Chapter Six

Summary of Conclusions and Recommendations

Introduction

6.1 This chapter summarises the main conclusions and recommendations of the Expert Group on the Blood Transfusion Service Board. It is intended only as a summary and should be read in conjunction with the entire report. The examination of our terms of reference is divided between three major elements:

- Anti-D Immunoglobulin (Chapter Three);
- Organisation and Management of the BTSB (Chapter Four); and
- Licensing of Blood Products (Chapter Five).

• ANTI-D IMMUNOGLOBULIN

Anti-D Immunoglobulin and Rh Haemolytic Disease

6.2 Rh Haemolytic Disease occurs where a woman with Rh Negative blood gives birth to a baby with Rh Positive blood. The pregnant woman develops antibodies to her baby's Rh Positive blood which destroy foetal red cells and can lead to severe anaemia, brain damage or death of a baby in a subsequent pregnancy.

6.3 **Anti-D immunoglobulin is a product given to prevent Rh Haemolytic Disease. It is an extremely important product which has prevented death and serious illness in thousands of infants in Ireland since its introduction in 1970. The value of using Anti-D immunoglobulin, where medically indicated, is not in question. While a serious problem emerged in relation to the product manufactured by the Blood Transfusion Service Board up to February, 1994, there is no argument about the vital role of Anti-D immunoglobulin in preventing Rh Haemolytic Disease.**

Anti-D Immunoglobulin produced by BTSB

6.4 The Blood Transfusion Service Board (BTSB) first produced an Anti-D product, *Human Immunoglobulin — Anti-D*, for clinical use in 1970. It issued almost 200,000 doses of the product between 1970 and February, 1994 when production ceased.

In producing Anti-D immunoglobulin it is necessary to obtain plasma containing a high level of appropriate antibodies. Because of their clinical characteristics, suitable antibodies tend to be in short supply. The main sources of antibodies used by the BTSB in its Anti-D programme were:

(1) A panel of male Rh Negative volunteers who were immunised with Rh Positive blood cells to produce Anti-D antibody;

(2) Rh Negative women who had developed the antibody as a result of previous Rh Positive pregnancies; and

(3) Other sources such as women with Anti-D antibody undergoing plasma exchange treatment to lower their antibody level during pregnancy, post menopausal Rh Negative women, and Rh Negative men who had developed Anti-D from a transfusion of Rh Positive blood.

Infection of Anti-D with Hepatitis C

6.5 Women receiving plasma exchange treatment during pregnancy were a particularly rich source of antibody for the production of Anti-D. Plasma from one such woman was used to produce Anti-D between September and November, 1976. She then became jaundiced and the BTSB ceased using her plasma. She tested negative for Hepatitis B and appeared to make a full recovery after a few weeks. The BTSB then decided to recommence use of her plasma in the Anti-D programme.

6.6 In 1977, the BTSB was notified of six women who had developed clinical jaundice some weeks after having received Anti-D immunoglobulin. Samples from these cases were sent to Middlesex Hospital Medical School where they tested negative for Hepatitis B. In accordance with normal practice, Middlesex Hospital retained samples for further testing should additional tests become available at a later stage.

6.7 Hepatitis C was first described in 1989; previously it had been described as *Hepatitis Non A Non B* because its characteristics had not been adequately identified. An internationally accepted test for Hepatitis C was developed in 1991, at which time the BTSB commenced testing all blood and plasma donations for the virus.

6.8 In December, 1991, Middlesex Hospital used the new test for Hepatitis C on the archived samples from the 1977 cases of jaundice. It tested samples from one plasma donor and three recipients of Anti-D from the 1977 incident. It also tested archived samples of batches of *Human Immunoglobulin — Anti-D* that had been used in 1977. Middlesex Hospital found evidence of Hepatitis C in some of the samples. In a letter of 16 December, 1991 to the Chief Medical Consultant (CMC) of the BTSB, the Hospital reported that there was 'considerable evidence' that Anti-D was implicated in the occurrence of Hepatitis C in 1977 and put a series of questions to the CMC so that the matter could be investigated further. The CMC acknowledged the letter from Middlesex Hospital on 16 January, 1992 and referred it to the BTSB's Principal Biochemist for further investigation. No further action appears to have been taken at that time.

6.9 In early 1994, as part of a research study into the incidence of Hepatitis C in blood donors, the Regional Director of the Munster Blood Transfusion Service found a disproportionately high incidence of Hepatitis C in female Rh Negative blood donors. Further investigation established that a number of these women had given birth in 1977 and would probably have received Anti-D at the time. The CMC informed us that he then recalled the 1977 cases of clinical jaundice and the letter from Middlesex Hospital of 16 December, 1991. More samples from 1977 were sent to Middlesex Hospital for testing and were found to contain Hepatitis C. The BTSB immediately withdrew its *Human Immunoglobulin — Anti-D* on 18 February, 1994, and a national blood screening programme for recipients of the product was established.

The 1977 Incident

6.10 **On the available evidence, we conclude that the BTSB's product *Human Immunoglobulin — Anti-D* became infected with Hepatitis C Virus in the circumstances described to us by the BTSB. We have concluded that the most probable source of infection was the plasma exchange patient who developed jaundice in late 1976 and whose plasma was used as a source of Anti-D in the period immediately preceding the onset of her condition of clinical jaundice and again in 1976/77 after she had recovered. This conclusion is supported by recent research carried out by the BTSB which identifies the same genotype of the Hepatitis C virus in samples of the Anti-D product and a number of women who received Anti-D in 1977.**

6.11 **In 1977, the BTSB had clear standards governing the selection of donors for (a) ordinary blood donors and (b) the male donor panel for Anti-D production. In both categories, the BTSB's standards prohibited the use of donors with a history of infectious hepatitis or jaundice of unknown origin. We consider that the BTSB should have applied those same standards to the 1976/77 female plasma exchange patient. Her plasma would not have been accepted under the standards set down for the other categories of donor, and should not, we believe, have been used in the production of Anti-D in 1976/77 after she had become jaundiced.**

6.12 The Chief Medical Consultant of the BTSB received a letter dated 16 December, 1991 from Middlesex Hospital indicating that there was a clear link between *Human Immunoglobulin — Anti-D* and Hepatitis C in the cases of jaundice in 1977. **We consider that the failure to act upon this information promptly was a serious omission. Had the letter of 16 December, 1991 been followed up immediately it seems to us that the BTSB could have withdrawn its Anti-D product and commenced a screening programme in December, 1991, or early in 1992, rather than in February, 1994.**

Testing for Hepatitis C

6.13 We considered the timing of introducing a test for Hepatitis C in blood and blood products in Ireland. The earliest tests, developed in 1989 and early 1990, were

considered by some experts to be unreliable because of the high number of false negative and false positive results they produced. The question of introducing a test for Hepatitis C was the subject of regular correspondence between the Chief Medical Officers of the Departments of Health in the UK and Ireland. Routine screening for Hepatitis C was introduced in the UK on 1 September, 1991 and in Ireland on 1 October, 1991, when a sufficiently reliable test became available. **We are satisfied that the question of introducing a test for Hepatitis C was actively and properly considered in Ireland. The approach taken was based on available scientific evidence and was consistent with international developments.**

Manufacturing Process for Anti-D Immunoglobulin

6.14 When Anti-D immunoglobulin was first developed as a therapeutic agent in the late 1960s, there were two main methods of production. The one used by the BTSB was based on chromatography and was developed originally by the Central Institute for Blood Transfusion in Hamburg, headed by Dr. Hans Hoppe. Anti-D prepared in this way was administered *intravenously*. The other method of preparation was known as Cohn fractionation and the product was normally administered *intramuscularly*.

6.15 The BTSB's decision to use an intravenous product in the early 1970s was influenced in part by the scientific information available at the time. It would be reasonable to expect the BTSB to keep abreast of scientific developments since the early 1970s regarding the case for intramuscular and intravenous Anti-D products, and to review its own policy accordingly. In June, 1992, the BTSB Medical Sub-Committee examined issues relating to the production process for Anti-D, including the need for a refurbished fractionation laboratory and the introduction of a viral inactivation step in preparing Anti-D. However, **we could find no evidence that the BTSB formally reviewed its original decision to use an intravenous product at any stage prior to the discovery of the Hepatitis C incident in February, 1994.** We note that in August, 1994, the Medical Sub-Committee recommended to the Board that a virally inactivated intramuscular Anti-D product would be the optimum choice for the future. In December, 1994, the BTSB informed us of steps they had taken to bring an intramuscular product to the Irish market.

Use of *WinRho SD* as a Replacement Product

6.16 When the Hepatitis C incident was discovered in February, 1994, the BTSB immediately ceased production of its own Anti-D product and made arrangements for the supply of an alternative product, *WinRho SD*, from Rh Pharmaceuticals Inc, Canada. **We consider that it was reasonable to use *WinRho SD* on an emergency basis in February, 1994, since an alternative Anti-D product was required immediately. However, we could find no evidence that the BTSB examined alternative products with sufficient urgency after it took the initial decision to use *WinRho SD* as an emergency measure.** We must emphasise that any criticism here is not of the replacement product chosen; Rh

Pharmaceuticals is a highly reputable company and its products have a high standing internationally.

Role of Hospitals

6.17 We are concerned that hospitals appear to depend heavily on advice from the BTSB for key decisions about the most appropriate Anti-D product to be used. Given their almost exclusive role in the administration of Anti-D, it might be expected that maternity hospitals should be much more actively involved in these decisions. This issue is part of our wider concern to ensure that there are closer links between the BTSB's medical staff and the hospital system, including acute hospitals and maternity hospitals.

Withdrawal of BTSB's Anti-D Product

6.18 The BTSB notified hospitals and maternity units of the recall of its Anti-D product initially by telephone on 18 February, 1994, and by letter on 21 February. It followed up this recall with telephone calls between 30 March and 21 April, 1994, and again by letter on 11 July. Despite these steps, we were informed that eight doses of the product had been administered between 18 February and 14 September, 1994. We view with concern the fact that the product withdrawn by the BTSB in February, 1994 appears to have been still in use in a small number of cases some time after its official recall. The use of the product in these circumstances highlights the need for increasing collaboration between hospitals and the BTSB. **We recommend that all hospitals should not only designate an appropriate member of staff with responsibility for ensuring a complete and prompt withdrawal of recalled products, but should establish a system to check that the withdrawal has been completed.**

Notification of Public and Health Professionals

6.19 **We consider that the Department of Health and the BTSB took the correct decision in making the Hepatitis C incident public as soon as it was discovered.** We received a complaint that general medical practitioners were not adequately consulted prior to the launch of the national blood screening programme. However, we believe that any significant delay while general practitioners or other health professionals were being informed could have led to widespread concern since it is very likely that some of the details would have become public in advance of a formal announcement.

6.20 There was also some criticism about an apparent lack of information for General Practitioners regarding the nature and management of Hepatitis C for some days after the public announcement. The BTSB issued an information pack regarding Hepatitis C to general practitioners on 21 February, 1994, but a small number of them did not receive it until later because there was no single comprehensive list of GPs available to the Department of Health or the BTSB. **We recommend that a**

comprehensive list of all practising General Practitioners should be established and regularly updated in co-operation with the appropriate professional bodies so that GPs can be given urgent information on incidents such as the Hepatitis C episode without delay.

Counselling and Follow-Up Services

6.21 **We consider that in incidents such as the Hepatitis C episode, the BTSB should take a leading role in matters directly affecting blood and blood products, including any necessary screening programmes. In contrast, follow-up services, including counselling and advice about treatment options for particular conditions, should be done by those with relevant and expert knowledge of the subject. It is inappropriate to expect the BTSB to take a prominent part in counselling and related services which are outside its normal functions.**

• ORGANISATION AND MANAGEMENT OF THE BTSB

Organisation of BTSB

6.22 The BTSB was established in 1965. Its primary purpose is to organise a comprehensive transfusion service in Ireland. This includes collection and processing of blood, arranging for the provision of blood components and blood derivatives and advising on all aspects of transfusion medicine. The BTSB is headed jointly by a Chief Medical Consultant with clinical functions, and a Chief Executive Officer who is responsible for management issues. There is a separate Regional Director for the Cork Centre who combines medical and management responsibilities. The Board of the BTSB consists of twelve members appointed by the Minister for Health. The Chairman of the Board is also appointed by the Minister, from among its members.

6.23 Certain aspects of the organisation and structures of the BTSB raise concern. We set these out below. However, we also wish to emphasise the considerable strengths of the organisation. We were consistently told of the efficiency, dedication and commitment of BTSB staff in its dealings with hospitals. Without exception, the medical and nursing staff of the hospitals with whom we spoke praised the quality and speed of service provided by the BTSB over many years.

Board of the BTSB

6.24 From our examination of the minutes of meetings and our discussions with Board members, both past and present, **we conclude that the Board of the BTSB has tended to focus on day-to-day matters rather than on strategic issues.** Throughout the years, the minutes of Board meetings cover operational matters such as pay, staffing, special leave, industrial relations (often relating to individual cases) and purchase of equipment and supplies. Issues which we would have

expected to have been discussed by the Board are not referred to in the minutes of its meetings.

6.25 **It appears that there are substantial communication gaps between the Board, the medical staff and senior management.** A number of past and present Board members to whom we spoke felt that many key decisions with policy implications had effectively been taken by management before they were referred to the Board for formal approval. Some members expressed dissatisfaction with the quality and extent of information available.

6.26 Communication problems extend beyond the Board and senior management. In 1989, a study of internal communications commissioned by the BTSB pointed to differences in the reporting structure in the Dublin and Cork centres, to 'uneven' communications between departments in Dublin and to the need for better dissemination of information. While some progress has been made in implementing its recommendations, **we could find little evidence that communications had improved significantly since the report was prepared.**

Medical and Scientific Advice to the Board

6.27 The Board of the BTSB decided to set up a Medical Sub-Committee in September, 1990 to report on all medical matters referred to it by the Board and to raise any matters that it wished the Board to consider. We found significant problems of communication between the Board and the Medical Sub-Committee. We were told that certain issues referred to the Board by the Sub-Committee received no response. We were also given instances of cases where the Board made decisions on matters affecting the work of the BTSB medical consultants either without consulting the Medical Sub-Committee or ignoring its views entirely. The Sub-Committee does not appear to have held regular meetings and, until recently, formal minutes do not seem to have been taken.

6.28 **In these circumstances, it appears to us that the Medical Sub-Committee has not fulfilled the role assigned to it. We believe that in any future structure there must be close collaboration and communication between the Board of the BTSB and the medical staff of the BTSB. Whether or not this is to be achieved through a Medical Sub-Committee, there must be clearly defined mechanisms for ensuring that the considered views of the medical personnel are channelled effectively to the Board.**

6.29 **We consider that the non-medical members of the Board must be kept fully briefed about the medical and scientific implications of the decisions that the Board is called upon to make. Given the nature of many issues that come before the Board, it is clear that the non-specialist members of the Board cannot make a full contribution unless they are adequately informed by medical, scientific and technical staff.**

Attendances and Vacancies in the Board

6.30 **We believe it is vital that the Minister for Health should ensure that there are no avoidable delays in appointing persons to the Board of the BTSB.** There were considerable delays in filling vacancies on the Board in the mid to late 1980s but the problem has not recurred since then.

6.31 The average rate of attendance at meetings of the BTSB Board varied between 57 per cent and 75 per cent of serving members in the years 1974 to mid 1994. While we do not doubt the commitment of those agreeing to serve as members and recognise that the attendance record may not compare unfavourably with that of other boards, **we consider that the performance of the Board of the BTSB is inevitably influenced by the availability of its members to participate fully in its decision-making.**

Management Structure

6.32 The relationship between a number of the key posts in the management structure of the BTSB is complex. The *Chief Medical Consultant* (CMC) is responsible for clinical matters, while the *Chief Executive Officer* (CEO) is responsible for the management of the organisation and for implementing the policies of the Board. The *Regional Director, Munster* (RD) combines both management and medical responsibilities. There is no written description of the relationships that should obtain between the CMC, CEO and RD. **We consider that whatever revised management structures are put in place in the BTSB, there is an urgent need to clarify the roles and working relationships of the Board, the management and the medical staff. There is a danger that inadequate definition of roles will continue to hinder the decision-making process unless clearly defined functions and inter-relationships are established.**

National Director of Transfusion Services

6.33 Prior to 1986, there was a single post of National Director of the BTSB. The post was then divided between a CEO with management functions and a CMC with medical responsibilities. We consider that the division of authority between a CEO and CMC, each with differing responsibilities, has given rise to serious difficulties in the operation of the BTSB. It has not been conducive to long-term planning in the organisation, and has led to serious difficulties of communication and co-ordination.

6.34 **We recommend that there should be a single post of National Director of Blood Transfusion Services in Ireland. The National Director should be a member of the Board of the BTSB and should be appointed for a fixed term, possibly of between five and seven years. Ideally the National Director should have medical or scientific qualifications appropriate to transfusion medicine. The National Director must be supported by a strong management team and should be able to draw upon a range of disciplines**

(whether medical, scientific, technical or financial), as appropriate, in running the organisation.

6.35 Underpinning our recommendation regarding the post of National Director is our view that **the BTSB should develop more fully into a Centre for Transfusion Medicine which would have clearly defined medical, teaching and research functions, as well as its current role in operating a blood transfusion service.**

6.36 Our report contains recommendations on a number of the major elements that we believe should form part of any revised management structure in the BTSB. However, we do not consider it appropriate for us to go into greater detail. **Our proposals concentrate on the major elements that we believe should underlie any structure chosen.**

Developing the BTSB

6.37 We consider that there are several ways in which the BTSB should be developed in order to meet the requirements of modern transfusion medicine. In particular, **there is an urgent need to strengthen the BTSB's capacity for research and development.** Some of the factors influencing the research and development function, and the performance of the BTSB in meeting modern service requirements, require closer attention. In particular, we consider that:

- there is a need for more scientific staff, particularly at doctoral level, in the BTSB to provide for continuing research and development in transfusion medicine;
- the question of increasing the complement of consultant medical staff in the Blood Transfusion Service Board merits serious and urgent consideration;
- consideration should be given to using the services of a virologist and an immunologist to support the work of the BTSB, either directly or through an existing agency such as the Virus Reference Laboratory;
- the Board's medical staff must develop closer day to day links with the haematology departments of Irish hospitals and keep themselves fully informed of local and international developments in their field. They should act as a conduit for information to their hospital colleagues; and
- there should be an early review of the number and distribution of consultant haematologist posts in Irish hospitals.

• LICENSING OF BLOOD PRODUCTS

6.38 Sellers or distributors of blood products, including Anti-D immunoglobulin, have been required to have a valid Product Authorisation (PA) for each product since 1 April, 1983. There are also legal requirements regarding Manufacturer's Licences and Wholesale Licences. PAs for blood products, as for other medicines for human use, are issued by the Minister for Health on the advice of the National Drugs Advisory Board (NDAB).

6.39 The Expert Group noted a number of unsatisfactory aspects relating to the issue of PAs in respect of the BTSB's product *Human Immunoglobulin — Anti-D*:

- There were delays by the BTSB in submitting applications for a PA in respect of its Anti-D product.
- There appears to have been confusion about the date on which the first PA for *Human Immunoglobulin — Anti-D* expired and a renewal PA was required.
- There were delays by the NDAB in processing applications for PAs in respect of the BTSB's Anti-D product.
- Owing to the delays in submitting and processing applications, the BTSB's Anti-D product was without a valid PA for substantial periods of time.
- It became common practice to issue PAs retrospectively. **We believe that the practice of authorising PAs retrospectively is undesirable, especially when long delays arise, as in the case of Anti-D. The Department of Health has supplied details of improved procedures to ensure prompt processing of renewal applications so that the need for retrospection should not arise in the future.**

6.40 We also noted other unsatisfactory aspects regarding the issue of PAs. These are summarised as follows:

- We were told that there is no mechanism to ensure that new products have a PA, or to check that companies do not continue to market an existing product after its PA has expired. **We recommend that a formal system for monitoring and enforcing licences issued for medicinal products, including blood products, be introduced.**
- The BTSB took some time to pursue an application for a PA in respect of the Anti-D product *WinRho SD* which it imported from Canada as a replacement for its own product in February, 1994. The PA was not issued until 2 August, 1994. While we do not believe that the NDAB should have rushed consideration of the product, the time taken to process the application seems very long, given the urgency of the situation. We stress that *WinRho SD* is produced by a highly reputable company and that our criticism of the handling of the PA application in no way reflects upon the product itself.
- The present system of issuing certain medicinal products on a *named patient* basis is unsatisfactory. This was the basis on which *WinRho SD* was used between February, 1994 and the date on which a PA was issued, 2 August, 1994. **We recommend that the arrangements for importing and supplying medicinal products on a *named patient* basis be placed on a formal footing and that the circumstances in which products may be issued on this basis should be clearly specified. We do not believe that it should be applied to compensate for the absence of a PA in widely-used products (such as Anti-D immunoglobulin).**

National Drugs Advisory Board

6.41 The NDAB's functions have expanded significantly since its establishment in 1966. This may have contributed to the problem of delays in processing applications for PAs. It is clear to us that the machinery for dealing with applications for new and renewal PAs did not operate satisfactorily in the case of Anti-D immunoglobulin, and that this is part of a wider problem in dealing with a backlog of applications that has accumulated over a number of years.

6.42 From our investigation of Anti-D, we offer the following conclusions and recommendations relating to the NDAB:

- **There is an urgent need to strengthen the Board and management of the NDAB so that it can discharge its functions in relation to medicinal products, including blood products, with sufficient speed and efficiency.**

- **We recommend that the NDAB should become the licensing authority for all medicinal products for human consumption. The present arrangement whereby the Minister for Health issues licences on the advice of the NDAB is cumbersome and unsatisfactory.**

6.43 **We note that the Department of Heath has prepared proposals in these areas.** The Department supplied us with details of a plan to re-organise the NDAB with the aim of resolving its backlog of work by March, 1995. A Government decision was taken in June, 1991, to make the NDAB the licensing authority in relation to medicines for human consumption. This will involve legislation which, we have been informed, is currently being prepared. We understand that the Board of the NDAB has established a Management Working Party to advise it on the implementation of a programme of re-organisation and re-structuring to equip the Board for the discharge of its new role.

Signed:

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