carried out during 1998. This project was placed on hold principally because of the non-availability of a suitable source of Methylene Blue. In addition, because of its potential for interaction with essential cell molecules there remains an element of concern regarding the clinical safety of this substance. Therefore, it is essential that it be completely eliminated from the plasma following the treatment step.

An alternative approach in this area is to quarantine all plasma for therapeutic use for six months. This allows the donor in the interim, to have given at least one further donation, which would be fully tested.

(2) Leucodepletion

Research has indicated that CJD and new variant (nv) CJD may be concentrated in leucocytes. Therefore, reduction in the level of leucocytes in blood and in component donations has been proposed as a method of lessening the risk of transmission of these diseases.

Work on leucocyte depletion was carried out at both Centres during 1998. Differing approaches were taken at the two Centres principally because of the different sizes of the donor populations.

The work at the Dublin Centre was hampered by a defect in commercially supplied filters. This defect was discovered during testing carried out by the quality control laboratory in the Dublin Centre. This led to the recall of these filters. Some components which had been processed using these filters were transfused in Irish hospitals but the IMB was informed by the BTSB that no adverse events had occurred. In addition, some leucodepleted components were recalled by the BTSB due to this filter problem.

The leucodepletion project was ongoing at the end of 1998.

See also 9.6.3 below.

Compliance Summary

The ongoing problems in the Cross Match Department at the Cork Centre were of considerable concern. The stock reconciliation issue was not concluded during 1998 and a number of units cannot be definitively traced.

A double check verification system should require each checker to physically review the data rather than rely on what is said by another person. Efforts to further improve the safety of the blood supply continued during 1998. These were in line with international developments.

9.6 Quality Control

GMP Requirement

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

Actual Status

9.6.1 As part of the continuing integration of laboratory test results and computerised control of status of donations, transmission from testing equipment to the Blood Bank Control System (BBCS) of results of syphilis testing and liver function testing were validated during 1998. However, it was considered that the validation was not acceptable to the IMB as it did not include adequate challenge testing. At the November 1998 inspections the BTSB was requested to rectify this.

9.6.2 The Quality Control of red cell products was not in compliance with the Council of Europe recommendations. The test for haemolysis at the end of storage was not carried out.

9.6.3 A proposal to use Nucleic Acid Amplification Technology (NAT) in testing donations was ongoing during 1998. NAT allows the detection of Hepatitis C or other viruses at very low levels. The initial part of the project was concentrated upon detection of Hepatitis C virus only. During 1998 the BTSB took samples for NAT testing from plasma donations which were to be used in the manufacture of medicinal products. These samples were NAT tested by Pharmacia & Upjohn, Sweden, the manufacturer of the medicinal products. This NAT testing is intended to become a mandatory EU requirement for plasma used in the manufacture of medicinal products from the 1st July 1999.

By the end of 1998, for all other donations, plans were at an advanced stage for pooled samples to be NAT tested by the Scottish National Blood Transfusion Service (SNBTS).

The eventual aim is for NAT testing capability to be installed at the new Dublin Centre.

It should be noted that NAT testing will be additional to existing virology testing.

Compliance Summary

Adequate validation and challenge testing of laboratory information management systems is essential. It is not acceptable to the IMB that established quality standards such as Council of Europe recommendations fail to be implemented because of resource issues. These are an integral component of a Blood Transfusion Service. The impending implementation of NAT is an essential and welcome development which will assist in improving the safety of the blood supply.

9.7 Contract Manufacture and Analysis

GMP Requirement

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party.

Actual Status

9.7.1 Syphilis confirmatory testing, and quality control testing relating to syphilis, were carried out by separate contract laboratories on behalf of the two Centres. However, neither of the contract laboratories concerned (one in Cork and one in Dublin) had been audited by the BTSB.

9.7.2 Technical contracts were not in place with any of the contract laboratories used by the BTSB.

Compliance Summary

It is a GMP requirement that the BTSB should perform regular audits of companies which supply contract services which are GMP related.

The absence of technical contracts with outside testing laboratories is not in compliance with GMP.

9.8 Complaints and Product Recall

GMP Requirement

All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. In order to provide for all contingencies a system should be designed to recall, if necessary, promptly and effectively, products known or suspected to be defective from the market.

Actual Status

9.8.1 A number of precautionary recalls of components were carried out during 1998. These occurred where, for example, a donor reported subsequent to a donation that he/she had a cold, flu etc.

9.8.2 Some leucodepleted components were recalled due to the filter problem referred to under 9.5.6(2) above.

9.8.3 Two precautionary recalls of blood derivatives were carried out during 1998. These related to donors whose plasma had been used in these products reporting subsequently that they had received tissue grafts. These donors had not suffered any adverse effects from these tissue grafts. In one case, some of the batches of derivatives had passed their expiry date when the information came to light.

This policy of precautionary recall is in line with that of the Department of Health & Children where any possibility of the transmission of CJD or, nv CJD exists.

9.8.4 A national recall procedure was drafted during 1998 but was not yet in place at the end of the year. Each of the Centres continued to have its own recall procedure.

Compliance Summary

The handling of complaints during 1998 was considered to be satisfactory. Any recalls carried out during 1998 were precautionary. The decisions to institute precautionary recalls of blood derivatives exceeded current international requirements. The requirement for a national recall procedure is one of the recommendations of the Hepatitis C Tribunal Report and had not been finalised at the end of 1998.

9.9 Self Inspection

GMP Requirement

Self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

Actual Status

9.9.1 There were insufficient QA resources at both Centres to implement effective self inspection programmes.

Compliance Summary

The implementation of an effective self inspection programme is considered to be an essential element for any licensed manufacturer. Compliance with GMP requirements is ultimately the responsibility of the licence holder and a self inspection programme which critically assesses compliance levels is one of the best ways of ensuring compliance. It is essential that sufficient resources be made available to implement self inspection programmes.

10. HAEMOVIGILANCE/PHARMACOVIGILANCE

10.1 Haemovigilance

During 1998, requirements for a haemovigilance system were included as an agenda item for discussion at two BTSB/IMB meetings (January and April) and at a special meeting of the IMB and Department of Health & Children (June).

Following these meetings, the Department of Health & Children confirmed its decision to establish a National Haemovigilance Office (NHO) within the BTSB, with the IMB acting in an advisory capacity. Subsequently, the IMB and Department of Health & Children prepared and exchanged draft proposals for the establishment of a haemovigilance system and the BTSB and IMB continued to liaise regarding the development of the haemovigilance system.

Late in 1998 the BTSB appointed a Haemovigilance Administrator, who, since her appointment, has reviewed the SHOT system, the IMB's pharmacovigilance database and arranged a training programme for haemovigilance officers, scheduled to take place in April 1999.

A pilot project on haemovigilance was undertaken at a major teaching hospital during 1998. This project identified the following reactions associated with blood components.

Product	*Reaction*	*No. of Cases*
Red Cells	Febrile Reaction	32
	Urticaria	6
	Rigors	3
	Tachycardia	1
	Respiratory Distress	1
	Hypotension	1
No. of Units Transfused		10,465
Platelets	Febrile Reaction	6
	Urticaria	8
	Hypotension	1
No. of Units Transfused		10,999
Fresh Frozen Plasma		
	Urticaria	7
	Rigors/Hypotension/Dyspnoea	2
No. of Units Transfused		3,715

No reports of suspected adverse drug reactions associated with administration of blood or its components were notified directly to the IMB during 1998.

10.2 Pharmacovigilance

During 1998, the IMB received one report of a suspected adverse reaction associated with use of a blood derived medicinal product which, at the time, was imported, released and distributed by the BTSB. This case was notified directly to the IMB by the marketing authorisation holder.

The product involved was the Anti D immunoglobulin, WinRho SD. The patient concerned was noted to have Hepatitis C infection following administration of the product. Classification of the case is not possible as the patient concerned has a history of intravenous drug use and has undergone a number of surgical procedures including tattooing.

It is important to note that the product had been manufactured using a range of techniques, including solvent detergent treatment and a specific virus filtration step, designed to inactivate/remove blood borne viruses such as HIV and Hepatitis C. In addition, each batch of product undergoes independent batch release by an EU approved independent control authority.

11. REPORT ON MEDICAL TRAINING

During 1998, the BTSB's medical staff attended meetings in both the Dublin and Cork Centres as part of the continuing medical education programme for existing clinical medical staff. The meetings consisted of updates on relevant advances in transfusion medicine, discussion and training on procedural changes as required, review of specific complaints and non-conformances along with general communication. Documentation, as appropriate to the topic, was provided and a record of each meeting, including attendance, was kept. The continuing medical education programme remained under the responsibility of the Medical Director in both the Dublin and Cork Centres. As part of the medical resource plan of the BTSB, it is envisaged that a donor consultant will be appointed who will take over co-ordination at national level of the continuing medical education programme for clinical medical staff during 1999.

12. CONCLUSIONS

12.1 The many GMP non compliances identified, the lack of resources, and concerns relating to computer systems, are considered to represent a potentially critical situation.

The BTSB has not yet achieved an acceptable level of GMP compliance. It is of ongoing concern to the IMB that no significant improvement in GMP compliance was evident in 1998 and that appropriate resources are still not available in key areas in order to achieve full compliance.

In particular, the status and resources of the Quality Assurance function need to be addressed.

12.2 The computer systems controlling the status of donations are vital to ensuring the safety of the blood supply. It was of great concern to the IMB that validation work on the BBCS should be placed on hold without any reference to the IMB. Indeed, in June 1998 the IMB was given to understand that validation was ongoing. The IMB has insisted that validation of the BBCS be continued and an end of May 1999 deadline has been set for provision of a report by the BTSB.

12.3 The plans for the new Dublin Centre indicate that it will be one of the most modern blood processing Centres in the world. However, in addition to its design, it is essential that sufficient resources be put into the qualification, validation and ongoing running of this new Centre. In relation to ongoing running of the new Centre, it is considered that the resources available for engineering will have to be considerably increased.

12.4 The new Components Area at the Cork Centre is of a good standard. However, there are a number of problems with other parts of the Centre where GMP related activities are carried out.

The IMB has sought clarification from the BTSB in relation to the timetable which was presented in November 1997 for construction of a new Cork Centre.

12.5 The role of the IMB is to:

(a) define the standard for GMP compliance by reference to international standards (see Annex 1) and its own experience;

(b) monitor adherence by the BTSB to that standard by review of documentary evidence and work practices; and

(c) to take regulatory action in the event of consistent or critical non-compliance.

It is essential that this be clearly understood by all parties concerned.

12.6 The introduction of new processes and tests aimed at increasing the safety of the blood supply have not progressed at the rate intended by the BTSB during 1998. There is, however, a balance between introducing new measures and their actually performing as intended. The early phases of the introduction of any new technology can be problematic and can set back timetables. The IMB will continue to monitor the introduction of these measures.

12.7 Deficiencies under section 9 above which are considered to be of particular importance and which require remedial action as a matter of priority are:

Quality Management:

9.1.1
9.1.2 (& 9.3.6)

Personnel:

9.2.1 & 9.2.2
9.2.3

Premises and Equipment:

9.3.1 & 9.3.2
9.3.3
9.3.6 (& 9.1.2)

Documentation:

9.4.5

Production:

9.5.1
9.5.2
9.5.4
9.5.5

Quality Control:

9.6.1
9.6.3

Contract Manufacture and Analysis:

9.7.1
9.7.2

Complaints & Product Recall:

9.8.4

Self Inspection:

9.9.1

ANNEX 1

GUIDELINES AND RECOMMENDATIONS REFERENCED BY THE IRISH MEDICINES BOARD IN ITS ASSESSMENT OF THE OPERATIONS OF THE BLOOD TRANSFUSION SERVICE BOARD DURING 1998

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1. European Community Guide to Good Manufacturing Practice for Medicinal Products (Volume IV of the Rules Governing Medicinal Products in the European Community).

2. Guide to the Preparation, Use and Quality Assurance of Blood Components Third and Fourth Editions - published by Council of Europe.

3. Guidelines for the Blood Transfusion Services in the United Kingdom, Third Edition, - published by the United Kingdom National Blood Service.

4. Recommendations on Validation Master Plan, Installation and Operational Qualification - published by the Pharmaceutical Inspection Co-Operation Scheme.

5. Good Automated Manufacturing Practice (GAMP) - published by UK Pharmaceutical Industry Computer Validation Forum.

6. Inspection of Computer Systems - Pharmaceutical Inspection Co-Operation Scheme. Seminar, Sydney 1996.

ANNEX 2

BLOOD TRANSFUSION SERVICE BOARD

LICENCE DOCUMENTS COVERING PARTIAL MANUFACTURE OF MEDICINAL PRODUCTS DURNG THE PERIOD 1ST JANUARY TO 31ST DECEMBER 1998

IRISH MEDICINES BOARD

DATA INPUT
DATE: Aug 1998

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

GENERAL CONDITIONS OF LICENCE
SCHEDULE I

licence Holder:-

hall 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 which is 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 by m.

hall 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, of ich 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 or ich other premises as may be approved in writing from time to time by the Board.

hall provide and maintain such premises, equipment, facilities, and staff for the handling, storage and distribution of the medical preparations which he handles, stores or distributes ader 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 premises hich may be approved in writing from time to time by the Board.

hall 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 whether ader the relevant product authorizations, or under any pharmacopoeial standard or other specification to which they may be manufactured.

hall either -

) 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 he manufactures as required by the relevant product authorization and in accordance with the requirements of good manufacturing practice for medicinal products, as may be specified by the Board, or

) make arrangements with a person approved in writing by the Board for such tests to be carried out on his behalf by that person.

hall 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 shall otify the Board in writing of any change that he proposes to make in any personnel named in his licence as respectively being -

) 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 this Schedule, or

) responsible for supervising the production operations, or

) responsible for biological or microbiological controls used in the manufacture or testing of the medical preparations being manufactured.

) 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 respects qualifications and experience satisfies the provisions of Schedule II of the Medical Preparations (Licensing of Manufacture) Regulations, 1993 (as amended) to carry out the functions specified in sub-paragraph (3) below.

) 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

) 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 satisfies 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 in such register or other document are made as soon as practicable after each such batch has been manufactured.

) 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 the 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 licence 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.

) The Board may require the licence holder temporarily to suspend the person acting as such qualified person upon the commencement of administrative or disciplinary proceedings 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 the determination of such proceedings.

hall 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 of very 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, in uch 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 shall ermit 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 which nds one year after the labelled expiry date of the medical preparation whichever is the longer period.

hall 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 be vailable for inspection by an officer responsible for the enforcement or execution of these regulations.

hall 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 one ear 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 analysis which may be required by the Board.

hall, 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, quality 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 as may be practicable, immediately recall all supplies already sold, supplied or exported from that batch.

hall, 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 the Board, immediately withhold that preparation from sale, supply or exportation and, insofar as may be practicable, immediately recall all supplies of such preparation already sold, supplied or exported.

hall 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 the 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 been completed, and/or at such earlier stage(s) in the manufacture as may be required or approved in writing by the Board.

hall 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 a 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 or restriction as to sale or supply to any person to whom the licence holder sells or supplies that medical preparation.

hall not dispose of any medical preparation to which his licence relates except in accordance with the laws of the State.

hall 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 the operations being carried out in relation to such manufacture.

hall, 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 Regulations 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 execution 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 purpose of verifying any statement contained in an application for a licence or authorization.

hall comply with the principles and guidelines of good manufacturing practice for medicinal products for human use laid down in Commission Directive 91/356/EEC (OJNo.L193,17/7/91, P.30-33).

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	Collection and Processing of Whole Human Blood and Human Plasma for use in the manufacture of medicinal products.
IMPORTATION OF MEDICAL PREPARATIONS FROM COUNTRIES OTHER THAN MEMBER STATES OF THE EUROPEAN ECONOMIC AREA The following Class is covered: Sterile Biological 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.

Posted 24/3/99

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 August, 1998, to the 31st day of October, 1999.

Signed on behalf of the Irish Medicines Board
this 24 day of March ,1999.

Karen Long

A person authorised in that behalf by the said Board.

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

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	Collection and Processing of Whole Human Blood and Human Plasma for use in the manufacture of medicinal products.

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 Storage of Human Plasma	(A) 40/42 Mespil Road, Dublin 4. **AND** (B) St. Finbarr's Hospital, Douglas Road, Cork. **AND** Reinhard Meyer International Ltd., The Old Dublin Road, Enniscorthy, Co. Wexford.
5. Testing	40/42 Mespil Road, Dublin 4. **AND** St. Finbarr's Hospital, Douglas Road, Cork.

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 replaced. A timetable for the 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.

BLOOD TRANSFUSION SERVICE BOARD

LICENCE DOCUMENTS COVERING WHOLESALING OF MEDICINAL PRODUCTS DURING THE PERIOD 1ST JANUARY TO 31ST JANUARY 1998

NOTE: W 11/1 - COVERING DUBLIN CENTRE
W 11/2 - COVERING CORK CENTRE

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 Loughman

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

he 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).

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 Leighton

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).