NOT FOR PUBLICATION

DR M E DUNCAN

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

THE SAFETY OF IMMUNOGLOBULIN PREPARATIONS

BACKGROUND

In July 1985 CSM(B) reviewed the Safety of Intravenous Immunoglobulins licensed for use in the UK and advised that licence holders be asked to provide additional information as follows:-

a. further data concerning the ability of the manufacturing process to inactivate viruses

b. ongoing evidence of the safety in clinical use of the product

c. information regarding the company's plans for screening of donors.

There are 5 licence holders - Miles, Biotest, Sandoz, Kabi-Vitrum and PFC Edinburgh. All have been asked to supply additional information and all have indicated their willingness to do so, but so far no new data have been received from any of them.

In addition to the 5 licensed materials, intravenous immunoglobulin prepared by BPL Elstree is distributed under Crown Immunity. We understand that the present method of manufacture is the same as that used by PFC Edinburgh.

Following consideration of the intravenous immunoglobulins, it was considered appropriate that the sub-committee be asked to review the safety of the intramuscular preparations and to endorse a recommendation that additional safety data be required for these preparations as well as for the intravenous ones.

There are 2 licensed products, prepared by Kabi and by Immuno, and 2 unlicensed products, distributed under Crown Privilege by BPL, Elstree and PFC, Edinburgh. Although the Edinburgh material is unlicensed, samples from each batch prepared are submitted to NIBSC.

It was felt that it was now no longer the case to ask manufacturers what plans they had to screen donors for antibodies to HTLV-III but to require that, for all immunoglobulin preparations, individual donations of plasma should be screened using an ELISA test - the details of the test to be made available to the licensing authority and to NIBSC. Indeed, in November 1985, CSM(B) remarked that:-

> "The Committee are anxious that individual donations for all blood products should be screened for HTLV-III from the earliest possible date. Manufacturers should be requested to confirm that donations are being screened and to provide information about the nature of the screening tests used."

The Main Committee endorsed this remark when it met at the end of November 1985.

RECENT REPORTS

a. Intramuscular Immunoglobulins

Since early November 1985, NIBSC has been screening samples of immunoglobulin received by them under the batch release procedure. In late November they reported to the Licensing Authority that intramuscular immunoglobulin from both licence holders (Kabi and Immuno) had given a positive test for antibodies to HTLV-III.

Three batches of material are involved, two from Kabi and one from Immuno. All were positive in 2 different ELISA tests, and were again positive when the tests were repeated. These results have been confirmed by immunoblotting. The two companies have been asked to state the source of the plasma used, and to give details of any screening carried out by them for antibodies to HTLV-III (nature of test, stage of manufacture when it was carried out).

Material from PFC, Edinburgh, screened at the same time by the same ELISA tests has given negative results. Thus the present position is that of 4 possible sources of supply of intramuscular immunoglobulin 2 are producing end product which appear to have antibodies to HTLV-III, and have therefore not been relased by NIBSC, one is producing a 'clean' final product, and in the 4th case the final product has not been available for examination.

b. Intravenous Immunoglobulins

Exactly one week after NIBSC had first communicated their findings with intramuscular immunoglobulins Sandoz reported to us that retrovirus, morphologically indistinguishable from HTLV-III, had been isolated from 2 patients at Northwick Park. Both patients had been treated with intravenous immunoglobuli prepared by Sandoz.

The background to this report is complex, and the details need not be entered into here. Briefly both patients are diagnosed as having common variable hypogammaglobulinaemia, and at Northwick Park such patients are being screened for retrovirus as part of a research programme. Isolation of the virus resul from routine screening in the course of this investigation.

In one case the link with Sandoglobulin is tenuous. The patient has received a variety of treatments over many years. These have included intramuscular gammaglobulin and plasma as well as intravenous immunoglobulins from Elstree and Miles (Gamimune) in addition to Sandoglobulin. Only 1 viral isolate has been obtained, and subsequent attempts to isolate the virus have been negative. It has been suggested that the first isolate may have been a laboratory contaminant.

In the second case the picture is different. Virus isolated on more than one occasion is morphologically identical to HTLV-III although there are some differences in immunoblotting patterns. The patient is an 18 year old girl who has no history of contact with high risk groups and who has received no blood products other than Sandoglobulin. Clinically she is suffering from AIDS, and the possibility that this might have been transmitted by Sandoglobulin cannot be excluded.

Batches of material received by the 2 patients have been traced and quarantined. They will be tested for antibody to HTLV-III, and attempts will be made to isolate and culture virus. Other recipients of these batches will be screened for HTLV-III.

A 20 month old infant who received material from one of the suspect batches is reported to be suffering from AIDS. In this case, however, the mother is a known heroin addict whose husband is a drug pusher, and the disease may have been transmitted from her to the infant. Further information is awaited.

CURRENT POSITION

Whatever else has emerged from the events of the last few weeks it is clear that, certainly under present conditions of manufacture, there cannot be any confidence in the safety of immunoglobulin preparations which have not been derived from individually screened plasma donations. However an insistence that only 'donation tested' products be used could lead to a temporary difficulty in maintaining adequate supplies of material.

a. Intramuscular Immunoglobulin

- PFC Edinburgh will have material from individually screened donations by March/April 1986. The material currently available is from unscreened donations but screened plasma pools. Final material is also screened.

- Immuno intend to issue only "donation tested" batches after 1st January 1986.

- Kabi have been screening individual plasma donations since early this year, but we have no information on how long it will be before material prepared exclusively from individually tested donations will be available.

- BPL Elstree, on the basis of their current stocks of plasma, will not have material from individually tested donations for 18 months to 2 years. Current material is from screened plasma pools. Final material is also screened.

b. Intravenous Immunoglobulin

- Miles material is not, at present, being released by NIBSC because the strucuture and functional integrity of the molecule is in doubt. It is now known when material prepared exclusively from individually tested donations will be available, but in any case the company has obviously got more than one problem to sort out.

- Biotest have been screening individual donations since July 1985 and expect to have material prepared exclusively from these sources by January 1986. They also screen plasma pools for antibody to HTLV-III.

- Kabi material has not yet been launched on the UK market. It is not known how long it will be before they can supply material exclusively from individually tested plasma donations, although they have been screening individually plasma donations, since early 1985.

- Sandoz will have material from individually screened plasma donations by March/April 1986. Current material has not been subjected to any screening.

- PFC Edinburgh will have material from individually screened donations by March/April 1986. Current material is from screened plasma pools. Final material is also screened.

- BPL Elstree on the basis of their current stocks of plasma, will not have material from individually tested donations for 18 months to 2 years. Current material is from screened plasma pools. Final material is also screened.

SUMMARY

In the light of recent events it may be appropriate that only those immunoglobulin preparations made from individually screened plasma donations should be used. In the short term this could cause a supply problem.

BY January 1986 we expect to have at least one source of intramuscular immunoglobulin and one source of intravenous immunoglobulin prepared from individually screened plasma donations. By March/April 1986 at least one additional source of intramuscular immunoglobulin and two additional sources of intravenous immunoglobulin should be available.

In the event of a shortfall of material in the first few months one option would be to allow the use of material where the plasma pool has been screened. Another would be to restrict the use of material to certain very serious clinical situtations. It is possible that a combination of these options will have to be considered, and expect guidance is required.

SPECIFIC IMMUNOGLOBULINS

With the exception of Humotet, an antitetanus immunoglobulin prepared by Immuno amd marketed by Wellcome, the national requirement for the various specific immunoglobulins is met by PFC, Edinburgh and BPL, Estree who manufacture and distribute these preparations under Crown Privilege. Obviously the same requirements must apply to these products, ie individually screened plasma donations and provision or protocols and samples to NIBSC, and ideally all manufacturers should also be licence holders.

RECOMMENDATIONS

1. No immunoglobulin preparations should be used other than those made from plasma where individual donations have been screened for antibodies to HTLV-III (and for HBsAg).

2. Details of the nature and sensitivity of the screening test used should be provided.

3. In the event of a shortfall of material prepared from individually screened plasma donations, consideration shoud be given to

a. restricting the use of the material to certain serious clinical situations

b. allowing some use of material prepared from screened plasma pools

4. Data should be provided on the ability of the manufacturing process to inactivate viruses.

5. Evidence should be provided of the safety of the product in clinical use.

APPENDICIES

1. Intramuscular immunoglobulins (NIBSC paper).

2. Intravenous immunoglobulins (Secretariat paper).

NIBSC

Appendix 1

Comment on the safety of human immunoglobulin products intended for intramuscular use

Introduction

Although there has recently been considerable concern over the transmission of viral infection by intravenous administration of human immunoglobulin preparations which are prepared specifically for intravenous use, 'intramuscular' products have an outstanding safety record. The principal problem associated with intravenous immunoglobulin preparations has been incidences of raised liver enzymes which are directly attributable to use of intravenous IgG products (Ochs et al. 1985 Lancet I, 404; Leon et al. 1984 Lancet II, 1062). Some of these patients were subsequently diagnosed as having suffered from non A - non B hepatitis. To date there are no reports of transmission of HTLV-III/LAV injection by either intramuscular or intravenous immunoglobulin preparations.

This paper briefly reviews the safety aspects of human immunoglobulin prepared for intramuscular use.

Human immunoglobulin products intended for intramuscular use

At present four intramuscular immunoglobulin products are used routinely in the UK. Two of these, which are made by KabiVitrum (Kabiglobulin) and Immuno (Gammabulin) are licensed (PLR and PL respectively) and subject to the batch release procedure involving evaluation of samples and protocols at NIBSC.

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The other two products, which are produced by the Scottish BPL and BPL Elstree are issued under Crown Privilege and are therefore not subject to the Batch Release process. However samples and protocols of the Scottish BPL immunoglobulin are routinely sent to NIBSC, and are subjected to the same testing as the licensed products. Although samples and protocols of the BPL Elstree material have in the past been sent to NIBSC, none have been submitted since April 1982.

All human immunoglobulin products intended for intramuscular or intravenous use are prepared using the Cohn (cold ethanol) fractionation technique or modifications of this procedure (Hein et al. 1985 Lancet i, 405). Intravenous products are normally further purified or treated to reduce immunoglobulin aggregates, prekallikrein activator and/or other impurities. Intramuscular IgG preparations are not usually subjected to further processing after cold ethanol fractionation; they are all essentially Cohn II fractions.

Clinical indications for use of intramuscular immunoglobulins includes the treatment of primary immunodeficiency (hypogammaglobulinaemia), severe bacterial infections and burns. The preparations are also used for prophylaxis of hepatitis A, measles and rubella.

Batch release of immunoglobulin products intended for intramuscular use

Samples submitted to NIBSC are tested to establish purity, identity, sterility, antibody content against viruses and bacteria, antibody dependent complement fixation, and

pyrogenicity. The following specific tests are applied:

(1) Assay of human IgG by single radial immunodiffusion using monoclonal antibodies.

(2) Immunoelectrophoresis.

(3) SDS polyacrylamide gel electrophoresis run under reducing and non-reducing conditions and also immuno-blotting using monoclonal antibodies.

(4) Sterility.

(5) Pyrogenicity (using limulus amoebocyte lysate).

(6) Testing for the presence of hepatitis B surface antigen (IRMA).

(7) Assay of prekallikrein activator.

(8) Estimation of antibodies against:

(i) Polio virus (viral neutralization)

(ii) Rubella (single radial haemolysis)

(iii) Measles (" " ")

(iv) Hepatitis B virus (IRMA)

(v) Tetanus toxin (ELISA)

(vi) Diptheria toxin (ELISA)

(vii) Tests for the presence of antibodies to LAV/HTLV-III (ELISA, Immunoblotting).

All batches submitted for evaluation at NIBSC have been found to comply with license specifications in terms of purity, potency and biological function as claimed in the specification by the manufacturer. This contrasts with some intravenous immunoglobulin preparations and is probably due to the relatively simple manufacturing procedure, which produces little alteration of the 'native' immunoglobulin structure.

Safety of intramuscular immunoglobulin

Problems associated with the use of human immunoglobulin preparations can be divided into two principal groups, ie the occurrence of adverse reactions and the transmission of viral agents.

a) Adverse reactions

It is well documented that adverse reactions do occur following injection of human immunoglobulin and such reactions, which can be severe, are of the anaphylactic or anaphylactoid type. These adverse reactions have been attributed tentatively to immunoglobulin aggregates present in the preparations, allergic reactions to preservatives, production of antibodies by the recipient to IgA or subtypes of other immunoglobulins present in the preparations, or possibly to PKA, which is present in high levels in some but not all preparations (Shemin 1968, JAMA 203, 113; Kamme et al. 1966, Acta. Med. Scand. 179, 679; Kleinman & Weksler 1973, J. Paediatrics 83, 827; Lederman & Winkelstein 1985 Medicine 64, 145).

Such reactions often occur if immunoglobulin preparations intended for intramuscular use are injected intravenously and this has been interpreted to suggest that procedures used to further purify or modify Cohn fraction II as used for production of intravenous immunoglobulin help to eliminate or reduce such adverse side effects. Adverse reactions occur mainly in patients being treated for hypogammaglobulinaemia and this may reflect the relatively large doses used for this indication. Pain associated with

administration of such large volumes can also be problematical in such patients, (Soothill, 1971 in Hypogammaglobulinaemia in the UK, MRC special report series No 310 p106), and intravenous immunoglobulin is usually preferred for this reason.

Transmission of viral diseases

Human immunoglobulin preparations intended for intramuscular use have an outstanding safety record regarding transmission of viral agents (Iwarson et al. 1985, Transfusion 25, 15; Gerety & Aronson 1982 Tranfusion 22, 347). For example Kabiglobulin has been licensed in the UK since 1973 and there has been no reported incidence of transmission of viral disease. However it has been shown using chimpanzees that it is possible in rare instances to transmit hepatitis B using human immunoglobulin (Tabor & Gerrety 1979, Lancet ii, 1293). There is also a single report of transmission of non A - non B hepatitis by Anti-D (Rho) immunoglobulin prepared from the sera of donors who had been immunized with erythrocytes from an individual affected with the disease (Renger et al. 1981, Z. Aerztl Fortbild 75, 894). There is no description of the procedure(s) used to purify this immunoglobulin. This report has probably little relevance to immunoglobulin products used in the UK.

In general it can be assumed that the intramuscular products licensed in the UK are unlikely to cause viral diseases. This safety record contrasts with that of intravenous immunoglobulin where transmission of non A - non B hepatitis is now a known potential hazard. As production of both intra-

muscular and intravenous immunoglobulins initially involves fractionation using cold ethanol (as Cohn fraction II), this conflicting record of transmission of non A - non B hepatitis is difficult to explain. It is possible that the intravenous route is advantageous for viral infection or that viral contamination of immunoglobulin preparations occurred during the post Cohn fractionation procedures used in the preparation of intravenous immunoglobulin, or that the manufacturer did not follow the Cohn type procedure. Intramuscular immunoglobulin preparations are known to contain anti- hepatitis B antibodies and this fact together with the nature of the fractionation procedure used would suggest that risk of hepatitis B infection is very low with such materials.

To date there have been no reports of cases of AIDS transmission attributable to human immunoglobulin preparations. However the potential risk of such infection has resulted in discussion in the medical literature (Kane & Geiko 1984, JAMA 252, 1057). Also antibodies to LAV/HTLV-III have been found in a German intramuscular immunoglobulin preparation high in antibodies against hepatitis B virus ('gamma protect hepatitis' - Biotest Pharma), although an intravenous immunoglobulin preparation (Intraglobin) produced by the same manufacturer did not contain such antibodies (Tedder et al. 1985, Lancet i, 815). It has been reported that the cold ethanol fractionation process used to prepare intramuscular immunoglobulin causes inactivation of LAV/HTLV-III (Spire et al. 1984, Lancet ii, 899). Investigation concerning the inactivation of LAV/HTLV-III by such procedures are in

progress at NIBSC.

Conclusions

The preparations of human immunoglobulin intended for intramuscular use which are licensed in the UK are safe products when used as intended. Serious adverse reactions may occur with patients suffering from hypogammaglobulinaemia, and in these cases the use of intravenous immunoglobulins may be preferred.

The risk of transmission of viral disease is minimal. In this context it is essential that manufacturers screen all individual plasma donations and product batches for the absence of hepatitis B surface antigen and evidence of infection with LAV/HTLV-III virus.

It is recommended that manufacturers provide detailed information in licence applications and manufacturing protocols for individual production batches, confirming that screening of individual donors for LAV/HTLV-III is undertaken and detailed information on the nature and sensitivity of the screening tests used.

Tests for antibody to LAV/HTLV-III virus are routinely carried out at NIBSC on all batches of immunoglobulins submitted for batch release purposes.

APPENDIX 2
CSM/BSC/1985/3rd Meeting
CSM/1986/7th Meetin

NOT FOR PUBLICATION

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

SAFETY OF INTRAVENOUS IMMUNOGLOBULINS

Human Immunoglobulin preparations for intramuscular administration have a long history of safety in clinical use and when, more recently, preparations for intravenous use became available, there seemed no reason to suppose that they would be any less safe.

Since January 1984, four intravenous preparations have been licensed in the UK, and PL applications for a further two products are pending. In addition, human i.v. immunoglobulin is manufactured and distributed under Crown Immunity by B.P.L. Elstree.

Manufacturer	Product	Licensing Position
Miles Laboratories	Gamimune PL 0055/0104	Granted 16/1/84
Biotest Pharm.	Intraglobin PL 4500/0002	Granted 22/6/84
Sandoz	Sandoglobulin PL 0101/0181-2	Granted 13/11/84
Kabi-Vitrum	Gammonativ PL 0022/0056	Granted 18/2/85
BPL Elstree	i.v. Immunoglobulin type GGV	Distributed under Crown Immunity
PFC Edinburgh	Human Immunoglobulin PL 3473/0011	Pending
Immuno	Endobulin PL 0215 /0023	Pending

ntravenous immunoglobulin like intramuscular immunoglobulin is prepared by cold ethanol fractionation of pooled plasma. The Cohn fraction II is then treated to make it suitable for i.v. administration. It was widely believed that Cohn fractionation of plasma was capable of inactivating virus. The first indication that this might not always be the case came with a report from BPL[1] that 12 patients treated with their i.v. preparation had all developed non A non B (NANB) hepatitis. Correspondence in the Lancet[2] suggested that there might now be a case for incorporating into the process a step capable of inactivating hepatitis viruses and HTLV-III, while a leading article in the same journal[3] noted the finding of American workers that blood donors with a raised serum ALT are more likely to transmit non A non B hepatitis than are those with normal transaminases. They estimated that elimination of donations with an ALT greater than 60 units would prevent 29% of transfusion NANB hepatitis with loss of only 1.6% of donations.

There has now been another published report[4] of NANB hepatitis occurring in 7/16 patients treated with the Hyland (Travenol) material. There is a further (unpublished) report of NANB hepatitis in some patients treated with the Kabi preparation, 'Gammonativ', but no details are available.

In view of these reports it seems timely to stop and take a critical look at the products already available in the UK and at those for which licence applications are pending; to consider, particularly with regard to HBV, HTLV-III and NANB virus,

1. the acceptability of the starting material

2. evidence of virus inactivation during the preparation of the products

3. evidence of clinical safety with respect to transmission of viral infection.

Acceptability of the starting material essentially means screening of individual donors. At the moment all are screened for HBsAg, and it is intended that all should be screened for presence of HTLV-III antibodies as soon as a reliable test is available. Licence holders and applicants should be asked to confirm that this will be the case.

There is no screening test for NANB, but in the light of the American findings it seems desirable to eliminate donations from subjects with a raised serum ALT. This might not be easy to achieve since not all laboratories have the facilities for doing ALT estimations, but it is worth suggesting.

Evidence of virus inactivation during manufacture

A variety of methods is used to render Cohn fraction II immunoglobulin suitable for intravenous use.
Each manufacturer should provide evidence that his procedure is also capable of inactivating viruses.

Evidence of clinical safety

Ultimately the evidence of safety must be provided by adequate follow-up of patients. For monitoring of liver function by ALT, timing of samples is important, and BPL regard a pre-sample, 1 week post, and subsequently fortnightly up to 16 weeks as the minimum acceptable for NANB follow-up. For Hepatitis B and HTLV-III longer follow-up is required (a minimum of 6-12 months).

UK PRODUCTS: EVIDENCE OF SAFETY

Product	Procedure	Evidence of viral inactivation by procedure used	Evidence of clinical safety
Gamimune (Miles)	- Reduction by dithiothreitol - Alkylation with Iodocetamide	None provided	66 patients followed up for 2-5 years. No details given
Intraglobin (Biotest)	- Acetylation with B-propiolactone	None provided but is known to be effective	- 28 volunteers followed up at 3-week intervals for 35 weeks. - Data on large numbers of children, in some cases up to 6 years
Sandoglobulin (Sandoz)	- Limited pepsin digestion at pH4	None provided but is known to be effective	- Several hundred patients treated for 2 years
Gammonativ (KabiVitrum)	- Adsorption on DEAE Sephadex	None provided	- 43 patients treated for up to 9 months
Endobulin (Immuno)	PEG precipitation	None provided	16 patients followed up for average of 14 months. Monitoring included estimates of liver enzyme levels before and after each infusion

(Contd.)

Product	Procedure	Evidence of viral inactivation	Evidence of clinical safety
Human Immunoglobulin (PFC, Edinburgh)	Limited pepsin digestion at pH4	None provided but is known to be effective	No volunteer(5) or patient (26) developed clinical or laboratory features of NANB hepatitis and no changes in Hepatitis B serology occurred during follow-up of 2-9 months.
i.v. Immunoglobulin type GGV (BPL Elstree) - present method	Same method used as at PFC Edinburgh		
i.v. Immunoglobulin type IV (BPL Elstree) - former method	Gel filtration (Sephadex G25)		NANB reported in 12 patients.

From the table, it is clear that none of the manufacturers has provided evidence of the ability of the procedure to inactivate viruses. However pepsin digestion and treatment with B propiolactone are both known to do so.

There is adequate supporting evidence for only 3 licensed or licence pending products

- Human Immunoglobulin (PFE, Edinburgh)
- Sandoglobin (Sandoz)
- Intraglobin (Biotest)

Manufacturers of the other 3 products have not provided evidence of viral inactivation by the process used nor of safety in clinical use, and they should be required to do so

- Gamimune (Miles
- Gammonativ (Kabi-Vitrum)
- Endobulin (Immuno)

Endobulin is not licensed but the other 2 products are, and it is suggested that, in the first instance, an informal approach be made to Miles and to Kabi-Vitrum to ask them to supply the necessary information.

P.F.C. Edinburgh has provided an interesting and useful pre-publication document, and BPL has provided copies of the protocols used for follow-up of haemophiliacs, and which could be modified for follow-up of patients receiving i.v. immunoglobulin. Unfortunately neither of these documents was available in time to be abstracted in the paper, and they are attached as Appendices 1 and 2 respectively. A copy of a 'pre-draft draft' of FDA requirements for Immunoglobulins is also attached.

Index of Appendices

Appendix 1 : Paper from PFC, Edinburgh

Appendix 2 : Protocols for clinical follow-up studies, from BPL, Elstree

Appendix 3 : Draft of FDA requirements for immunoglobulins

References

1. LANE, R. S., 1983, Lancet ii 974 - 975

2. WELCH, A. G. et al, 1983, Lancet ii 1198 - 1199

3. Leading Article, Lancet, 1983, ii 1077 - 1078

4. OCHS, H. D. et al, 1985, Lancet, i 404 - 405

Appendix I

THE RISK OF INFECTIVITY ASSOCIATED WITH INTRAVENOUS IMMUNOGLOBULIN

- A GENERAL OVERVIEW

June 1985

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THE RISK OF INFECTIVITY ASSOCIATED WITH INTRAVENOUS IMMUNOGLOBULIN

- A GENERAL OVERVIEW

1. INTRODUCTION

All plasma pools used for the manufacture of therapeutic blood products are liable to be contaminated with a range of viruses. From experience, the most significant of these are Hepatitis B virus, Hepatitis Non-A Non-B virus(es) (NANB), HTLVIII(LAV).

Certain Human blood products have a high probability of viral transmission and, for example, 100% of haemophiliacs exposed to unheated FVIII for the first time are liable to develop NANB hepatitis[1]. In contrast, intramuscular immunoglobulins manufactured by cold-ethanol (Cohn) fractionation[2] have an excellent safety record with, to date, no recorded cases of AIDS transmission (WHO Expert Committee - reported by A. Zuckerman at Symposium on AIDS In Blood Transfusion, 3rd April 1985) and very few reported cases of Hepatitis transmission (3-5).

The impressive safety record of intramuscular immunoglobulin led to the belief that IgG manufactured by cold-ethanol fractionation is inherently safe. This conclusion has required modification in the light of recent reports of Non-A, Non-B hepatitis transmission by intravenous immunoglobulin products prepared by three different manufacturers, these being BPL (Elstree)[6,7], Hyland[8] and Kabi (Hanson, L.A. and Björkander, J, personal communication). There is, however, no evidence that administration of immunoglobulin products by the intravenous route is inherently infective. In this brief paper, an overview will be given of factors which are likely to contribute to the manufacture and validation of a safe intravenous product.

2. FACTORS CONTRIBUTING TO PRODUCT SAFETY

As stated above, all plasma pools used in the manufacture of blood products are likely to contain viral contamination. The infectivity of intravenous immunoglobulin derived from contaminated plasma is likely to depend on the interaction of several different factors. These factors are:-

2.1 Plasma Quality

Viral inactivation procedures rarely give absolute assurance that no infective virus will survive. For example, it has been shown that pasteurisation of human albumin by heating at 60°C for 10 hours will inactivate no more than 10^4 chimpanzee infective doses of Hepatitis B virus[9]. Therefore, the plasma pools used in the manufacture of blood products should contain the lowest possible levels of viral contamination, and so minimise the demands on any inactivation processes, including neutralisation by specific antibodies in the plasma pool. The level of viral contamination is likely to depend on a number of factors:-

2.1.1 Exclusion Of Potentially Infective Donations

The most efficient means of excluding infective donations is by the use of assays for specific markers of potential infectivity. We believe that all input plasma must be tested for HBsAg by the most sensitive "third generation" assay methods available. Exclusion of HTLVIII antibody positive donations would also be desirable once the technology has been validated.

The exclusion of some infective donations can also be achieved by persuading donors in "high-risk" categories, particularly homosexuals and intravenous drug abusers, that they should not donate. This exclusion process should be mandatory.

2.1.2 Donor Type

It has been demonstrated[10] that plasma pools from unpaid volunteer donors are generally of lower infectivity than pools derived from paid donors.

2.2 Fractionation Technology

The use of cold-ethanol fractionation could, potentially, contribute to product safety in a number of ways.

2.2.1 Fractional Separation of Viral Contaminants

Viral contaminants may be preferentially fractionated into other protein fractions.[11-13] For example, there is evidence that HBsAg is not fractionated into Cohn Fraction II to any significant extent.

2.2.2 Direct Inactivation By Contact With Ethanol

Alcohol inactivates viruses with a lipid envelope. A recent example of this phenomenon was reported by Spire et al[14] who found that 19% ethanol rapidly inactivated HTLVIII on exposure at room temperature. Ethanol concentrations above this value are routinely used in the manufacture of immunoglobulin preparations and, despite the use of lower temperatures in the fractionation process, there is still reason to believe that some inactivation of lipid-enveloped viruses will occur.

In view of these comments, it seems reasonable to expect that protein separation procedures should follow established cold-ethanol methodologies for the isolation of the IgG fraction, until further information on the consequences of alternative methods is available.

2.3/

2.3 Finishing Options

After fractionation, an IgG preparation is generated which still contains significant levels of ethanol. This must be removed and other finishing steps may also be necessary to generate a product in its final formulation. The potential virucidal impact of typical finishing technologies can be assessed as follows:-

2.3.1 Intramuscular Immunoglobulin

In the manufacture of intramuscular immunoglobulin, a freeze-drying step is normally employed for the removal of ethanol from the IgG solutions. Serum or albumin solutions of similar protein concentration are known to stabilise viruses during freeze-drying operations[15]. However, the initial presence of ethanol may result in a significant degree of viral inactivation during the freeze-drying procedure.

2.3.2 Intravenous Immunoglobulin

2.3.2.1 Ethanol Removal

In intravenous immunoglobulin manufacture, ethanol is removed under conditions designed to prevent the formation of aggregated immunoglobulin.

Typically, ethanol removal may be by

i. Freeze-drying in the presence of sugar stabilisers.

ii. Diafiltration.

iii. Gel filtration chromatography.

It seems improbable that any of these techniques will lead to any significant degree of viral inactivation.

2.3.2.2 Further Treatment

The manufacture of intravenous immunoglobulin usually involves further processing to reduce the level of spontaneous anti-complementary activity and of vasoactive enzymes. Several of the techniques used at this stage have recognised or potential virucidal activity, and these are listed below. References are given where the stage is known to be virucidal.

a. Reduction and Alkylation.

b. Reduction and Sulphonation.

c. Beta-propiolactone and ultraviolet irradiation [16]

d. Acid treatment (pH4.0) [17]

e. Complete proteolysis using plasmin.

f. Limited or complete proteolysis using pepsin at low Ph [18,19]

It is believed that one of the three products known to have transmitted NANB Hepatitis received no further treatment following ethanol removal (by gel filtration chromatography) and that ion-exchange chromatography was used in the further treatment of the other two products. Thus, none of these products were subjected to a recognised virucidal finishing procedure.

2.4 GMP Failure

Good Manufacturing Practice is of vital importance in all manufacturing processes. GMP failure could contribute to infectivity in two ways.

2.4.1 Failure to properly carry out the effective virucidal stage of a manufacturing process.

2.4.2 Cross contamination due to failure to correctly sanitise equipment used in the manufacture of other batches of blood product. Of particular concern are equipment and materials which are difficult to sterilise (eg chromatography gels) and items such as freeze-driers which are used in the manufacture of other blood products, such as FVIII, which carry a high risk of viral contamination.

3. NON-CLINICAL ASSESSMENTS OF PRODUCT SAFETY

Having chosen a technology which is believed to be safe, it is necessary for a manufacturer to demonstrate that the expected degree of safety is achieved. The best measure of safety is by infusion into patients with careful clinical follow-up (see section 4). Two other methods are available for product evaluation, as follows:-

3.1 Chimpanzee Studies

Since NANB and Hepatitis B viruses cannot be cultured in vitro, the chimpanzee infectivity model has been adopted for a range of products in order to demonstrate that products are safe or processes effective. While such studies have been of value throughout/

throughout the development of the fractionation industry, a number of disadvantages have come to be associated with this approach.

3.1.1 The value of information from chimpanzee studies is uncertain as at least one report is available of a blood product (FVIII, Hyland) which was found to be non-infective in chimpanzee studies[20] but which has caused NANB hepatitis on clinical evaluation (Mannucci, personal communication).

3.1.2 The chimpanzee is an endangered species. This severely limits the availability of suitable animals for proper scientific study and experiments are inevitably compromised by lack of data.

3.1.3 Results take a long time to accumulate. A typical experiment must run for 18 months before a procedure can be declared "non-infective" on the basis of champanzee studies.

3.2 In-Vitro Viral Inactivation Models

In vitro models have the advantage of being rapid and relatively cheap. They are, however, of restricted value as they are limited to the investigation of viruses which can be cultured. Nevertheless, they do have some value in evaluating manufacturing procedures for the following reasons:-

3.2.1 They can confirm the general virucidal activity of a process step or an entire manufacturing procedure.

3.2.2 They can be used to evaluate the relative performance of alternative manufacturing procedures.

3.2.3 They can be used to evaluate the likely effect of minor or major changes in a manufacturing procedure.

There is therefore a role for this type of study and there is a continuing programme of work on this topic at the PFC.

4. CLINICAL EVALUATION OF PRODUCT INFECTIVITY

There is no simple formula for defining suitable clinical studies which unequivocally demonstrate product safety. The interpretation of clinical trial results may be hampered by low patient numbers and previous exposure to other blood products. Such constraints emphasise the need for detailed prospective patient follow-up and interpretation of clinical data.

Thus, whilst it is not appropriate to propose a universal clinical trial design at the present time, guidelines may be constructed which take account of potential risk of product infectivity and defined areas of product application. It is suggested that for hypogammaglobulinaemia, a minimum of 20 patients should be followed up over a period of six months each/

each. It would be expected that a minimum of five different product lots would be included in the evaluation. Trial patients should have no pre-existing markers of infection determined over a suitable period before/
before commencement of the trial. If risk of product infectivity exists then it seems sensible and good ethical practice, in trialling a new product, to minimise patient exposure, consistent with acquisition of sufficient interpretable scientific data.

Criteria for assessment of infection in patients requires definition.

4.1 Hepatitis B

Following the first infusion, patients should be monitored for at least six months for appropriate markers of Hepatitis B infection (HBsAg, HBsAb, HBcAb). The latter two markers are unlikely to appear in hypogammaglobulinaemic patients.

Samples should be taken at approximately monthly intervals.

4.2 NANB Hepatitis

Liver function tests (either ALT or AST) are the accepted method for the detection of NANB hepatitis. Infectivity is indicated by elevated ALT or AST levels (2.0 times upper normal limit) over two consecutive monthly samples, in the absence of other known causes of elevated liver enzymes.

Follow-up should be for a duration of six months post infusion. Pre-infusion patterns of ALT or AST levels are clearly of significance in such a study since transient episodes of hepatitis may occur which are not product related and may modify interpretation of post infusion follow-up measurements.

The reported incidents of NANB Hepatitis transmission have been unequivocal, involving sustained elevations of ALT or AST levels.

4.3 HTLVIII

In hypogammaglobulinaemic patients, seroconversion is improbable and clinical symptoms are the only available indicator of HTLVIII infection. In non-immunodeficient individuals, e.g. ITP patients, the possibility of HTLVIII infection should be excluded by testing for seroconversion to HTLVIII at a suitable period (eg six months) after the initial exposure to the immunoglobulin preparation.

5. SUMMARY

It is apparent that intravenous immunoglobulin is capable of transmitting NANB Hepatitis. It is our belief that maximal safety will be achieved if the following manufacturing procedures are adopted.

5.1 Plasma is collected from healthy unpaid volunteer donors.

5.2/

5.2 Where possible, plasma donations are screened to eliminate contaminated donations.

5.3 Cold-ethanol fractionation is employed to isolate the IgG fraction.

5.4 Finishing of the immunoglobulin must include a step recognised as being virucidal.

5.5 The highest standards of Good Manufacturing Practice are adopted.

In addition, the need for detailed clinical follow-up studies is emphasised.

REFERENCES

1. Fletcher, M.L.; Trowell, J.M.; Craske, J.; et al; Non-A, Non-B Hepatitis After Transfusion Of Factor VIII In Infrequently Treated Patients. BMJ 287: 1754-1757, 1983.

2. Finlayson, J.S.; Immune Globulins. Seminars in Thrombosis and Haemostasis 6 : 44-76, 1979.

3. Petrilli, F.L.; Crovari, P.; De Flora, J.; Hepatitis B In Subjects Treated With A Drug Containing Immunoglobulins. J. Infect Dis. 135: 252-258, 1977.

4. John, T.J.; Ninan, G.T.; Rajagoplan, M.S. et al; Epidemic Hepatitis B Caused By Commercial Human Immunoglobulin. Lancet I: 1074, 1979.

5. Tabor, E.; Gerety, R.J.; Transmission of Hepatitis B By Immune Serum Globulin. Lancet II: 1293, 1979.

6. Lane, R.S.; Non-A, Non-B Hepatitis From Intravenous Immunoglobulin. Lancet II: 974-975, 1983.

7. Lever, A.M.L.; Webster, A.D.B.; Brown, D.; Thomas, H.C.; Non-A, Non-B Hepatitis Occurring In Agammaglobulinaemic Patients After Intravenous Immunoglobulin. Lancet II: 1062-1064, 1984.

8. Ochs, H.D.; Fischer, S.H.; Virant, F.S.; et al; Non-A, Non-B Hepatitis and Intravenous Immunoglobulin. Lancet I, 404-405, 1985.

9. Shikata, T; Karasawa, T; Takahashi, T; Mayumi, M; Incomplete Inactivation Of Hepatitis B Virus After Heat Treatment At 60 Degrees for 10 Hours. J. Inf Dis. 138: 242-244, 1978.

10. Goldfield, M; Bill, J.; Colosimo, F; The Control of Transfusion - Associated Hepatitis. In Vyas, G.; Cohen, S.M.; Schmid, R.: eds Viral Hepatitis, Philadelphia: Franklin Institute Press: 405-414, 1978.

11. Schroeder, B.D.; Mozen, M.M.; Australia Antigen. Distribution During Cold Ethanol Fractionation Of Human Plasma. Science 168: 1462-1463, 1970.

12. Holland, P.V.; Alter, H.J.; Purcell, R.H.; et al; Hepatitis B Antigen And Antibody In Cold-Ethanol Fractions Of Human Plasma. Transfusion 12: 363-370, 1972.

13. Trepo, C.; Hantz, O.; Jacquier, M.F.; et al; Different Fates Of Hepatitis B markers During Plasma Fractionation. A Clue To The Infectivity Of Blood Derivatives. Vox Sang 35: 143-148, 1978.

14. Spire, B.; Barre-Sinoussi, F.; Montganier, L.; Chermann, J.C.; Inactivation of Lymphadenopathy Virus By Chemical Disinfectants.

Lancet II: 899-901, 1984.

15. Ward, T.G.: Methods Of Storage And Preservation Of Animal Viruses In Methods In Virology IV, Maramorosch, K.; Kowprowsk, H.; eds; Academic Press, London; 480-490, 1968.

16. Prince, A.M.; Stephan, W.; Brotman, B; Beta Propiolactone/Ultraviolet Irradiation: A Review Of Its Effectiveness For Inactivation Of Viruses In Blood Derivatives, Rev. Inf. Dis. 5: 92-107, 1983.

17. Andrewes, C.; Pereira, H.G.; Wildy, P; Viruses Of Vertebrates. Pub. Bailliere Tindall, London, 1978.

18. Tabor, E.; Buynak, E.; Smallwood, L.A.; et al; Inactivation Of Hepatitis B Virus By Three Methods : Treatment With Pepsin Urea Or Formalin. J. Med. Virol 11: 1-9, 1983.

19. Anonymous; Hepatitis B Virus Vaccine Safety: Report Of An Inter-Agency Group. MMWR 31: 465-467, 1982.

20. Hollinger, F.B.; Dolana, G.; Thomas, W.; Gyorkey, F.; Reduction In Risk Of Hepatitis Transmission By Heat-Treatment Of A Human Factor VIII Concentrate. J. Inf. Dis. 150: 250-262, 1984.

Appendix 3

BPL PRODUCTS LABORATORY, DAGGER LANE, ELSTREE, HERTS., WD6 3BX.
Tel: 01-953 6191.

Protocol for follow-up study of patients receiving heated high-purity factor VIII concentrate 8Y.

Patients to be treated and followed up

The physician in charge shall nominate to BPL those patients who may receive heat-treated concentrate and acknowledge receipt of individual batches of concentrate assigned to each patient or group of patients.

Information is sought on the safety, efficacy and possible transmission of virus diseases only on patients:

(a) not suspected of having liver disease at presentation (see definition of hepatitis below).

(b) having received no more than two transfusions of any blood product in the last 12 months.

(c) having received no blood products in the previous six months.

(d) found to have their serum negative for HBsAg, anti-HBs and anti-HBc.

(e) giving informed consent.

Procedure

(1) At first presentation for treatment with this concentrate 8Y, each patient will undergo a clinical examination with specific reference to liver disease. A record should be made of his detailed transfusion history and past attacks of hepatitis. Pre-treatment LFTs and tests for HB markers will be recorded. Blood will be taken for HTLV III antibody testing, immediately if possible, or a serum sample kept frozen for retrospective testing. Pre-treatment serum will be stored frozen for retrospective tests should the patient show later laboratory or clinical signs of infection, or should e.g. tests for NANBH be developed. If a patient is seen in an emergency, the control "pre" blood sample may if necessary be taken within 24h of first infusion with heated factor VIII.

On at least the first occasion on which the patient is treated with this concentrate, pre- and 30 minute post-infusion factor VIII assays are required, with further assays during the next 24h if this can be arranged, to confirm whether the half-disappearance time is in the usual range. It is assumed that on the patient's first infusion with the new concentrate, the physician will wish in any case to observe the patient for an hour or more in case any idiosyncratic unwanted reaction should occur.

Part 1 of the follow-up form will be started, and completed at the end of the course of treatment. Fresh Part 1 (Extension) sheets may be attached if there is not enough space to cover all infusions and factor assays in the first treatment. Part 1 will be photocopied to Dr. J.K. Smith, PFL, immediately after completion.

Part 2 of the follow-up form should also be started, to include the results of pre-infusion tests.

(2) At specified intervals after infusion, or at recorded dates as near as possible to these intervals, further blood samples will be taken for LFTs, hepatitis B markers and HTLV III antibody as indicated in Part 2

...e follow-up form. As with the "pre" sample, the replicate samples should be kept for retrospective tests. Part 2 should also be used for monthly post-infusion tests for HTLV III antibody, which may be done retrospectively on stored samples; this frequency may be altered during the course of the trial as new evidence accumulates on the range of delays between infection and seroconversion.

It must be emphasised that even monthly follow-up testing for LFTs and hepatitis markers, or samples which may be tested retrospectively, may provide very important information where the patient is not seen at the stated intervals.

On completion of each sub-table of Part 2, i.e. after 8, 24 and 52 weeks follow-up, Part 2 will be photocopied to Dr. J.K. Smith, PFL.

(3) If the patient shows laboratory or clinical signs of viral hepatitis, the clinician will initiate investigations, probably including anti-HBc, anti-HAV IgG, anti-HAV IgM, CMV and EBV. The physician should report to Dr. T.J. Snape, BPL, or Dr. J.K. Smith, PFL, his interpretation of these investigations, specifically which type of hepatitis has been diagnosed and whether this batch of concentrate is considered to have caused it.

(4) If the patient has to be treated with another batch of this product 8Y during the follow-up period

(a) record the immediate results of the second infusion on a new Part 1 Extension sheet and photocopy this to Dr. J.K. Smith, PFL.

(b) record infusion details for the second batch on the Remarks section of the original Part 1 and Part 2 relating to the first batch.

(c) continue to record viral follow-up on Part 2 relating to the first batch.

(5) If the patient has to be treated with another type of concentrate, plasma or cryoprecipitate:

(a) record infusion details for the second batch on the Remarks section of the original Part 1 and Part 2 relating to the first batch.

(b) continue to record viral follow-up on Part 2 relating to the first batch.

Definition of hepatitis

A patient will be considered to be suffering from hepatitis if he develops clinical symptoms and signs described in form C1, or shows an increase of at least 2.5 times the upper limit of normal serum aminotransferase levels, having had normal values previously.

Having excluded other causes, the physician should classify the disease as hepatitis B or non-A non-B; and acute icteric, anicteric or

s ptomless.

Dr. Craske at the Public Health Laboratory, Withington Hospital, Manchester, M20 8LR, will advise on interpretation of tests, and may wish to receive replicate specimens.

THE PHYSICIAN SHOULD INFORM BPL OR PFL IMMEDIATELY IF ANY OBSERVATIONS INDICATE UNEQUIVOCAL INFECTION OF THE PATIENT BY A PARTICULAR BATCH - THIS MAY ALLOW US TO RECALL THE IMPLICATED BATCH BEFORE OTHERS RECEIVE IT.

Resolution of acute hepatitis

BPL is actively interested in the resolution of acute hepatitis occurring after treatment with our products and would like to receive results of any clinical studies in which the course of resolution has been observed.

Part 2. Viral follow-up.

First dose (index date) | | Batch | BY |

Patient's name	Case No.	Haemophilia Centre

Please summarise data on possible virus transmission on the tables and photocopy the partially completed page to Dr. J.K. Smith, PFL, at 8, 24 and 52 weeks after the first dose with this batch, even if you have recorded further treatment with a different therapeutic material in Part 1 and Part 2.

Test enquiry / Date	Pre	Week 1	Week 2	Week 4	Week 6	Week 8
Bilirubin						
AST/ALT (delete one)						
Alk. phos.						
HBsAg						
Anti-HBs						
Anti-HTLV III						
Remarks/Note no.						

Test enquiry / Date		Week 10	Week 12	Week 16	Week 20	Week 24
Bilirubin						
AST/ALT (delete one)						
Alk. phos.						
HBsAg						
Anti-HBs						
Anti-HTLV III						
Remarks/Note no.						

Test enquiry / Date		Week 28	Week 32	Week 40	Week 52	
Bilirubin						
AST/ALT (delete one)						
Alk. phos.						
HBsAg						
Anti-HBs						
Anti-HTLV III						
Remarks/Note no.						

Summarise any treatment with other products/clinical notes during this period:

BLOOD PRODUCTS LABORATORY, DAGGER LANE, ELSTREE, HERTS., WD6 3BX.
Tel: 01-953 6191.

Protocol for follow-up study of patients receiving heated factor VIII concentrate HL(H) and 8CRV(H).

Patients to be treated and followed up

The physician in charge shall nominate to BPL those patients who may receive heat-treated concentrate and acknowledge receipt of individual batches of concentrate assigned to each patient or group of patients.

Whether or not the patient is suitable for viral follow-up, Part 1 (Efficacy) of the follow-up form will be completed for at least the first course of treatment. Part 2 should be used in every case to record pre-infusion viral status of the patient, even when no viral follow-up is appropriate.

Information is sought on the safety, efficacy and possible transmission of virus diseases on the following categories of patient:

Category 1 - Intensive hepatitis and HTLV III follow-up of patients who have received little or no treatment in the past

Patients meriting full follow-up for hepatitis are those:

(a) not suspected of having liver disease at presentation (see definition of hepatitis below).

(b) having received no more than two transfusions of any blood product in the last 12 months.

(c) having received no blood products in the previous six months.

(d) found to have their serum negative for HBsAg, anti-HBs and anti-HBc.

(e) giving informed consent.

The later sections of this protocol describe the procedure to be used for Category 1 patients. Patients in this category should also provide information, at least for the first infusion with heated factor VIII, on efficacy (Part 1). Monthly sampling for follow-up of HTLV III antibody is necessary, at least until the patient is found to be positive for antibody.

Category 2 - follow-up for HTLV III transmission

Any patient who has received treatment too recently to be eligible for full Category 1 follow-up and who is not known to have HTLV III antibody, should be sampled before treatment and at monthly intervals at least until found positive for antibody. Pre- and post-infusion factor VIII assays should be carried out, at least for the first course of treatment.
Full hepatitis follow-up may still be considered for individual patients who do not meet all the criteria for Category 1, but they may have to be excluded from a statistical analysis.

Category 3 - immediate safety and efficacy only

Any patient who has received treatment too recently to be eligible for full Category 1 follow-up and is known to have HTLV III antibody may derive no benefit from heat treatment of the product or from follow-up for HTLV III antibody. However, if the physician elects to carry out such tests, the results should be recorded in Part 2.

Pre- and post-infusion factor VIII assays should be carried out, at least for the first course of treatment.

Procedure

(1) At first presentation for treatment with heated concentrate, each patient will undergo a clinical examination with specific reference to liver disease. A record should be made of all his detailed transfusion history and past attacks of hepatitis. Pre-treatment LFTs and tests for HB markers will be recorded. Blood will be taken for HTLV III antibody testing, immediately if possible, or a serum sample kept frozen for retrospective testing. Pre-treatment serum will be stored frozen for retrospective tests should the patient show later laboratory or clinical signs of infection, or should e.g. tests for NANBH be developed. If a patient is seen in an emergency, the control "pre" blood sample may if necessary be taken within 24h of first infusion with heated factor VIII.

On at least the first occasion on which the patient is treated with this heated concentrate, pre- and 30 minute post-infusion factor VIII assays are required, with further assays during the next 24h if this can be arranged, to confirm whether the half-disappearance time is in the usual range. It is assumed that on the patient's first infusion with the new concentrate, the physician will wish in any case to observe the patient for at least an hour in case any idiosyncratic unwanted reaction should occur.

Part 1 of the follow-up form will be started, and completed at the end of the course of treatment. Fresh Part 1 (Extension) sheets may be attached if there is not enough space to cover all infusions and factor assays in the first treatment. Part 1 will be photocopied to Dr. T.J. Snape, BPL, immediately after completion.

Part 2 of the follow-up form should also be started, to include at least the results of "pre" HTLV III antibody tests, whether or not the patient is suitable for hepatitis follow-up.

(2) At specified intervals after infusion, or at recorded dates as near as possible to these intervals, further blood samples will be taken for LFTs, hepatitis B markers and HTLV III antibody as indiated in Part 2 of the follow-up form. As with the "pre" sample, the replicate samples should be kept for retrospective tests. For those patients ineligible for hepatitis follow-up, Part 2 should be used for monthly post-infusion tests for HTLV III antibody, which may be done retrospectively on stored samples. It must be emphasised that even monthly follow-up testing for hepatitis markers, or samples which may be tested retrospectively, may provide very important information where full test facilities are not available or the patient is not seen at the stated intervals.

On completion of each sub-table of Part 2, i.e. after 8, 24 and 52 weeks follow-up, Part 2 will be photocopied to Dr. T.J. Snape, BPL.

(3) If the patient shows laboratory or clinical signs of viral hepatitis, the clinician will initiate investigations, probably including anti-HBc, anti-HAV IgG, anti-HAV IgM, CMV and EBV. The physician should report to Dr. T.J. Snape, BPL, his interpretation of these investigations, specifically which type of hepatitis has been diagnosed and whether this batch of concentrate is considered to have caused it.

(4) If the patient has to be treated with another batch of this type of product during the follow-up period

(a) record the immediate results of the second infusion on a new Part 1 Extension sheet and photocopy this to Dr. T.J. Snape.

(b) record infusion details for the second batch on the Remarks section of the original Part 1 and Part 2 relating to the first batch.

(c) continue to record viral follow-up on Part 2 relating to the first batch.

(5) If the patient has to be treated with another batch of concentrate, plasma or cryoprecipitate:

(a) record infusion details for the second batch on the Remarks section of the original Part 1 and Part 2 relating to the first batch.

(b) continue to record viral follow-up on Part 2 relating to the first batch.

Definition of hepatitis

A patient will be considered to be suffering from hepatitis if he develops clinical symptoms and signs described in form C1, or shows an increase of at least 2.5 times the upper limit of normal serum aminotransferase levels, having had normal values previously.

Having excluded other causes, the physician should classify the disease as hepatitis B or non-A non-B; and acute icteric, anicteric or symptomless.

Dr. Craske at the Public Health Laboratory, Withington Hospital, Manchester, M20 8LR, will advise on interpretation of tests, and may wish to receive replicate specimens.

THE PHYSICIAN SHOULD INFORM BPL IMMEDIATELY IF ANY OBSERVATIONS INDICATE UNEQUIVOCAL INFECTION OF THE PATIENT BY A PARTICULAR BATCH - THIS MAY ALLOW BPL TO RECALL THE OFFENDING BATCH BEFORE OTHERS RECEIVE IT.

Follow-up

Although BPL do not ask for information on the resolution of acute hepatitis occuring during treatment, some suggestions are offered on a minimum course of action which might be taken.

If a patient develops evidence of acute hepatitis, his liver function tests and hepatitis B serology will be followed fortnightly until his condition resolves, or for three months after the onset and, if his condition is not resolved, then monthly for six months. Follow-up after this will be three-monthly for the next two years.

Patients whose liver function tests remain elevated for one year after the acute attack of non-A non-B hepatitis, or become carriers of hepatitis B virus, will be referred to the local liver clinic for investigation of chronic liver disease. Liver biopsy will not be carried out unless clinical indicated.

Part 2. Viral follow-up.

First dose (index date) _____ Batch _____

Patient's name Case No. Haemophilia Centre

Please summarise data on possible virus transmission on the tables and photocopy the partially completed page to Dr. T.J. Snape, BPL, at 8, 24 and 52 weeks after the first dose with this batch, even if you have recorded further treatment with a different therapeutic material in Part 1 and Part 2.

Test enquiry	Pre	Week 1	Week 2	Week 4	Week 6	Week 8
Date						
Bilirubin						
AST/ALT (delete one)						
Alk. phos.						
HBsAg						
Anti-HBs						
Anti-HTLV III						
Remarks/Note no.						

Test enquiry	Week 10	Week 12	Week 16	Week 20	Week 24
Date					
Bilirubin					
AST/ALT (delete one)					
Alk. phos.					
HBsAg					
Anti-HBs					
Anti-HTLV III					
Remarks/Note no.					

Test enquiry	Week 28	Week 32	Week 40	Week 52
Date				
Bilirubin				
AST/ALT (delete one)				
Alk. phos.				
HBsAg				
Anti-HBs				
Anti-HTLV III				
Remarks/Note no.				

Summarise any treatment with other products/clinical notes during this period:

CFR section

Subpart J—Immune Serum Globulin (Human)

§ 610.100 Immune Serum Globulin (Human).

(a) *Proper name and definition.* The proper name of this product shall be Immune Serum Globulin (Human). The product is defined as a sterile solution containing antibodies derived from human blood.

640.100(b)

(b) *Source material.* The source of Immune Serum Globulin (Human) shall be blood, plasma or serum from human donors determined at the time of donation to have been free of causative agents of diseases that are not destroyed or removed by the processing methods, as determined by the donor's history and from such physical examination and clinical tests as appear necessary for each donor at the time the blood was obtained. The source blood, plasma or serum shall not contain a preservative and shall be stored in a manner that will prevent contamination by microorganisms, pyrogens or other impurities.

W+

Summary of Change

Name change

change (b) & (c) to read just like 640.80(b) and (c) (Albumin)

delete serum and blood
change "property" to "propriety"

Description of Action

Name changes (Panel) have been proposed (FR October 31, 1980) and commented upon. We did not review the proposal or the comments but merely used the names we consider most appropriate.

Note that this section and following sections have been re-ordered in conformance with 640.80-86. (Albumin)

Inasmuch as only plasma is fractionated in the U.S. to obtain this product, "blood," "serum" and "placentas" (Panel) were deleted.

There is no reason for the source material specifications for this product to be different from those for Albumin (or Plasma Protein Fraction) since they are often prepared from the same pools of starting plasma. Therefore, this section now coincides with 640.80(b) and 640.80(c). (Albumin)

Change W

Immune Globulin G

Subpart J—~~Immune Serum Globulin~~ (Human)

Immunoglobulin G

§ 610.100 ~~Immune Serum Globulin~~ (Human).

(a) *Proper name and definition.* The proper name of this product shall be Immunoglobulin G (Human). The product is defined as a sterile solution containing antibodies derived from human blood. *

(b) *Source material.* The source material of Immunoglobulin G (Human) shall be blood, plasma, ~~serum or placentas~~ from human donors determined at the time of donation to have been free from disease-causative agents that are not destroyed or removed by the processing method, as determined by the medical history of the donor and from such physical examination and clinical tests as may appear necessary for each donor at the time the blood was obtained. Where source material is a product for which additional standards are effective, the requirements of those additional standards shall determine the ~~Property~~ propriety of the source material for use in the production of Immunoglobulin G (Human). Where no additional standards are effective with respect to source material for the production of Immunoglobulin G (Human), such source material shall:

(1) Be collected by a procedure which is designed to assure the integrity and to minimize the risk of contamination of the source material. The manufacturer of Immunoglobulin G (Human) shall ensure that the collection procedure shall be as described in its license.

(2) Be identified to relate it accurately to the individual donor and the dates of collection.

(3) Not contain a preservative.

(4) Be stored and transported in a manner designed to prevent contamination by microorganisms, pyrogens, or other impurities.

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Appendix 3

* This suggestion is now obsolete. See Federal Register ("FR") 50:4128ff; January 29, 1985

CFR Section

640.100c

(c) *Additives in source material.* Source blood, plasma or serum shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the processing method yields a final product free of the additive to such extent that the continued safety, purity, potency, and effectiveness of the final product will not be adversely affected.

640.101

renumber and change name to Processing

640.101(a)

§640.101 *General requirements.*

(a) *Heat stability test.* Approximately 2 ml. of completely processed material of each lot shall not show any visible sign of gelation after heating in a 12 x 75 mm. stoppered glass tube at 57° C. for 4 hours.

delete if Molecular Distribution Test is adopted

So many factors other than the quality of the protein (e.g., protein concentration, heavy metals) affect this test that a "failure" may be difficult to interpret and a "pass" may give a false sense of security.

640.101 Processing

(c) Date of manufacture. The date of manufacture shall be the date of final sterile filtration of a uniform pool of bulk solution, and §610.50 shall not apply.

§640.101(a) The date of manufacture has been changed to that used for Albumin. It is recognized that, in the future, there might arise situations in which this definition is not strictly applicable and must be interpreted on a case-by-case basis. However, the new definition, especially when applied in consort with tests for Molecular Distribution and enzyme content, should discourage the practice of extending the time of in-house storage (of bulk solutions) simply by delaying or repeating the performance of potency tests, which was permissible under 640.101(d).

CFR Section	Summary of Change	Description of Change	Change to
640.101 (b) *Hydrogen ion concentration.* The pH of final container material shall be 6.8±0.4 when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.	change [H+] to pH and move to Tests on Final Product	The quantity measured is really pH, rather than hydrogen ion concentration per se, and the revision indicates this.	640.187 (d) pH. . . . The pH of final container material shall be 6.8±0.4 when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.
640.101(c) (c) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.	turbidity section should be moved to processing section and renumbered		640.101 (f) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.
640.101(d) (d) *Date of manufacture.* The date of manufacture is the date of initiating the last valid measles or poliomyelitis antibody test (§ 640.104(b) (2) and (3)) whichever date is earlier.	Date of manufacture will be renumbered and reworded as 640.81(a), date of sterile filtration	640.101(a) The date of manufacture has been changed to that used for Albumin. It is recognized that, in the future, there might arise situations in which this definition is not strictly applicable and must be interpreted on a case-by-case basis. However, the new definition, especially when applied in consort with tests for Molecular Distribution and enzyme content, [illegible] should discourage the practice of extending the time of in-house storage (of bulk solutions) simply by delaying or repeating the performance of potency tests, which was permissible under 640.101(d).	640.101 Processing (c) Date of manufacture. The date of manufacture shall be the date of final sterile filtration of a uniform pool of bulk solution, and § 610.50 shall not apply.

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CFR Section — Summary of Change — Description of Change — Justification

640.101

(a) *Labeling.* In addition to complying with all applicable labeling required in this subchapter, labeling shall indicate that:
(1) There is no prescribed potency for viral hepatitis antibodies.
(2) The product is not recommended for intravenous administration.
(3) The lot is or is not suitable for use with Measles Virus Vaccine, Live, Attenuated.
(4) The lot is or is not recommended for poliomyelitis.

renumber to A640.104 Labeling
add 201.56 and 201.57
delete (1) & (3)
(4) delete "is or"

§640.104 This section was derived from 640.101(a). Part (1) of that section was deleted because it would contradict the anti-HBs potency prescribed by §640.102(f). Part (3) of 640.101(a) was deleted because the product is not used with the current measles vaccines. The statement that the product is not recommended for poliomyelitis is in the current package insert.

640.104 Labeling

In addition to complying with all applicable labeling required in this subchapter labeling shall indicate that:
(1) ~~There is no prescribed potency for viral hepatitis antibodies.~~
(2) The product is not recommended for intravenous administration.
(3) ~~The lot is or is not suitable for use with Measles Virus Vaccine, Live, Attenuated.~~
(4) The lot is or is not recommended for poliomyelitis.

and in §201.56 and 201.57,

640.101(f)

(f) *Samples and protocols.* For each lot of Immune Serum Globulin (Human) the following material shall be submitted to the Director, Bureau of Biologics, Food and Drug Administration, Building 29A, 8000 Rockville Pike, Bethesda, MD 20205:
(1) A 50 ml. sample of the final product.
(2) All protocols relating to the history of each lot and all results of all tests prescribed in these additional standards.

renumber as §640.105
change 9000 to 8800
in address

(1) add "in at least 2 final containers intended for distribution".
add another volume

§640.105 This section is the same as 640.101(f) except for two changes. The first permits BoB to require less of the product if it is not necessary for testing. The second is patterned after 640.85(a); it is intended to eliminate confusion about the type of sample required and to assure that the sample received by BoB is indeed representative of those intended for distribution.

§640.105 Samples; protocols; official release.

~~(f) Samples and protocols.~~ For each lot of ~~Immune Serum Globulin~~ (Human) the following material shall be submitted to the Director, Bureau of Biologics, Food and Drug Administration, Building 29A, 8800 Rockville Pike, Bethesda, MD 20205:

(1) A sample consisting of no less than 50 ml of the final product in at least 5 final containers intended for distribution, unless another volume is specified by the Director, Bureau of Biologics, Food and Drug Administration

(2) All protocols relating to the history of each lot and all results of all tests prescribed in these additional standards.

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DHSC0000368_0040

CFR Section ISG Summary of Change, Description of Change Change to

640.102

§ 640.102 Manufacture of Immune Serum Globulin (Human).

(a) *Processing method.* The processing method shall be one that has been shown: (1) To be capable of concentrating tenfold from source material at least two different antibodies; (2) not to affect the integrity of the globulins; (3) to consistently yield a product which is safe for subcutaneous and intramuscular injection and (4) not to transmit viral hepatitis.

(b) *Microbial contamination.* Low temperatures or aseptic techniques shall be used to minimize contamination by microorganisms. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(c) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in clearly identified hermetically closed vessels. Globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature of — 10° C. or lower. Globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at a temperature of 0° C. or lower.

(d) *Determination of the lot.* Each lot of Immune Serum Globulin (Human) shall represent a pooling of approximately equal amounts of material from not less than 1,000 donors.

(e) *Sterilization and heating.* The final product shall be sterilized promptly after solution. At no time during processing shall the product be exposed to temperatures above 45°C. and after sterilization the product shall not be exposed to temperatures above 30° to 32° C. for more than 72 hours.

change name of section
to Tests on Final Product
move 640.102(a)(b) and (c)
to Processing Section,

correct split infinitive

640.102(d) Determination of Lot--change "material" to "plasma"
move to processing section. To avoid the appearance of imposing an unnecessary regulatory burden, BoB should assure manufacturers that we will continue to accept statistical evidence of compliance with this requirement.

640.102(e) This has been deleted. The section had several disadvantages in addition to the confusion it sometimes engendered. One was that it appeared to contradict the requirement for low temperatures stated by 640.102(b), now §640.101(c). Second, it implied that such heating constitutes good manufacturing practice. In fact, although mild heating can partially inactivate plasmin--see [illegible] --it also has adverse effects on the product, is not necessary, and should be discouraged. The sentence dealing with prompt sterilization is redundant since good manufacturing practice must be used and the final product must be tested for sterility and pyrogenicity.

640.101

(b) *Processing method.* The processing method shall be one that has been shown: (1) To be capable of concentrating tenfold from source material at least two different antibodies; (2) not to affect the integrity of the globulins; (3) to consistently yield a product which is safe for subcutaneous and intramuscular injection and (4) not to transmit viral hepatitis.

(c) *Microbial contamination.* Low temperatures or aseptic techniques shall be used to minimize contamination by microorganisms. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in clearly identified hermetically closed vessels. Globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature of — 10° C. or lower. Globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at a temperature of 0° C. or lower. *

(e) *Determination of the lot.* Each lot of Immune Globulin (Human) shall represent a pooling of approximately equal amounts of plasma from not less than 1,000 donors.

~~(f) *Sterilization and heating.* The final product shall be sterilized promptly after solution. At no time during processing shall the product be exposed to temperatures above 45°C. and after sterilization the product shall not be exposed to temperatures above 30° to 32° C. for more than 72 hours.~~

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* In practice, these are stored appreciably colder. We encourage the use of -20 °C. (or colder) facilities.

CFR Section ISG	Summary of Change	Description of Change	Change to
640.102	change name of Section to "Tests on Final Product"	To make ISG Section consistant with more recently written sections.	640.102 Tests on Final Product. Tests shall be performed consistent with § 610.1, after the final sterile filtration of the product, by methods that have been approved for each manufacturer by the Director, Bureau of Biologics, Food and Drug Administration, to determine that each lot of final product meets the following standards: (a) Protein content. The final product shall be a 16.5 ± 1.5 percent solution of protein. (b) Protein composition. At least 96 percent of the total protein shall be immunoglobulin G. (c) Molecular distribution. At least 90 percent of the total protein, shall have a molecular weight in the range of ~~140,000~~ * 85 000 to 350,000.
640.103		(14) The part which required glycine and a preservative has been deleted, although §640.103(a) permits either or both of these in the final product.	
		(b) According to the Panel, the regulations for this product appeared to reflect the technology of the 1960's. The specification of absolute electrophoretic mobility has been deleted because few moving boundary apparati remain in existence. A definition in terms of immunoglobulin G is consistent with the best name for the product, is realistic, is flexible and is appropriate when applied in conjunction with Molecular Distribution. Nearly all current lots of product exceed the proposed minimum content of immunoglobulin G,	
		(1) It is intended to minimize the content of immunoglobulin fragments, which are not retained in the body ... , and therefore may have little efficacy, and the content of aggregated immunoglobulin, which has been associated with adverse reactions. The method chosen for expressing the requirement, i.e., a range spanning the molecular weights of immunoglobulin G monomer and dimer, is based on the knowledge that these are interconvertible and that at body temperature the equilibrium favors dissociation of dimer, * and that, in some analytical systems, 5 S component (primarily Fab/Fc) does not resolve from monomeric IgG.	

640.103 The final product.

(a) *Final solution.* The final product shall be a 16.5±1.5 percent solution of globulin containing 0.3 molar glycine and a preservative.

(b) *Protein composition.* At least 90 percent of the globulin shall have an electrophoretic mobility not faster than -2.8×10^{-5} centimeters² per volt per second, when measured at a 1 percent protein concentration in sodium diethylbarbiturate buffer at pH 8.6 and 0.1 ionic strength.

Move to "Tests on Final Product"

Delete glycine - preservative statement

Revise "Protein Composition"

Add "Molecular Distribution"

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CFR Section & Subj

Summary of Change

Description of Change

Add Enzyme Content Section

Whereas the Molecular Distribution Section is intended to minimize the content of immunoglobulin fragments at the time of product release, this section is intended to minimize fragmentation during storage. This fragmentation can result from the proteolytic action of plasmin present at time of release or from that which arises by activation of plasminogen during storage. Lots of product with levels of plasmin and plasminogen below those indicated should meet the requirements of the Molecular Distribution Section throughout the proposed dating period.

Change to

640.102

(e) Enzyme content. The final product shall not contain more than 0.010 CTA unit of plasmin per milliliter and shall not contain more than 0.080 CTA unit of plasminogen per milliliter. *

* This requirement is not in place. Its placement depends upon studies in progress to develop appropriately sensitive methods for measurement.

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CFR Section	Summary of Change	Description of Change	Change to
§ 640.103 The final product. (a) *Final solution.* The final product shall be a 18.5 ± 1.5 percent solution of globulin containing 0.3 molar glycine and a preservative. (b) *Protein composition.* At least 90 percent of the globulin shall have a electrophoretic mobility not faster than -2.6×10^{-5} centimeters^2 per volt per second, when measured at a 1 percent protein concentration in sodium diethylbarbiturate buffer at pH 8.6 and 0.1 ionic strength.	delete as it is now, but rename as General Requirements Add a preservative section reworded more leniently from 640.103(a) and a bulk storage section worded as 640.83(b) (Albumin)	This deletion permits manufacturers to prepare single dose containers of Immunoglobulin G without a preservative. This is consistent with the recommendations of the Panel on Viral Vaccines and Rickettsial Vaccines (FR April 15, 1980). It is anticipated that by the time this deletion is implemented, clinical data demonstrating the safety of intramuscularly administered preservative-free Immunoglobulin G * will be available. Such data have already been obtained for a preservative-free modified immunoglobulin G preparation which is given intravenously. This deletion also permits the manufacturer to use glycine at a concentration other than 0.3 M (as has already been done in the case of a specific immunoglobulin G) or to seek better stabilizing agent(s). This is the requirement currently in effect for Albumin (640.83(b)). It will necessitate no manufacturing changes since manufacturers now store the final sterile bulk solutions of this product between 2 and 8 °C.	640.103 General Requirements (a) Preservative. The final product may contain glycine and/or a preservative. (b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of the final product prescribed in § 610.53 of this chapter.

ff

*This has been accumulated.

CFR Section	ISG	Summary of Change	Description of Change	Change to
§640.104 Potency. (a) *Antibody levels and tests.* Each lot of final product shall contain at least the minimum levels of antibodies for diphtheria, measles, and for at least one type of poliomyelitis. In the event the final bulk solution is stored at a temperature above 5° C. the antibody level tests shall be performed after such storage with a sample of the stored material.		Potency renumber as A640,102(f) in Tests on Final Product renumber in Section "Tests on Final Product" replace one type of poliomyelitis with HBsAg correct wording by adding "for" before "measles" delete sentence on "storage"	The primary changes proposed in this section are the elimination of the requirement for poliomyelitis antibodies and the introduction of a requirement for anti-HBs. See Dr. Gerety's memo for more information. Other changes were made so that the remainder would be consistent with these requirements and to avoid the current situation in which the regulation becomes obsolete each time a new reference material is introduced. One additional change is the deletion of the second sentence of 640.104(a). This was done because the requirement will no longer be relevant when the Storage of Bulk Solution Section is in effect.	640.107 (f) Potency. (1) Antibody levels and tests. Tests for antibody levels shall be performed on the product in final containers intended for distribution. Each lot of final product shall contain at least the minimum levels of antibodies for diphtheria, measles, and for ~~at least one type of poliomyelitis. In the event the final bulk solution is stored at a temperature above 5° C. the antibody level tests shall be performed after such storage with a sample of the stored material.~~ for hepatitis B surface antigen (anti-HBs). *

SF

* This has not been implemented. The requirement for poliomyelitis antibody is still in place.

CFR Section

640.104

(b) *Minimum levels.* The minimum antibody levels are as follows:

(1) No less than 2 units of diphtheria antitoxin per ml.

(2) A measles neutralizing antibody level of no less than 0.50 times the level of the Reference Measles Immune Globulin, except that when recommended for use with Measles Virus Vaccine, Live, Attenuated, the measles antibody level shall be as prescribed in § 640.114.

(3) A poliomyelitis neutralizing antibody level of no less than 1.0 for Type 1, 1.0 for Type 2, and 2.5 for Type 3, times the antibody level of the Reference Poliomyelitis Immune Globulin.

(c) *Reference materials.* The following reference materials shall be obtained from the Bureau of Biologics:

(1) Reference Measles Immune Globulin for correlation of measles antibody titers.

(2) Reference Poliomyelitis Immune Globulin for correlation of poliomyelitis antibody titers, Types 1, 2, and 3.

[38 FR 32088, Nov. 20, 1973, as amended at 39 FR 8661, Mar. 13, 1974]

Summary of change

reword measles potency to reflect change in Reference Sample

replace with requirements for Anti-HBs

reword to make more general, add Reference for Anti-HBs and delete Polio Reference

Description of change

Because of the uses of this product, it is clear that improved potency requirements should be sought. Obvious candidates are antibodies to hepatitis A virus, to gram-negative bacteria, and to varicella-zoster virus.

Change to

640.102

(b) *Minimum levels.* The minimum antibody levels are as follows:

(1) No less than 2 units of diphtheria antitoxin per ml.

(ii) A measles neutralizing antibody level that bears the relationship to a reference preparation, obtained as indicated in part (3) of this section, specified by the Director, Bureau of Biologics, Food and Drug Administration.

(iii) An anti-HBs titer of 1:100 by end-point dilution in a radioimmunoassay or other test approved by the Director, Bureau of Biologics, Food and Drug Administration.

(3) Reference materials. Reference materials available from the Bureau of Biologics shall include, but not be limited to:

(i) a reference globulin for correlation of measles antibody levels, and

(ii) a reference globulin for calibration of anti-HBs tests.

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DHSC0000368_0046

CFR Section	+DH	Summary of Changes	Description of Change	Change to
640.106		Add as 640.86 (Albumin) Equivalent Methods Section	This section is the same as 640.86. It is intended to be an explicit statement that will prevent misunderstanding on the part of manufacturers, while assuring them that equivalent alternate methods (including processing, analytical, and administrative procedures) are not precluded.	§ 640.106 Equivalent methods. Modification of any particular manufacturing method or process, or the conditions under which it is conducted, as set forth in the additional standards for Immunoglobulin G (Human), shall be permitted only upon the submission by the manufacturer to the Director, Bureau of Biologics, Food and Drug Administration, of substantial evidence demonstrating that the modification will assure the continued safety, purity, potency, and effectiveness of Immunoglobulin G (Human) to an extent equal to, or greater than, the methods or processes provided in §§ 640.100 through 640.105, and after the equivalent method has received the written approval of the Director, Bureau of Biologics, Food and Drug Administration.

New

+D

CFR Section | Measles IG | Summary of Changes | Description of Changes | Change to

Subpart K—Measles Immune Globulin (Human)

delete

§ 640.110 Measles Immune Globulin (Human).

(a) *Proper name and definition.* The proper name of the product shall be Measles Immune Globulin (Human). It shall consist of a sterile solution of 10 to 18 percent globulin derived from human blood, having the same measles antibody level as the Reference Measles Immune Globulin. Measles Immune Globulin shall be made from a sterile 16.5 ±1.5 percent solution of human globulin.

(b) *Source material.* The source of Measles Immune Globulin (Human) shall be blood, plasma or serum from human donors determined at the time of donation to have been free of causative agents of diseases that are not destroyed or removed by the processing method, as determined by the donor's history and from such physical exami-

and so on through 640.114 (Potency).

640.110-640.114 Armour Pharmaceutical Company, the only firm licensed for this product, has not manufactured it for years. As stated by the Panel on Viral and Rickettsial Vaccines in its report (FR April 15, 1980), there is no need for the product. Armour should be asked to give up its license for this product, and these sections should be deleted. The numbers can be reassigned.

* There is now no manufacturer licensed for Measles Immune Globulin in the U.S.

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DHSC0000368_0048

Affected

NEW

Hyper Immune Globulins

Description of Changes

Except for the specific provisions indicated below specific immunoglobulin G preparations for intramuscular use should have the same generic requirements as does Immunoglobulin G. An "equivalent methods" section permits alternate standards, provided the manufacturer can support them and they have been approved by BoB.

This provision is consistent with current practice and WHO guidelines; it can easily be met by all present manufacturers.

It reflects current practice, and all current lots of these products would comply.

Change to:

§40.110 Specific Immunoglobulin Preparations for Intramuscular Administration

(a) Definition and requirements. The product is defined as a sterile solution containing antibodies derived from human blood. Unless indicated otherwise by the following sections, it shall meet all requirements for Immunoglobulin G (Human). (1)

(b) Proper names. Each product shall have a proper name that is approved by the Director, Bureau of Biologics, Food and Drug Administration. The approved proper names include, but need not be limited to, Hepatitis B Immunoglobulin G (Human), Rabies Immunoglobulin G (Human), $Rh_0(D)$ Immunoglobulin G (Human), Tetanus Immunoglobulin G (Human), and Varicella-Zoster Immunoglobulin G (Human). (2)

§40.111 Processing

Each lot of specific immunoglobulin G for intramuscular use shall represent a pooling of approximately equal amounts of plasma from not fewer than 20 donors.

§40.112 Tests on Final Product

(a) Protein content. The final product shall be a 10.0 to 18.0 percent solution of protein. (3)

(1) This is an important statement. It avoids repetition in the document. In fact, however, many of the specific immune globulins have been meeting the "new" (e.g., molecular size distribution) requirements all along.

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(2) Obsolete. See Federal Register of January 29, 1985.

(3) Of course, a manufacturer could petition for an exception (to this or other section) by presenting evidence of

21 CFR section "Human Globulins" Description of changes

NEW

This section has been prepared with the intent of minimizing ambiguity, codifying current good practices, and avoiding the necessity for changing the regulations when a new reference preparation is adopted.

50

Change 10 640.112

(b) Potency. Tests for antibody levels shall be carried out on product in final containers intended for distribution. Each lot of final product shall contain at least the minimum level of the appropriate antibody specified in the following subsections.

(1) Hepatitis B Immunoglobulin G (Human) shall have a level of anti-HBs that bears the relationship to a reference preparation, obtained as indicated in part (6) of this section, specified by the Director, Bureau of Biologics, Food and Drug Administration. *

(2) Rabies Immunoglobulin G (Human) shall have an antibody level of at least 110 International Units of rabies antibody per milliliter (IU/ml) as determined in a minimum of four potency tests in parallel with the U.S. standard reference preparation.

(3) Rh_0(D) Immunoglobulin G (Human) shall have such a level of anti-D (anti-Rh_0) and be filled into final containers in such a way that the potency of the contents of each final container bears the relationship to a reference preparation, obtained as indicated in part (6) of this section, specified by the Director, Bureau of Biologics, Food and Drug Administration. The relationship specified shall assure that one final container of the standard postpartum dose of the product will completely suppress immune response to at least 15 ml of D-positive (Rh_0-positive) red blood cells and that one final container of the micro-dose form of the product will completely suppress immune response to at least 2.5 ml of D-positive red blood cells. In no case, however, shall the filled volume of a final container be less than 0.5 ml or more than 2.0 ml.

(4) Tetanus Immunoglobulin G (Human) shall contain at least 170 units of tetanus antitoxin per milliliter and the filled volume shall assure that each final container contain 250 units of tetanus antitoxin throughout its dating period. (1) (2)

(5) Each final container of Varicella-Zoster Immunoglobulin G (Human) shall contain at least 125 units of antibody to varicella-zoster virus. The product shall contain at least 50 units of the antibody per milliliter.

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(1) This is not a requirement at present, though it is usually met and far exceeded.

(2) This is a requirement at present.

* Note that the current US Reference and

DHSC0000368_0050

CFR Section — Hyper-Immune Globulins — Description of Changes

NEW

Except for specific indications, potency, and directions for use, the labeling will be the same as that for Immunoglobulin G. Accordingly, §640.113 should be the same as §640.104, except that the irrelevant statement regarding poliomyelitis has been deleted.

This section is the same as 640.86. It is intended to be an explicit statement that will prevent misunderstanding on the part of manufacturers, while assuring them that equivalent alternate methods (including processing, analytical, and administrative procedures) are not precluded.

Change to

640.112

(6) Reference materials available from the Bureau of Biologics shall include, but not be limited to:

(i) a reference for correlation of anti-HBs levels,

(ii) A U.S. standard antirabies preparation, as indicated in 610.20(a),

(iii) a reference for correlation of anti-D potency,

(iv) a standard tetanus antitoxin preparation, as indicated in 610.20(a), and

(v) a reference for correlation of anti-varicella-zoster virus unitage.

640.113 Labeling

In addition to complying with all applicable labeling required in this Title, labeling shall indicate that the product is not recommended for intravenous administration.

640.114 Equivalent Methods

Modification of any particular manufacturing method or process or the conditions under which it is conducted, as set forth in these additional standards for [redacted] (Human), shall be permitted only upon the submission by the manufacturer to the Director, Bureau of Biologics, Food and Drug Administration, of substantial evidence demonstrating that the modification will assure the continued safety, purity, potency, and effectiveness of any [redacted] (Human) to an extent equal to or greater than the methods or processes provided in §§640.110 through 640.113, and after the equivalent method has received the written approval of the Director, Bureau of Biologics, Food and Drug Administration.

CFR Section IV-F-5H

DEXTRANS
HES

No Proposals at this time.

25

NDIEDs

Immunoglobulin Products for Intravenous Use

61. At present, only one such product is licensed by BoB; therefore, it would be premature to propose regulations (guidelines, points-to-consider, etc.) for them. Furthermore, the intravenous immunoglobulin products being used and/or studied in Europe, Japan, and U.S. are made by a wide variety of manufacturing methods and vary widely in certain properties. For example, various protein concentrations are used, and some products are in dried form. This diversity suggests that it will be impossible to develop one set of complete specifications for all intravenous immunoglobulin products. However, in the future, it may be reasonable to propose a limited set of specifications for certain common properties of these products.

Non-Blood Plasma Volume Extenders

62. We have been unable to locate any written requirements, guidelines, or general specifications for these products. Nevertheless, a wide variety of dextrans, including dextran-40 and dextran-70 or -75 in several combinations of solvents and containers, and hydroxyethyl starch are marketed and are the regulatory responsibility of the Branch. In view of the limited regulation of these products, such a set of specifications would appear to be helpful both to BoB and to potential new manufacturers. It is anticipated that development of such specifications, if it is to be undertaken, would require the collaboration of the Plasma Derivatives Branch and the Licensing Branch, which holds the NDAs for these products.

* Now two.

CFR Section — Dating Period — Summary of Change — Description of Change — Changes To

610.53

Factor IX Complex (Human)	One year (§610.51 does not apply)
Fibrinogen (Human)	Five years
Fibrinogen with Antihemophilic Factor (Human)	Five years
Fibrinolysin (Human)	Two years
Fibrinolysin and Desoxyribonuclease Combined (Bovine)	Three years, provided labeling recommends storage at no warmer than 30° C.
Fibrinolysin and Desoxyribonuclease Combined (Bovine) with Chloramphenicol	Three years, provided labeling recommends storage at no warmer than 30° C.
Gas Gangrene Polyvalent Antitoxin	Five years with an initial 30 percent excess of potency.
Haemophilus influenzae Typing Serum	One year
Hepatitis B Surface Antigen	Six months (5° C., six months). Unlyophilized coated red blood cells, 14 days (§610.51 does not apply). Iodinated (^{125}I) products, 45 days (§610.51 does not apply)
Histamine Azoprotein	Two years
Histoplasmin	Two years (5° C., one year)
Immune Serum Globulin (Human)	Three years (5° C., three years)
Influenza Virus Vaccine	Eighteen months (5° C., one year)
Leukocyte Typing Serum (Direct)	Two years
Anti-HL-A †	Two years

Factor IX Complex (Human)	One year (§610.51 does not apply)
Fibrinogen (Human)	Five years
Fibrinogen with Antihemophilic Factor (Human)	Five years
Fibrinolysin (Human)	Two years
Fibrinolysin and Desoxyribonuclease Combined (Bovine)	Three years, provided labeling recommends storage at no warmer than 30° C.
Fibrinolysin and Desoxyribonuclease Combined (Bovine) with Chloramphenicol	Three years, provided labeling recommends storage at no warmer than 30° C.
Gas Gangrene Polyvalent Antitoxin	Five years with an initial 30 percent excess of potency.
Haemophilus influenzae Typing Serum	One year
Hepatitis B Immunoglobulin G	One year (5°C., one year).
Hepatitis B Surface Antigen	Six months (5° C., six months). Unlyophilized coated red blood cells, 14 days (§610.51 does not apply). Iodinated (^{125}I) products, 45 days (§610.51 does not apply)
Histamine Azoprotein	Two years
Histoplasmin	Two years (5° C., one year)
Immune Globulin G (Human)	Three years (5°C., three years). One year (5°C., one year)
Influenza Virus Vaccine	Eighteen months (5° C., one year)
Leukocyte Typing Serum (Direct)	Two years
Anti-HL-A †	Two years

delete Fibrinogen

delete Fibrinogen with AHF

Add Hepatitis B Immunoglobulin G

change name of Immune Serum Globulin

change dating period of Immune Serum Globulin

610.53 Many immunoglobulin G preparations undergo fragmentation during storage. Generic dating periods of up to 3 years plus 3 years are thus far too long. Our proposal is to set the generic dating period at 1 year plus 1 year and to allow manufacturers to support extensions on an individual basis. If a manufacturer has documented stability and BoB has the supporting data, only a summary would need to be submitted. This section would permit some flexibility of judgment on the part of BoB. For example, data from a study carried out in 1960 with potency in vitro as the only endpoint could be considered inadequate evidence of stability. All of the specific immunoglobulin G preparations listed in §640.112(b), as well as Immunoglobulin G, should have the same generic dating period. Concurrent application of this revised dating period and the provisions of §640.102(c) and §640.102(a) (Molecular Distribution and enzyme content) should substantially improve the quality of products in distribution.

* This has not been done.

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SW

CFR Section Dating Period Summary of Change Description of Change Change to.

610.53(a)

Measles and Rubella Virus Vaccine, Live	Do
Measles Immune Globulin (Human)	Three years (5° C. three years)
Measles Smallpox Vaccine, Live	One year § 610.51 does not apply
Normal Horse Serum	Five years
Normal Serum Albumin (Human)	(a) Five years, provided labeling recommends storage between 2° and 10° C (5° C. three years), or (b) Three years, provided labeling recommends storage at room temperature, no warmer than 30° C. (5° C. three years), or (c) Ten years, if in an hermetically sealed metal container and provided labeling recommends storage between 2° and 10° C § 610.51 does not apply
Pertussis Immune Globulin (Human)	Three years from date the dried or frozen bulk product is placed in final solution (5° C. three years).
Pertussis Vaccine	Eighteen months (5° C., one year).
Plague Vaccine	Eighteen months (5° C., one year).
Plasma Protein Fraction (Human)	(a) Five years (5° C., one year) (b) Three years, provided labeling recommends storage at no warmer than 30° C. (5° C., one year).

Delete Measles Immune Globulin

Change the name in NSA, and temperature

Delete Pertussis Immune Globulin

Measles and Rubella Virus Vaccine Live	Do
Measles Immune Globulin (Human)	Three years (5° C. three years)
Measles Smallpox Vaccine, Live	One year § 610.51 does not apply
Normal Horse Serum	Five years
Normal Serum Albumin (Human)	(a) Five years, provided labeling recommends storage between 2 and 8° C (5° C. three years), or (b) Three years, provided labeling recommends storage at room temperature, no warmer than 30° C (5° C. three years), or (c) Ten years, if in an hermetically sealed metal container and provided labeling recommends storage between 2° and 10° C § 610.51, does not apply
Pertussis Immune Globulin (Human)	Three years from date dried or frozen bulk product is placed in final solution (5° C. three years)
Pertussis Vaccine	Eighteen months (5° C., one year)
Plague Vaccine	Eighteen months (5° C., one year)
Plasma Protein Fraction (Human)	(a) Five years (5° C., one year) (b) Three years, provided labeling recommends storage at no warmer than 30° C (5° C., one year)

Measles Immune Globulin should be deleted from this section (as is 610). In view of its well documented lack of efficacy, so should Pertussis Immune Globulin.

610.53 No change has been proposed in the dating periods for Albumin. However, a disconcerting dichotomy was noted during our review. No licensed manufacturer recommends storage between 2 and 10 °C, a recommendation that permits a 5-year dating period. All use labeling that permits storage at temperatures up to 37 °C. Studies carried out in BoB have indicated that a carefully prepared Albumin can be stored for 5 years at 5 °C with minimal change, (Note that 5 + 3 °C is 2 to 8 °C; we could find no basis for the "2 to 10 °C" specification or see why it should differ from the range indicated in 610.53(a).) By contrast, the studies of warm storage of Albumin carried out in BoB used a temperature of 32 °C. Reports of manufacturers' stability studies that are now underway suggest that storage near 37 °C may not be desirable. Changes in Albumin stored at such temperatures occur much faster than those in product stored near 4 or 5 °C.