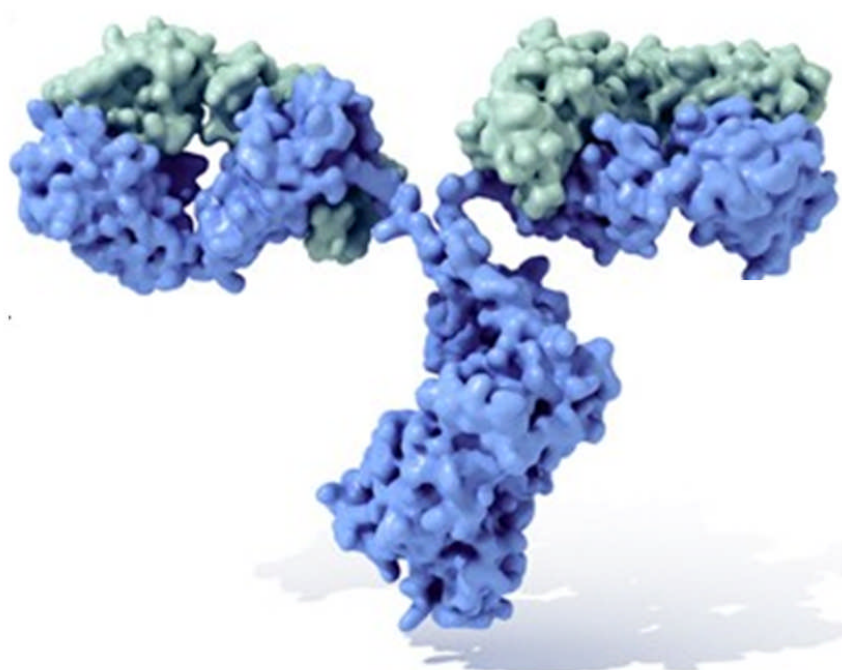


SAFETY AND EFFICACY OF IMMUNOGLOBULIN THERAPIES



**A GUIDE FOR USERS, ASSESSORS AND
FUNDERS**

ALBERT FARRUGIA





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Any opinions expressed in this Guide are the author's, and should not be ascribed to any organization.



TABLE OF CONTENTS

SECTION I:	Immunoglobulin therapy for immunodeficiency disorders	Page 6
SECTION II:	Licensing, regulation, and control of IG treatment products in Europe and North America	Page 28
SECTION III:	Establishing licensing, regulation, and control procedures in countries without well-established regulatory systems	Page 35
SECTION IV:	Evaluating IG treatment products	Page 41
SECTION V:	Conclusion	Page 48
APPENDICES		
	Appendix A: IG products available on world market	Page 49
	Appendix B: Model Product assessment questionnaire	Page 50
	Appendix C: Glossary	Page 57
	Appendix D: Bibliography of useful reviews on IG products and relevant regulatory documents	Page 61



INTRODUCTION

Within a national healthcare system, selection of immunoglobulin (IG) therapies for immunodeficiency disorders (IDs) is difficult. In well-resourced countries, regulatory agencies make key decisions regarding such therapies' quality and safety; such regulatory agencies, including the U.S. Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMA), are dedicated to assessing products and to granting marketing licenses. However, even in countries lacking resources to form such regulatory agencies, selection of IG therapies for IDs, within a national healthcare system, can occur. For such selection to occur, national regulatory authorities (NRAs) need to understand and to use several well-established principles; this guide offers such principles to NRAs and others who are responsible for selection of IG therapies for IDs, within their respective national healthcare systems. While this guide was written with IG therapies in mind, many of its principles apply to all plasma-derived medicinal products.

When produced from well-managed manufacturing processes, IG therapies are as safe as most other pharmaceuticals; however, it is important to ensure the safety of such therapies. Section I of this guide describes factors that contribute to the manufacture, safety, and efficacy of IG therapies and, in particular, provisions that ensure such therapies are free of pathogens. Regulatory systems to license, regulate, and control pharmaceutical medicinal products are well-established in Europe and North America; such systems may help some other countries form their respective systems. Section II of this guide summarizes, with comment, such systems. However, such systems are complex and, thus, may not be appropriate for all other countries forming respective systems. Section III provides guidance for NRAs in countries that lack well-established regulatory systems but want to ensure quality and safety of IG therapies. In particular, the section explores the use of distributors of imported products and the role of end-product testing by NRAs. Drawing on the principles in Sections I-III, Section IV offers a model for evaluating IG therapies to NRAs in countries that lack well-established regulatory systems. In particular, the section describes basic requirements for such therapies and example scenarios of therapy evaluations.



The appendices include materials to help NRAs assess therapies. Appendix A provides a link to a comprehensive country by country database of IG therapies. Appendix B is a model product assessment questionnaire that includes information necessary to assess therapies' quality and safety. Manufacturers should complete the questionnaire before beginning any therapy assessments. Acronyms and other language, used by NRAs, often are difficult to understand. Appendix C is a glossary that defines processes used in manufacture and control of IG therapies. Appendix D is a bibliography of useful reviews on IG therapies and relevant regulatory documents.

SECTION I

IMMUNOGLOBULIN (IG) THERAPY FOR IMMUNODEFICIENCY DISORDERS (IDs)

General introduction

Background of IG for IDs

Persons with some form of primary or secondary immunodeficiency have low or absent IG, resulting in a high risk of infections which, if not prevented or immediately treated, can lead to a severe and chronic illness. Those deficiencies involving the B lymphocytes are characterized by low or absent levels of antibodies. The identification of the globulin fraction of plasma, as the major antibody-containing component, together with the development of fractionation technology by Edwin Cohn in the 1940s, allowed the isolation of concentrated protein fractions rich in antibodies.

The earliest preparations were formulated at protein levels of around 15% and could be administered through intramuscular IG (IMIG). These were used to treat and prevent infections in otherwise healthy individuals. It was recognized that, compared to IMIG, intravenous (IV) IG (IVIG) can achieve a more rapid rise in antibody concentration. This required new technology to remove substances in the IVIG preparations that caused reactions.

The first PID patient described and treated suffered from agammaglobulinaemia, and was treated with a preparation which was administered subcutaneously. These early preparations frequently caused reactions due to bacterial contamination despite passing sterility tests. IMIG administration became state of the art and remained so for many years. The reactions accompanying IVIG administration were particularly severe and sometimes life-threatening in patients with PID. However, the amount of antibody which could be delivered intramuscularly was limited and patients still experienced infections and chronic lung injury.

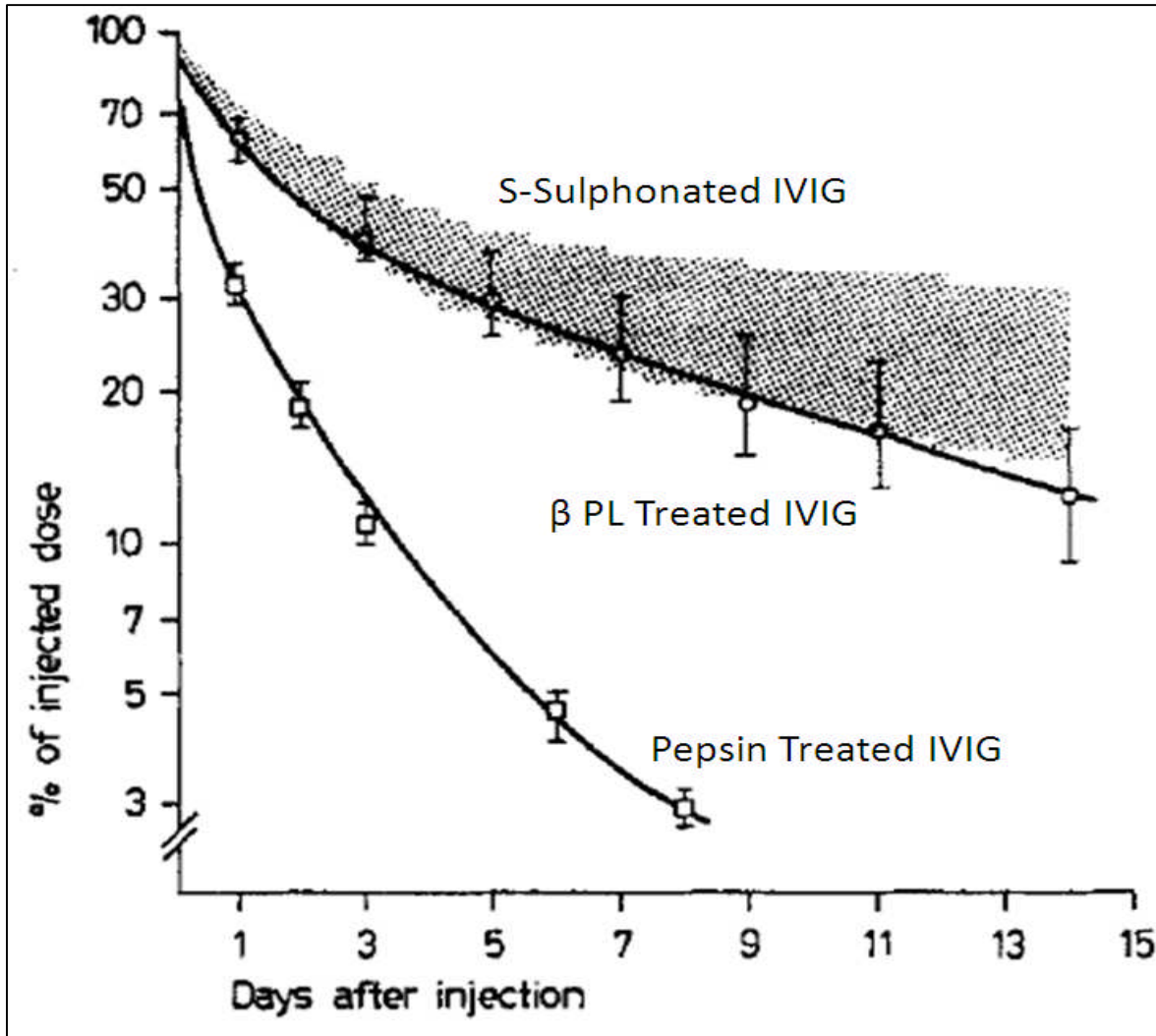


Figure 1. Fate of injected IVIG treated to remove aggregates. These early preparations were modified in ways that decreased their lifetime in the body after infusion.

As the pathology of these reactions was studied, it became apparent that concentrates of IG prepared by alcohol fractionation of plasma included aggregates of immunoglobulin G (IgG) in the product. Early studies, in which aggregates were removed, showed that patients given IVIG had significantly fewer acute and chronic infections. This spurred the plasma fractionators to introduce modifications to their manufacturing schemes so as to minimize the generation of IgG aggregates during production. This was achieved initially, by chemical processes which decreased the effectiveness and/or the survival of the administered IgG in the body (**Figure 1**).



With time, the current generation of IVIG products was developed which all have excellent effectiveness and biological properties. The ability to deliver large amounts of IgG intravenously has seen IG products being used to modulate the immune system in various neurological, haematological and inflammatory states. This has contributed to IVIG's ascendancy as the currently most economically important plasma protein therapy. Interestingly, the history of IG supplementation therapy in the IG has gone full circle with the use of new preparations of SCIG which have the capacity to deliver steady levels of therapeutic IgG with minimal side reactions in a home therapy environment.

Purpose of this section

The availability of concentrated solutions of IgG in a number of formats has given patients with IDs an enhanced and prolonged life (**Figure 2**). Therefore, assurance regarding the safety, quality, and efficacy of these products is important for patients, prescribers, NRAs, and funders of these therapies. While such an assurance is implicit for the products supplied under the oversight of NRAs in North America, Europe, Australia, and New Zealand, the criteria used by these agencies are not always apparent to end users of these products.

Furthermore, patients in countries with incomplete regulatory provisions, as well as NRAs that are charged with providing therapies in such countries, would benefit from an awareness of the principles involved in assuring the safety, quality, and efficacy of IgG therapies.

This work will therefore outline the issues around the manufacture of IgG therapies that are important in assuring safety, quality, and efficacy. It is hoped that this will enhance the understanding of all end-users of these products. It is also the purpose of this work to provide guidance for decision-makers so as to ensure that products purchased for patients with IDs will reflect best-practice standards.

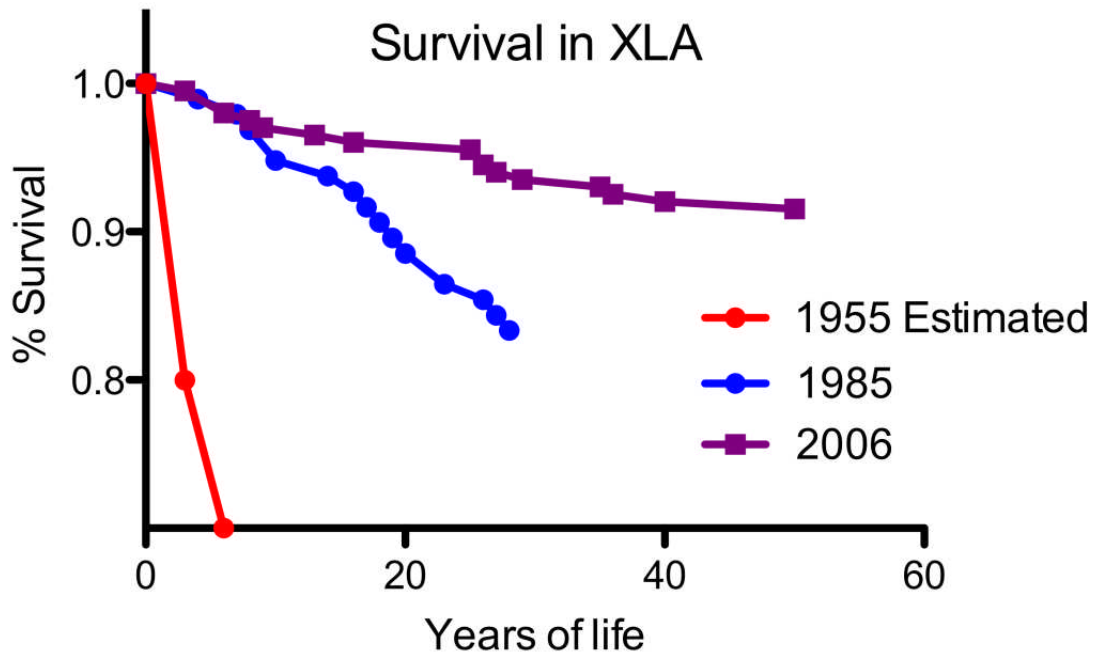


Figure 2. Survival in patients with X-linked agammaglobulinemia (XLA). Increased availability of IgG products increases patient life span. (Source: Presentation by Dr Jordan Orange, PPTA Plasma Forum, June 2010)

IgG products – manufacture, safety and efficacy

IgG products are biologics

Medicinal therapies are broadly categorized as *pharmaceuticals* and *biologics*. Both types are generally composed of a molecule – the *active ingredient* (AI), which is responsible for the therapeutic action – and a number of *additives* or *excipients* which have no therapeutic action but are included in order to assist stability, solubility, etc., of the AI. In pharmaceuticals, the AI is derived from chemical synthesis using fully specified ingredients, to result in molecules that are generally small and well-characterized. These constitute the majority of drugs in medical practice.

In biologics, the AI is derived from a biological source (e.g., blood, tissue, cell culture, etc.). Biological AIs are isolated using complex processes that can have important effects on the properties of the AI. For example, the isolation of

coagulation factor IX, used to treat hemophilia B, can lead to activation of the factor IX molecule, making it thrombogenic and leading to serious side effects [1]. Albumin, isolated by certain fractionation techniques, can lose its capacity to bind drugs [2]. These changes can ensue from relatively small variations in the manufacturing process. For this reason, biologics can seldom be considered as *generic drugs*. This means that the AI produced by one manufacturer's technique cannot be considered equivalent, in its safety and efficacy, to the same AI produced by another manufacturer. Not only the AI, but also the excipients and impurities, can vary between the same biologic produced by different manufacturers, leading to different safety and efficacy profiles. For example, different brands of albumin products are associated with different incidences of adverse hypotensive reactions, as a result of different levels of impurities [3].

All IgG products are different

All the features described above for biologics are shown by IG therapies manufactured for treating IDs. While all the IgG therapies approved by the major regulatory agencies for marketing are safe and efficacious, different products show differences in relative efficacy in different patients and different adverse event profiles. This was even more marked in the products preceding the current generation of products, which have been on the market for the past five to ten years. Many of these differences ensued from the different extent to which the IgG molecule was altered as a result of measures introduced to decrease aggregates. Use of enzymes such as pepsin resulted in fragmentation of IG, which led to decreased IG survival in the body. While this issue has been resolved and such products are no longer available in the regulated markets, other aspects are also important. *Renal failure* is a rare adverse effect of IgG therapy, especially in patients with pre-existing renal disease. The majority of patients affected have received large amounts of products containing the excipient sucrose and have not been patients

¹ Gray E, Tubbs J, Thomas S, Oates A, Boisclair M, Kemball-Cook G, Barrowcliffe TW. Measurement of activated factor IX in factor IX concentrates: correlation with in vivo thrombogenicity. *J Thromb Haemost* 1995; **73(4)**: 675-9

²Klammt S, Brinkmann B, Mitzner S, Munzert E, Loock J, Stange J, Emmrich J, Liebe S. Albumin binding capacity (ABiC) is reduced in commercially available human serum albumin preparations with stabilizers. *Z Gastroenterol* 2001; **39 (Suppl 2)**: 24-7

³Che Y, Wilson FJ, Bertolini J, Schiff P, Maher DW. Impact of manufacturing improvements on clinical safety of albumin: Australian pharmacovigilance data for 1988-2005. *Crit Care Resusc* 2006; **8**: 334-8

with IDs. *Cardiovascular complications* such as deep venous thrombosis and pulmonary embolism have been reported, possibly associated with rapid infusion of highly concentrated and viscous products. **Figure 3** summarizes the adverse effects of IgG therapy. It must be emphasized that (1) such effects are rare and (2) they generally occur in patients at risk of the specific conditions precipitated by the events, e.g. patients at risk of renal or thrombotic disease. Therefore, knowledge of the particular features of each preparation that might precipitate these events in patients at risk, such as the type of excipient and the protein concentration, is important for treating clinicians so as to be able to choose the most appropriate therapy. This kind of information is included on: www.ipopi.org

Adverse Event	Examples
Infusion Reactions	<p>Non-anaphylactic: headache, chills, low-grade fever, flushing, back or abdominal pain, nausea, myalgias, hypotension. Associated with release of TNF and/or PAF.</p> <p>Anaphylactic: flushing, swelling, dyspnea, hypotension, nausea, vomiting, vascular collapse and rarely death. Associated with IgA deficiency and either IgG or IgE antibodies against IgA</p>
Vascular Events	<p>Congestive heart failure</p> <p>Thromboembolic events</p>
Renal failure: oliguric renal failure with high sucrose preparations. On biopsy renal tubular epithelial cells are swollen and contain vacuoles	
Aseptic meningitis	
Hematologic events	<p>Hemolytic anemia</p> <p>Neutropenia</p>
Pulmonary edema and transfusion-related acute lung injury	
Infections	<p>Hepatitis C</p> <p>Parvovirus B19</p>
Skin rash	
<p>PAF = Platelet activating factor</p> <p>TNF = Tumor necrosis factor</p>	

Figure 3. Adverse events as a result of IgG therapy

Efficacy aspects

Different IgG products have been reported to have varying capacities to generate therapeutic effects in certain conditions. As discussed above, some of the early measures used to eliminate harmful aggregates also resulted in shorter IgG survival times in the body. This would lead to a lower capacity to protect against infections in PID patients. Succeeding generations of IgG from one manufacturer have been shown to be better in preventing sinopulmonary infections in PID [4]. In patients given IVIG to treat idiopathic thrombocytopenic purpura (ITP) [5] and Kawasaki Disease [6] products differing in their manufacturing technologies had different efficacy profiles.

Therefore, in choosing the IgG product best suited for a particular patient's needs, both patient and prescriber have to be aware of the features of IgG products that may have a bearing on the safety and efficacy aspects reviewed above. These include the excipients, aggregate levels, IgG fragmentation, viral inactivation, methods and other features [7].

Pathogen safety

Overview of IG safety

The safety of plasma products from the transmission of blood-borne infectious agents is discussed in detail later. What follows is an overview of this aspect of IG safety.

Chronic recipients of plasma products are at risk of infection from blood-borne pathogens as a result of the inevitable exposure to agents that will contaminate a plasma pool made of thousands of donors. This risk will depend on the extent to

⁴ Roifman CM, Schroeder H, Berger M, Sorensen R, Ballow M, Buckley RH, Gewurz A, Korenblat P, Sussman G, Lemm G Comparison of the efficacy of IGIV-C, 10% caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency. A randomized double-blind trial. *Int Immunopharmacol* 2003; **3(9)**: 1325-33

⁵ Angiolillo, A.L. (2002), Comparison of Different IGIV Preparations in the Normalization of Platelet Counts in ITP, Poster session presented at the 44th American Society of Hematology Annual Meeting, Philadelphia, PA

⁶ Tsai MH, Huang YC, Yen YH, Li CC, Chiu CH, Lin PY, Lin TY, Chang LY. Clinical Responses of Patients with Kawasaki Disease to Different Brands of Intravenous Immunoglobulin. *J Pediatrics* 2006; **148**: 38-43

⁷ Radosevich M, Burnouf T. Intravenous immunoglobulin G: trends in production methods, quality control and quality assurance. *Vox Sang* 2010; **98(1)**: 12-28

which the infectious agent will be found in the plasma pool – its *prevalence* in the donor population. This will be decreased by testing plasma donations for the agent but is unlikely to be fully removed in this way, as tests have limited sensitivity and are not always able to detect the early phase of an infection (the “*window period*”).

Exposure will also depend on the frequency of treatment, with a higher probability of infection with more frequent treatment. These various factors are analysed by Lynch et al [8] and are summarized diagrammatically in **Figure 4**.

No of donors	No of independent infusions					
	1		10		100	
	Prevalence 1/500K	1/50K	Prevalence 1/500K	1/50K	Prevalence 1/500K	1/50K
60 K	11%	70%	70%	100%	100%	100%
25 K	5%	39%	39%	99%	99%	100%
10 K	2%	18%	18%	86%	86%	100%
2.5 K	0.5%	5%	5%	39%	39%	99%
0.6 K	0.1%	1%	1%	11%	11%	70%
0.1 K	0.02%	2%	0.2%	2%	2%	18%

Figure 4. Effect of pool size, disease prevalence, and dosage on the risk of infection by an unscrined agent

Clearly, frequent recipients of IG are at a high risk of infection on this basis. They are infused frequently with products which, in order to have an antibody composition which can protect them from most infections, have to be made from pools containing up to 60,000 individual donations [9]. Yet IG products have, with some rare

⁸ Lynch TJ, Weinstein MJ, Tankersley DL, Fratantoni JC, Finlayson JS. Considerations of pool size in the manufacture of plasma derivatives. *Transfusion* 1996; **36(9)**: 770-5
⁹ Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson RP Jr, Patel DD, Secord E, Sorensen RU, Wasserman RL, Cunningham-Rundles C; Use of intravenous immunoglobulin in human disease: a review of evidence by members of the



exceptions, been historically safe from transmitting pathogens. The earliest products of plasma fractionation included albumin and fibrinogen and transmitted hepatitis. Albumin was made safe by heating in the late 1940s and has not transmitted hepatitis since. Fibrinogen was withdrawn because of safety concerns and has recently been introduced now that technological advances allow it to be subject to viral inactivation. The products developed to treat hemophiliacs transmitted infections until the mid 1980s when procedures to inactivate viruses made them safe. IG products started to be used to treat immunodeficiency in the 1950s, and the products used for the first twenty years, in IM and SC formats, did not transmit the infections that were present in plasma at this time and that infected the hemophilia community. Retrospectively, this is known to have been mostly due to the Cohn fractionation process's capacity to (fortuitously) steer pathogens away from the therapeutic IG fraction into other fractions that were not harvested. Therefore, despite the absence of viral inactivation steps in the manufacture, these products were safe.

With the introduction of IVIG products in the 1970s, a number of products were shown to transmit hepatitis C (HCV). As discussed above, in order to make IG products suitable for IV administration, modifications were introduced to Cohn's original fractionation scheme, some of which may have affected its capacity to steer viruses away from the product. In 1994, a widely reported outbreak of HCV was linked to the removal of antibodies to the virus in the plasma pool as a result of the introduction of HCV antibody testing in blood and plasma donors.

Complexes of the antibody and the virus were shown to be more likely to be removed through fractionation, and the removal of the antibody allowed some virus to escape into the therapeutic fraction. Over the 1990s, robust viral inactivation steps were introduced into the manufacture of all IG products leading to the current generation of products with an important viral safety record. Importantly, the IG purification schemes have been shown to remove prions from the therapeutic IG

fraction, and IG products from plasma pools including donations from donors who subsequently died of prion disease have not infected patients.

Pathogen safety of plasma products

Because PID treatment products are sourced from human blood, it is very important to ensure that products being considered for use are safe and free from infection from blood-borne pathogens. Following the development of sterile methods of manufacture, bacterial contamination of the plasma raw material was no longer a concern. Therefore, until recently (see Prions below), the transmission of blood-borne viruses has been the focus of preventive measures. Since the 1980s, manufacturers and government agencies have responded to concerns about transmission of blood-borne viruses by developing a comprehensive set of measures designed to reduce, if not eliminate, infectious risk. These measures are based on the following principles (**Figure 5**):

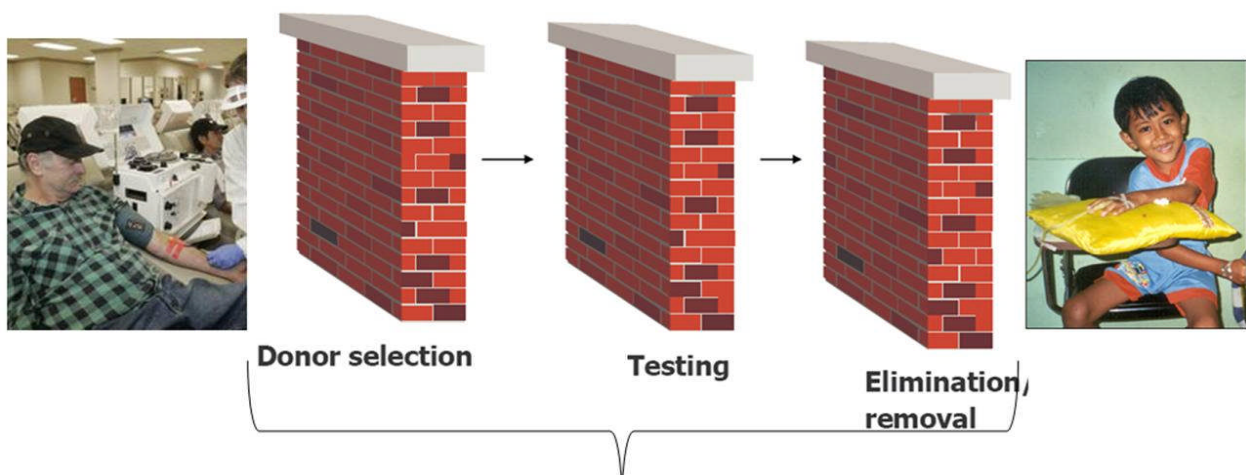


Figure 5. From donor to patient – the layers of safety of plasma therapies

- 1) Selection of appropriate blood and plasma donors
- 2) Screening of the plasma raw material with laboratory tests
- 3) Elimination of any contaminating viruses through the manufacturing process

Of these three principles, the elimination of viruses through the manufacturing process is the most important. In products such as hemophilia treatment products, transmission of viruses continued to occur after the introduction of selection and



testing procedures because these were not sufficiently sensitive to exclude all infected donations, which then went on to contaminate the large plasma pools used to make these products. Conversely, when new viruses got into the blood supply before scientific knowledge was sufficient to develop selection and screening methods, inactivation procedures ensured that patients were not infected. This happened with West Nile Virus (WNV), which infected the recipients of blood transfusions but did not infect any recipients of plasma products. As discussed in the General Introduction to this section, IG products have generally been safe from viral transmission because of the fortuitous capacity of the manufacturing process to steer viruses away from the therapeutic product. The transmission of HCV in some preparations has now been obviated by the development of validated manufacturing steps that are dedicated to the inactivation and removal of infectious agents.

These principles are executed through the following principles:

- Selection procedures that ensure that donors with high-risk behavior are excluded
- Mandatory serological testing on all plasma donations for HIV, hepatitis B (HBV), and HCV
- Plasma inventory hold and exclusion based on post-donation information
- Nucleic acid testing (NAT) of minipools for HCV-RNA (and increasingly for other viruses including HIV, HBV, human parvovirus (B19), and hepatitis A (HAV) and exclusion of reactive donations
- Testing start-manufacturing plasma pool samples for viral markers and viral genomic material
- Inclusion of validated specific viral inactivation and/or removal steps in the manufacturing process
- Full traceability of plasma from donors to end products

In addition, some agencies and manufacturers also test finished products for viral markers and genomic material. The merit of this as a measure of the safety of IG products is discussed in detail later on in this document.



The combination of appropriate donor selection procedures, screening with the current generation of standard serological tests, and, in particular, the inclusion of measures to inactivate or remove viruses has made fractionated plasma products free from serious known blood-borne viruses such as HIV, HBV and HCV. Fractionated plasma products manufactured by today's processes, and manufactured with attention to good manufacturing practices (GMPs), are among the lowest risk therapeutic products in use today.

Donors: Selection

Donor selection procedures are designed to identify and exclude donors at risk of being infected with viruses that can be transmitted by blood transfusion. In developed countries, donor selection procedures have reached a high level of sophistication and complexity, and regulators have included these procedures in their assessments of overall safety of material used to manufacture plasma products.

Exclusion criteria for donors used in different regulatory climates include:

- History of blood-borne infections
- IV drug use
- High risk sexual behaviour (male-to-male sex, prostitution)
- Having received blood, tissues, etc.
- Risky behavior (tattoos, piercing, etc.)
- Medical procedures, such as certain illnesses, surgery, etc.

Like all the measures described in this guide, the ability of different countries to implement these measures may vary. Each regulatory authority must assess a country's local needs before mandating specific measures.

Donors: Screening

Individual donations of blood are screened to ensure that blood-borne viruses do not enter the plasma pool. Screening is currently available for HBV, HCV, and HIV. All plasma donations should be tested for these three viruses.

Tests for detecting viral infection through the immune response of the donor are limited as there is a “window period” before the body’s immune response generates sufficient levels of the immunological marker. During this period, the donor is infectious, but the infection is undetectable. In HBV infection, the serological marker detected in traditional blood screening is an antigen (HbsAg) associated with the virus, rather than an indicator of the immune response, but the “window period” still exists. With NAT, this period is shortened by the detection of the viral genome, which appears in the blood before the immunological markers. The recent introduction of NAT has decreased the viral load of plasma pools and therefore increases the margin of safety should viral reduction procedures break down. However, it is very expensive and, given the effectiveness of viral reduction procedures, it is not an essential requirement.

Table 1: Donor screening tests for blood-borne viruses

TEST	RECOMMENDED	MANDATORY
Anti-HIV	Yes	Yes
Anti-HCV	Yes	Yes
HbsAg (HBV)	Yes	Yes
HIV RNA ¹⁰ (NAT)	Yes	No
HCV RNA (NAT)	Yes	No
HBV DNA ¹⁰	Yes	No
B19 DNA	Yes	No
HAV RNA	Yes	No



Plasma: *Quality*

Factors that have an impact on plasma quality and safety include:

- 1) Plasma handling factors such as separation, storage, and transport, which also depend on the methods used for collecting plasma (*recovered* from whole blood or obtained by *plasmapheresis*)
- 2) Donor epidemiology (viral infection, prion disease)
- 3) Donor selection and testing procedures (including NAT) to reduce the window period for infection with different viruses

All these factors affect the safety of fractionated plasma products with respect to transmissible infectious agents. They also affect the yield and specific activity of products.

Plasma: *Types*

Recovered plasma is a by-product of whole blood donated for transfusion of labile components in blood banks. *Source plasma* is collected from donors in plasma collection centers, most of which, in the U.S. and Europe, are owned by the fractionation companies, through a process known as plasmapheresis, which removes only the donor's plasma. When collected and processed with steps that exclude and inactivate or eliminate enveloped viruses (HIV, HCV, and HBV), both recovered and source plasma have the same level of viral safety in the derived products.

In the past, before the introduction of regulation in the blood sector, plasma for fractionation from paid donors was considered to be of higher risk of viral infection than plasma from voluntary donors drawn from the same population. However, nowadays, in the developed blood systems of North America and Europe, this is no longer the case. This is the result of the strict regulatory regimens found in these areas and the introduction of similarly strict industry standards. The inclusion of NAT for plasma fractionation in these systems has greatly reduced the viral load for HIV and HCV for all donor types. ***This equivalence in safety is not necessarily the***

¹⁰ DNA = Deoxyribonucleic Acid; RNA = Ribonucleic Acid. These constitute the essential elements of the genetic code.



case in other donor populations, and NRAs need to assess each plasma source for the safety factors described in this guide, whether it is from paid or unpaid donors.

The incorporation of viral reduction steps inactivates or removes this low viral load with equal efficacy for both recovered and source plasma. Furthermore, the introduction of measures by the source plasma industry (which is mostly drawn from paid donors), such as inventory hold and donor qualification, has made this plasma, in terms of its safety as a raw material, potentially safer than plasma recovered from whole blood for which many of these measures are not possible.

Different plasma sources have to be assessed individually and evaluated in relation to the whole range of safety measures outlined in this guide. It is known that in certain source plasma donor populations in developing countries, the risk from paid donors is high and may be higher than that from unpaid donors, although data to assess this is incomplete. Essentially, NRAs need to assess each plasma source on all its merits.

Inventory hold

Inventory hold is the holding of plasma in (frozen) storage before it is processed into products. The use of inventory hold pending qualification of plasma donors through re-testing further enhances safety and is an attractive feature. It is not mandated for plasma for manufacture by NRAs but is a feature of the industry standards overseen by the Plasma Protein Therapeutics Association (PPTA). This measure is generally only possible for source plasma, as the fresh components recovered from whole blood together with recovered plasma have short shelf lives and would expire during plasma inventory hold. Despite this, inventory hold is a feature of some systems producing recovered plasma for transfusion. Apheresis donors can donate more frequently, which may result in more donations during the infectious “window period,” and final qualification of the donor through testing (e.g., NAT, retesting) beyond the serological window is important. The particular features of an inventory hold vary across the organizations that practice it. It is most effective when donations that are not retested are not used, whether the donor returns or not. This is not always the

case, and the particular features of a plasma supplier's inventory hold should be kept in mind in assessing the relative safety merits of paid and unpaid plasma sources.

Ensuring the safety of raw materials

Donor selection procedures that exclude high-risk donors, combined with serological screening of plasma donations, are the mainstays of ensuring safe raw material for the fractionation process. The safety of the raw material can only be ensured by the fractionator through the use of suppliers that exclude high-risk donors and use good quality viral screening tests. Further guidance on how NRAs can make certain of the safety of raw material used for blood products is provided in Sections II, III, and IV. Some fractionators may purchase plasma from the open or so-called "spot" plasma market, rather than obtain it from their own centres or from centres subscribing to their own standards. ***The use of such "spot" plasma will not be subject to the same level of safety and regulatory control as the use of plasma from well-accredited centers, and NRAs should not consider using products manufactured from this type of plasma.***

Viruses: Viral reduction processes

There are two types of viral reduction processes: inactivation (viral kill) and removal of virus through purification of protein. Viral elimination procedures in the manufacturing process are essential, although the fortuitous viral clearance capacity of the Cohn fractionation system has contributed greatly to the safety of IG treatment products before dedicated steps were available. While all the components of the blood safety chain described in this guide are required for product safety, manufacturing processes can have an especially significant role. For example, IG treatment products did not transmit HIV, despite the undoubted presence of this virus before the introduction of current-generation serology and NAT testing. This was because of the manufacturing process's capacity to clear the virus from the therapeutic fraction. Conversely, the introduction of HCV testing had the effect, in some products, of causing free virus to be steered into the therapeutic fraction through the elimination of immune complex formation with HCV antibodies. This led to HCV transmission by these IG products, which were not protected by dedicated viral inactivation steps. NRAs tasked with assessing which measures are essential



for ensuring safe products – as opposed to those which, while enhancing safety, are not essential – need to keep in mind the features of plasma derivatives, such as IG products, relative to the hospital products of mainstream blood banking. What is necessary for transfusion products is not necessarily required for IG products, as is the case, for example, for WNV testing. Conversely, measures introduced for protecting transfusion recipients are not necessarily beneficial for IG recipients.

While donor selection and screening of donations, combined with appropriate NAT testing (and inventory hold where it can be achieved), have significantly reduced the risk of blood-borne viruses entering the fractionation pool, we must presume that any plasma pool for fractionation may contain levels of virus capable of transmitting infection. The inclusion, in the fractionation process, of one or more steps with validated capability to inactivate and/or remove relevant viruses, results in plasma products that are essentially free from risk of these viruses. However, current inactivation and removal processes are less effective for non-enveloped viruses (mainly HAV and B19, and the concern also can be extended to “unknown” viruses and infectious agents. IG products, containing as they do high levels of antibodies against viruses found in the normal population, such as HAV and B19, are generally safe and, in fact, therapeutically useful for treating these infections. With emerging viruses and other unknown agents, less certainty is possible, although the fractionation process’s robust capacity to clear agents is a significant safety factor.

There are a number of different viral reduction methods available for IG products. The advantages and limitations of these are outlined in **Table 2**.

Table 2: Advantages and other points worth considering for selecting viral reduction treatments of IG products

TREATMENT	ADVANTAGES	POINTS TO CONSIDER
Solvent-detergent	<ul style="list-style-type: none"> Extremely efficient against enveloped viruses, e.g., HIV, HCV, HBV Relatively simple equipment Non-denaturing effect on proteins High recovery of protein functional activity 	<ul style="list-style-type: none"> Requires a subsequent manufacturing step to eliminate the solvent-detergent agents Bench mark method for the elimination of enveloped viruses, i.e., HIV, HCV, HBV Not effective against non-enveloped viruses, e.g., B19, HAV
Pasteurization	<ul style="list-style-type: none"> Potential to inactivate enveloped and non-lipid enveloped viruses, including HAV Relatively simple equipment 	<ul style="list-style-type: none"> Protein stabilizers may protect viruses Does not inactivate B19
Nanofiltration	<ul style="list-style-type: none"> Elimination of viruses based on size-exclusion effect Eliminates all major viruses including HAV and B19 May possibly eliminate prions Filter's integrity and removal capacity is validated after use High recovery of protein activity Non-denaturing for proteins Risks of downstream contamination are limited when filtration is performed prior to aseptic filling Filters are commercially available; no royalties 	<ul style="list-style-type: none"> Sensitive to conditions used for filtration
Low pH treatment	<ul style="list-style-type: none"> Introduced in process or as final incubation prior to product release May be combined with enzymatic treatment 	<ul style="list-style-type: none"> Effective against some but not all model viruses On its own, cannot be viewed as providing full assurance of safety Useful in combination with other steps

Adapted from: Ala F, Burnouf T, El Nagueh M. *Plasma Fractionation Programmes for Developing Countries*, WHO Regional Publications, Eastern Mediterranean Series, No. 22, 1999; Burnouf T, Radosevich M. Reducing the risk of infection from plasma products; specific preventative strategies. *Blood Reviews* 2000; **14**: 94-110

Failures in testing, processing, or critical quality systems are more likely to result in the release of a batch of product with increased risk of infection than any fundamental deficiency in process design or competence. Failure in adherence to

GMPs is thought to be the reason for some cases of HCV transmission by IG products in the 1980s [11]. **Because of the importance of viral elimination in the ultimate safety of plasma products, there is no room for failure in the process steps upon which viral elimination depends.** Process validation, and those systems at the heart of good manufacturing practices – traceability, segregation of product manufacturing steps to avoid cross-contamination, training, documentation, change control, deviation reporting – are the keys to the reliable manufacture of safe, effective plasma products.

Viruses: Non-enveloped viruses

Current viral inactivation and/or removal steps are effective for enveloped viruses but less effective for non-enveloped viruses. While some viral elimination steps, notably nanofiltration, have been shown to offer at least a partial reduction of the viral burden from non-enveloped viruses during product manufacture, other strategies, particularly vaccination when possible (for HAV, for example) of people receiving plasma concentrates on a lifelong basis, should be used. For known non-enveloped viruses, several manufacturers have established schemes involving limited testing of the plasma pool using NAT, in which a maximum level of viral contamination, rather than an absolute elimination, is the aim. In the absence of validated viral reduction in-process steps, this offers probably the current best general approach for reducing the viral burden of the plasma pool and, therefore, for reducing the transmission potential for viruses tested using this methodology. It should be mentioned that the only non-enveloped viruses that, so far, have infected plasma product recipients are HAV and B19. One controversial report has claimed B19 transmission by an IG product [12], but the high content of HAV and B19 antibodies in IG products, as well as their use in treating these infections, urges strongly for the safety of IG products from the transmission of these viruses.

¹¹ Ochs HD, Fisher SH, Virant FS, Lee ML, Kingdon HS, Wedgwood RJ. Non-A, Non-B hepatitis and intravenous immunoglobulin. *Lancet* 1985; 404-5

¹² Hayakawa F, Imada K, Towatari M, Saito H. Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin. *Br J Haematol* 2002; **118(4)**: 1187-9

Prions and variant Creutzfeldt-Jakob disease (vCJD)

Prions are proteins that are found in normal individuals that, in certain conditions, assume infectious and abnormal structures that can cause disease. Diseases caused by these abnormal prions are called transmissible spongiform encephalopathies (TSEs) and affect a number of animals including sheep and cows. A number of human TSEs have been described that have genetic or infectious bases. One of these is vCJD, which has mostly affected people who have consumed beef from cows infected with another TSE called bovine spongiform encephalopathy (BSE). vCJD is transmitted by blood transfusion in animal models and in four people in the UK who received blood from donors who died from vCJD.

Currently, there is no test available that can be used to screen blood for the infective vCJD prion. The only way to minimize the risk through blood transfusion has been through the exclusion of at-risk donors. At the moment, the only established risk factor is residence in countries that have had bovine spongiform encephalopathy (BSE) in the cattle population, notably the U.K. and France. Because of the high number of BSE cases, the U.K. has stopped using its plasma for the production of plasma derivatives, and many other countries have defined U.K. residence as a criterion for excluding blood and plasma donation. North American NRAs have also excluded donors who have resided in some parts of Europe.

NRAs faced with making a decision on excluding donors at risk of vCJD need to assess carefully the effect of such deferral measures on the overall blood supply. In many developing countries, blood is in short supply, and these countries cannot afford to lose donors because of possible vCJD risk. Also, in areas of high prevalence for other more established risks, such as HIV and HCV infection, the deferral of well-accredited repeat donors because of possible vCJD risk may mean that new donors with a higher prevalence of these established infections are used instead. New donors always have higher viral marker rates than repeat donors, and NRAs in developing countries, where selection and screening procedures may not be optimized, need to ensure that unproven risks are not replaced by real ones.

In addition, the processes listed in **Table 2** are mostly ineffective in killing prions, with the notable exception of nanofiltration, which has been shown to remove prion

infectivity from plasma products. However, the manufacturing methods used for the production of many plasma products fortuitously remove the infective prion as a result of the protein purification, a process called prion clearance. It is especially encouraging that the manufacture of IG products on the market in North America and Europe has been shown to include particularly effective prion clearance steps. This may be why a patient known to have received IVIG from plasma including donations from a donor who died from vCJD did not show any evidence of infection when investigated after death from non-vCJD related causes [13], whereas a patient with hemophilia given product derived from a similar source was found to have infective prion after he died [14]. In this instance, the hemophilia product is known to have been manufactured using a process with minimal prion clearance.

Conclusions

Since the 1980s, various measures have been introduced to reduce the risk of viral transmission by fractionated plasma products. Not all practices are considered as mandatory standards by regulatory agencies, and their use by different fractionators must be assessed in the overall context of safety, availability, and cost. For example, donor source is rarely significant for the safety of plasma products, but other practices, such as NAT to narrow the “window period” and inventory hold, reduce the risk of infectious units being pooled. Some measures may have only limited benefits for users of IG products and may possibly affect the yield and financial viability of fractionation processes. For example, limiting donor pool size can reduce the risk of viral transmission, but probably only for infrequent users of plasma products (**Figure 4**), and cannot be implemented for IG products without affecting the content of therapeutically crucial antibodies. These possibilities must be kept in mind when making decisions about purchasing products.

Donor selection procedures that exclude high-risk donors and serological screening of plasma donations are the mainstays of ensuring safe raw material for the

¹³ El-Shanawany T et al. A recipient of immunoglobulin from a donor who developed vCJD. *Vox Sanguinis* (2009) 96 , 270

¹⁴ *vCJD risk assessment calculations for a patient with multiple routes of exposure*. Department of Health, 9 June 2009.

fractionation process. However, it is in-process inactivation and clearance of pathogens that has had the most profound impact on the safety of fractionated plasma products. Even allowing for limited effectiveness against non-lipid enveloped viruses (for which NAT may be used to limit plasma pool viral burden), in-process viral inactivation or clearance has made the risks of receiving an infected product extremely low – assuming adherence to validated process conditions. Establishment and maintenance of GMPs and licence-compliant (*i.e.*, validated) conditions are critical to eliminating these areas of risk.

Summary

- Fractionated plasma products have a history of transmitting blood-borne viruses (HBV, HCV, and HIV).
- Plasma products manufactured by today's processes and with attention to GMPs rank among the lowest risk therapeutic products in use today.
- Product safety is the result of efforts in several areas:
 - Improved donor selection (exclusion of at-risk donors)
 - Improved screening tests of donations (including NAT)
 - Type and number of in-process viral inactivation and/or removal steps***Of these, in-process viral inactivation is the single largest contributor to product safety.***
- The inclusion, in the fractionation process, of one or more steps with validated capability to inactivate or remove relevant viruses, primarily enveloped viruses (HIV, HBV, and HCV), results in plasma products that are essentially free from risk of these viruses. Inactivation and removal processes are less effective for non-enveloped viruses (mainly HAV and B19).



- Currently, there are no screening tests for vCJD or established manufacturing steps to inactivate the agent. vCJD in the U.K. donor population made it necessary to exclude plasma for fractionation from U.K. donors and has led to exclusion of perceived at-risk donors from other donor populations. The processes used to manufacture IG treatment products have been shown to clear the infective vCJD from the product, and the risk for patients with PID receiving IG products is very low.

SECTION II

LICENSING, REGULATION, AND CONTROL OF IG TREATMENT PRODUCTS IN EUROPE AND NORTH AMERICA

Introduction

Arrangements for the licensing, regulation, and control of medicinal products have been developed and formalized to ensure that the risk-to-benefit relationship, which is involved in any medical intervention, may be optimized to assure patient safety.

The responsibilities of NRAs under such arrangements include:

- Establishing and maintaining a system of licensing and control, including
 - Dossier review and pre-approval inspection
 - Facility and product registration
 - Facility and product inspection and enforcement
- Providing standards and guidelines
- Requiring that licence holders adopt and maintain appropriate quality systems
- Providing arrangements for post-marketing surveillance of products

Regulatory systems in Europe and North America are highly evolved and very complex and are beyond the capacity of most healthcare systems in developing countries with limited resources. However, it is beneficial if NRAs in developing countries are aware of the approaches used by the main regulatory agencies, which may help them to develop their own framework for assessing and choosing IG treatment products. The approaches of the FDA and the EMA are outlined in this section, along with other approaches aimed at harmonization.

Regulations, guidelines, and directives

FDA

The FDA is the largest regulatory body, with wide responsibilities for assuring the quality of foodstuffs, medicines, and medical devices manufactured for sale and supply in the U.S. Regulations to be observed in the manufacture and supply of



pharmaceuticals are defined in Title 21 of the Code of Federal Regulations (21 CFR) and in sections 1-999 of the United States Pharmacopoeia (USP). The parts of 21 CFR with specific relevance to plasma products are:

- Parts 210 and 211, which describe current GMPs (cGMPs) [15]
- Parts 600 to 680, which set out the requirements for biological products [16]

Additional guidance (distinct from regulations) is provided to manufacturers (and inspectors) in a range of paper and web-based publications [17], including:

- FDA draft guidelines
- FDA inspection guides
- USP sections 1000 *et seq.*

Biologics, including plasma products, are presently overseen by the Center for Biologics Evaluation and Research (CBER), with the following broad areas of oversight:

- Regulatory oversight, which addresses all aspects of licensing and enforcement
- Product evaluation and research, including standardization
- Acquisition and evaluation of new information, including surveillance

EMA

Regulatory provisions in Europe are defined through a comprehensive set of “directives,” published by the European Union (EU) and through the European Pharmacopoeia (EP), published by the Council of Europe (CoE) – an entity with wider membership than the EU. Individual member states of the EU are required to incorporate EU directives into national legislation for implementation. The key

¹⁵ Available from http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr210_01.html and http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr211_01.html

¹⁶ Available from http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfrv7_01.html

¹⁷ Many of the FDA’s blood-related documents are accessible at: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/default.htm>

directive [18] relevant to plasma products manufacture is 2001/83/EEC, which summarizes and supplants the previous directives:

- 65/65/EEC, which provides the basis for regulation of proprietary medicinal products
- 75/318/EEC, which provides standards for products regulated under 65/65/EEC
- 75/319/EEC, which establishes administrative procedure for use with 65/65/EEC
- 89/381/EEC, which extends the above to cover blood products

The specification of medicinal products in Europe is achieved through the EP Monograph 853 “Human Plasma for Fractionation,” the only EP monograph specifying a source material. Other monographs cover all plasma products supplied to the EU by two or more manufacturers. These monographs represent only the minimum specification for the product described. Products must comply with the relevant pharmacopoeial specification throughout their in-date period.

Standards for the manufacture and supply of pharmaceutical products for the EU are described in a nine-volume compendium, “The Rules Governing Medicinal Products in the European Union.” Volume 4, entitled “Good Manufacturing Practices,” sets out the minimum GMP requirements for compliance. Annex 1 (Sterile Products) and Annex 14 (Blood Products) have special relevance for IG treatment products.

The EMEA’s Biotechnology Working Party (BWP) also publishes, through its Committee for Proprietary Medicinal Products (CPMP), guidelines on several aspects of plasma derivatives which reflect best practices in the field (available at www.emea.eu.int).

European Commission (EC)

The EC’s Directive 2002/98/EC requires the EU member states to establish, within their NRAs, measures for the safety and quality of blood transfusable components. Because of the EC’s decision to include starting materials, such as plasma for fractionation, in the definition of blood components, this directive, and its three

¹⁸ Search for the relevant documents by entering the directive number in the search field at http://europa.eu.int/geninfo/query_en.htm. The first two digits of a directive’s designation correspond to the year the directive was drafted.

“daughter” Directives 2004/33/EC, 2005/61/EC, and 2005/62/EC, also apply to plasma collected for further manufacture. Furthermore, the Directives specify that the requirements apply to material imported for fractionation into the EU, as well as material for products exported outside the EU. Given Europe’s continued dependence on plasma and plasma products generated outside the EU, strict interpretation of the EU’s requirements would exclude much of the plasma and products imported, particularly from the USA, and result in severe product shortages. It appears that an undeclared flexibility on the part of the EU member states’ NRAs is preventing this harmful outcome, but a modification of the various Directives to take into account the special features of plasma for fractionation is very desirable. In the meantime, it is noted that practices among the EU member states, particularly in important issues related to infectious disease safety, still vary (Hansen-Magnusson H 2010), and, in some instances, fall below those mandated for plasma collected in the U.S. It must be emphasised that these variations have no effect on the safety of plasma products such as IG products.

Plasma master file (PMF) concept

The purpose of the PMF is to specify plasma for different plasma products to establish a rapid and simplified way to assure adequate levels of quality and safety in the plasma raw material. Key elements in the PMF are:

- Requirement for a formal contract governing purchase and supply of plasma
- Description of the quality assurance system applying to plasma supply and use
- Arrangements for donor selection (including population epidemiology)
- Requirements for testing of samples of donations and pools
- Arrangements for communication and review of post-donation information

The PMF will replace that part of the marketing authorization application (MAA) describing the raw material plasma (annex IIC) and will make the arrangements for movement of plasma, intermediates, and products across member state boundaries more transparent.



The key tenets of the PMF include:

- Exclusion of at-risk donors
- Mandatory serology on all plasma donations
- Exclusion of donations on the basis of post-donation information
- Traceability from donor to product

While the PMF has been developed and proposed for the European environment, it is an excellent model for assessing the safety of plasma and can be adapted for other countries to be a stand-alone document tailored to the needs of particular countries. It includes all the information NRAs need to have on plasma as a raw material to ensure its quality and safety. The model product assessment questionnaire in **Appendix B** includes elements drawn from the PMF guideline.

1. Common strengths of U.S. & EU regulatory provisions

- Review of data in marketing authorization application:
 - Commitments on plasma source – PMF
 - Process/batch consistency including effectiveness of viral inactivation/viral removal steps
 - Review data on safety and efficacy and of pharmacokinetics
- Inspection and enforcement of:
 - Plasma donor base, collection facilities, and quality systems
 - Manufacturing facility, process, and quality systems
- Control agency batch review and release
 - Batch specific review of protocols and testing of samples
 - Availability of trend information on batch performance over time
- Post-marketing surveillance – mandatory follow-up

Source: Snape T, "Assessment of Products Not Licensed by the FDA and the EMEA," WFH Global Forum, January 21-22, 2002



Harmonizing established regulatory requirements

A program is in place to facilitate harmonization of the requirements for manufacture and supply of pharmaceutical medicinal products in the U.S., EU, and Japan, the three trade areas where requirements are most formally established. This program, under the auspices of the International Conference on Harmonisation (ICH), has made some progress with respect to definitions, but much remains to be done in terms of implementation. Guidances¹⁹ presently established include:

- ICH Common Technical Document (format for registration submissions)
- ICH quality guidelines (testing and validation of test methods)
- ICH efficacy guidelines (good clinical practice)

Summary

- Arrangements for regulation, licensing, and control of plasma products are well established under U.S. and EU legislative procedures.
- The PMF concept allows safety assessments and facilitates the movement of plasma, intermediates, and products across national boundaries.
- Attempts are being made to harmonize the requirements for the manufacture and supply of pharmaceutical medicinal products in the U.S., EU, and Japan.

¹⁹ Guidances are available from <http://www.ich.org/cache/compo/276-254-1.html>

SECTION III

ESTABLISHING LICENSING, REGULATION, AND CONTROL PROCEDURES IN COUNTRIES WITHOUT WELL-ESTABLISHED REGULATORY SYSTEMS

Introduction

NRAs operating without well-established systems for licensing, regulation, and control of plasma products must act – and must be seen to act – in a way which safeguards public health without artificially restricting the availability of products and without unnecessarily escalating the cost.

The establishment and maintenance of a complex regulatory environment is beyond the capacity of most healthcare systems in the developing world. However, despite the lack of such an infrastructure, most countries can develop an appropriate decision-making framework for assessing and choosing IG treatment products.

There are some obstacles that may get in the way when assessing and choosing products, including:

- Limitations of NRAs themselves
 - Lack of experience
 - Lack of resources
- Plasma products supply is not a level playing field
 - Several generations of product (e.g., for protein purification and viral elimination methods) are typically still available and the benefits of a particular product are not always clear
 - Variability in the quality of the plasma used for manufacture
 - Variability in manufacturing standards employed
 - Local distributors may lack sufficient information on product specifications
- Decision-makers need to respond to changing circumstances

- Product availability and price will be driven by events elsewhere
- Perceptions of quality may not reflect reality

Recommended measures and pitfalls to avoid

To ensure the most control over the selection of treatment products, NRAs should try to incorporate some or all of the following measures into their approach:

- Build alliances with other purchasers to maximize resources
- Build a direct, managed relationship with suppliers or manufacturers, where possible
- Whenever possible, select products licensed with an established NRA
- Get information on plasma and the manufacturing process in advance using a pre-contract questionnaire (See model product assessment questionnaire in **Appendix B**)
- Audit potential suppliers who meet the NRA's safety and quality requirements, focusing on plasma supply (especially donor selection, testing, and traceability) and manufacturing and distribution processes
- Use pre-shipment samples to support selection, but **not** as the basis for choice (available test methods are unlikely to be validated for the product, and batch pre-selection limits the time to expiry of selected batches)

Potential pitfalls decision-makers and regulators should avoid include:

- Allowing the supplier or product to be selected on the basis of price alone. For example, low product price may be a result of non-conformance with (expensive) quality measures, such as ensuring that donors are coming from low-risk populations through appropriate selection procedures. If a manufacturer is able to access large volumes of plasma from paid donors of low socioeconomic status, strict selection measures are mandatory to ensure the product's safety.
- Allowing supplier and product selection to be driven by political expediency.
- Creating dependence on third-party suppliers (brokers/agents), which can limit communication on key quality matters.
- Relying on finished product testing to assure fitness-for-purpose.

Using distributors of imported products

Since many countries attempting to access IG products lack a domestic plasma fractionation capacity, local distributors or agents for the manufacturer are often used. They undertake a sponsorship role for the product and organize its presentation to NRAs, arrange its distribution once products are approved, and handle liability issues, etc. Using agents is generally less preferable than dealing directly with manufacturers because they are rarely familiar enough with the specialized products used for IG treatment. As agents tend to change periodically, and sometimes represent more than one manufacturer, it can be difficult to maintain a level of continuity and consistency in product choice processes. This is particularly the case when there is no established NRA because then there is similar instability on both sides.

If distributors are used, NRAs should establish procedures to ensure that distributors offer the following minimum standard features in their procurement of IG products:

- Evidence that the distributor is the sole agent for that particular manufacturer in the country in question, through a statement from the relevant manufacturer
- Demonstrated capacity to provide the required infrastructure, particularly adequate volumes of refrigerated storage
- Demonstrated capacity to ensure product traceability to the end-users and to carry out product recalls or withdrawals when required
- All other features specified in the requirements of the model product assessment questionnaire included in **Appendix B** of this guide

Whether the government agency interacts with a manufacturer directly or through an agent, it is extremely desirable to establish a contact at the manufacturer, preferably with the regulatory affairs department. All details regarding such contacts, including records of all past correspondence, should be included in documentation generated for each procurement, in order to maximize continuity.

Role of end-product testing by NRAs

Manufacturer testing of end product to a pre-determined specification is an essential feature of product quality control leading to release on the market. NRAs such as the FDA and the EMEA generally conduct some form of independent oversight of this process by routinely reviewing manufacturer test release results and/or conducting tests themselves in official medicine control laboratories (OMCL). This testing of products before official release is called batch release testing (BRT). It is not a universal practice among regulators, some of whom consider that there is little value added to assuring product quality by duplicating the manufacturer's release testing. Product quality depends on ensuring that testing methods and release criteria are approved as part of the overall review process and are subject to all the requirements of good manufacturing practice. It is important to emphasize that the overall process is what builds quality and safety into a product; it is not possible to ensure product quality by testing in the absence of these features.

If NRAs feel that end-product testing allows them a level of assurance on quality and safety, they should use (or adapt) the approach used by established regulators or the batch release protocol from the European Directorate for the Quality of Medicines (EDQM) [20]. However, authority-based end-product testing should not be a mandatory requirement to measure the safety of IG products for NRAs to whom this guide is directed. Whatever approach is adopted regarding end-product testing, it should not replace the review process detailed in this guide.

It is important to note also that end-product testing cannot be used to assure viral safety. The testing used for screening plasma for viral agents, whether performed on donations or pools, and whether serologic or molecular, is not designed or validated for testing end products. Using these tests for end products is highly inappropriate and adds nothing to the assurance of safety to the products. Its application may lead to incorrect assessments of product quality and safety and hold up product release. While the FDA introduced end product NAT testing for some IG products in the mid 1990s, this was an interim measure for products then not subject to viral inactivation. The use of such testing today, in the era when all IG products should be virally

²⁰ Accessible from:
http://www.edqm.eu/site/59_European_Guidelines_for_Blood_Products_and_vacczip-en-8388-2.html.



inactivated, is totally redundant. No amount of end product testing can be used as a substitute for viral inactivation procedures.

Summary

- Regulatory agencies in countries with no established arrangements for regulation of plasma products should ensure the safety and quality of plasma products by:
 - Forming alliances with similarly placed NRAs
 - Working directly with manufacturers, not through brokers or agents
 - Considering products licensed through established NRAs first
 - Establishing arrangements for pre-selection and audit of suppliers
 - Focusing on evidence of plasma quality and secure manufacturing rather than on testing finished product
 - Consulting with independent institutions or expert.

SECTION IV

EVALUATING IG TREATMENT PRODUCTS

Introduction

When it comes to assessing which product to purchase, there is no universally right answer. There are certain minimum requirements that should be met, but NRAs must assess each product on its own merits and weigh carefully the relative features of each product in making a decision. Similarly, prescribers need to assess which particular product features may affect their patients' particular illness and needs. This section focuses on the evaluation process, first outlining the key information that must be gathered from the manufacturer, and second summarizing the basic requirements that must be met for a product to be considered safe. Several scenarios are given in this chapter to provide examples of the assessment process.

Product information from manufacturer

To properly assess a product, national regulatory agencies must have information on:

1. The quality of plasma raw material, including
 - Regulatory status of the plasma supplier
 - Donor epidemiology
 - Donor exclusion criteria
 - Screening tests done on the blood/plasma
 - Quality assurance measures
 - Inventory hold
 - Plasma pool size
 - Testing of the plasma pool

2. The manufacturing process, including:
 - Crucial manufacturing steps and related in-process controls
 - Viral inactivation and/or removal steps
 - Process consistency
 - Batch release specification



3. The final product, including:

- Potency of the product and shelf life
- Other markets where product is available
- Product history
- Clinical studies demonstrating the product's efficacy

This information can be gathered from the manufacturer using the model product assessment questionnaire in **Appendix B**.

Basic requirements

There are a number of requirements that should be met in a satisfactory fashion for a product to be considered safe. These include:

1. **Manufacturer must have full confidence in safety and quality of plasma raw material through adequate contractual arrangements with plasma supplier.** The plasma supplier should be licensed by the relevant NRA. The manufacturer must specify the measures used to ensure that donors are selected on the basis of low risk for the transmission of blood-borne viruses, including questionnaires that identify high-risk behavior, exclusion of collecting sites from high-risk areas such as prisons, and attempting to build up a base of repeat and accredited donors. While plasma inventory hold and repeated donor qualification are viewed as very desirable features, they are not always possible, particularly when the plasma is recovered from whole blood donations. The manufacturer's confidence can best be acquired by performing audits of the collection centers based on these and other features of GMPs. These audits should be performed by the manufacturer, although references to audits performed by a NRA are satisfactory, as long as they occur within the period of contract between the supplier and the manufacturer.

Under no circumstances should NRAs accept product where the source of the raw material is unknown and unspecified, even if the

manufacturer claims that the blood has been tested or the product is viral inactivated. In this regard, the use of uncharacterized plasma from the “spot” market is not recommended.

2. Blood testing should include screening at individual donation level for serological markers of HIV, HBV, and HCV.

Screening should be done using test kits for the latest generation of the relevant test, preferably in a format registered by a licensing authority. While the technologies used for detecting infection during the serological window, such as NAT, are also desirable to increase viral safety margins, it is improbable that they will be critical to ensure the viral safety for products sourced from serologically screened plasma that is subjected to robust viral inactivation steps. This also applies for serological and/or NAT testing of the plasma pool by the manufacturer. Confidence in the quality of the serological screening tests is therefore crucial. **For this reason, a quality assurance system for ensuring the performance of viral screening tests is essential.**

3. Viral inactivation and/or removal in form of deliberate, well-validated manufacturing steps are essential for safety of IG products. While a number of viral inactivation steps have been shown to enhance greatly safety of IG products, solvent-detergent treatment is current gold standard for safety from highly infectious enveloped viruses and should be seriously considered as option of choice when assessing products. Similarly, nanofiltration is option of choice when considering non-enveloped viruses and also has potential to decrease risk of vCJD.

Solvent-detergent treatment is not effective at inactivating non-enveloped viruses, which are also resistant to other viral inactivation techniques, and therefore additional steps specifically targeting such viruses are highly advisable. Nanofiltration is an option for IG products, as is heating in solution and other techniques which have been shown to eliminate non-enveloped viruses. Another advantage of the solvent-detergent and nanofiltration procedures is the low risk of induction of protein neoantigens.

Any incidental elimination of viruses during the manufacturing procedure that contributes to the overall safety of the product should be welcomed as long as it has been validated by the manufacturer. However, any such contributions through the manufacturing process should be viewed as supplementing rather than substituting for a deliberate viral elimination step. In the case of prions, such steps are the main contributor to product safety and should be rigorously validated for their effectiveness. This is very relevant for IG products, where the manufacturing processes have been shown to remove prions. **Since small variations in processes affect the capacity for this to happen, each process for each product needs to be validated separately.**

Given the repeated demonstration that enveloped viruses including HCV, HIV, and HBV are the biggest threat to the PID population, NRAs should focus on products with proven safety records against these viruses through well-validated and controlled viral inactivation mechanisms.

- 4. Other measures to enhance safety from non-enveloped viruses, including vaccination of people receiving blood products where such vaccines are available (e.g., for HAV) and decreasing the viral load of the plasma pool to levels not associated with infection through testing (e.g., NAT), are recommended.** NAT has been shown to contribute to enhancing the safety from infection by B19. Manufacturers have started to incorporate such testing, and NRAs may want to require NAT for specific viruses, known to be prevalent in the donor population contributing to the product. With *validated* viral inactivation procedures for disease-causing enveloped viruses, such plasma pool testing is probably more beneficial for unscreened non-enveloped viruses. In combination with nanofiltration, NAT has significantly reduced the risk of small non-enveloped viruses such as B19 in the plasma pool.



Whenever possible, people who are going to receive plasma concentrates on a lifelong basis should be vaccinated against blood-borne viruses.

Example scenarios

As a result of a tendering process, the following IgG products have been offered:

Product A: An IgG product made from plasma about which the manufacturer has little knowledge except the country of origin. The manufacturer claims to test for the serological markers of the transfusion transmitted agents HIV, HCV, and HBV on the plasma pools after plasma has been thawed for manufacture. The manufacturer also performs NAT testing for HCV on these pools, and the final product is viral inactivated with solvent-detergent and acid-ph treatments. Limited viral inactivation studies have been generated by the manufacturer for the conditions and plasma source specific to the product. The product is the cheapest of those offered.

Product B: A product made from plasma that is characterized by a fully documented quality system incorporating the tenets of the European PMF concept. The product is subjected to solvent-detergent treatment. The manufacturer has validated this process for inactivation of viruses in accordance with the requirements of the CPMP.

Product C: A product made from plasma that is characterized by a fully documented quality system incorporating the tenets of the European PMF concept. The product's viral inactivation includes solvent-detergent and nanofiltration. The product is licensed for subcutaneous use on the basis of clinical trials using the product itself. The cost of the product is double that of the next most expensive product.

Product D: A product made by a national fractionator from recovered plasma collected by centers under contract to the manufacturer. A full quality system is not evident, but the manufacturer has data on donor viral epidemiology and selection protocols to exclude high-risk groups. The product is manufactured with ion-exchange chromatography in lieu of Cohn fractionation. The product undergoes two



viral inactivation steps: solvent-detergent and pasteurization. The manufacturer has limited clinical studies and has offered literature-based evidence for efficacy.

Some of the considerations when evaluating the products in this scenario should include:

1. There is a total lack of knowledge about the plasma quality of Product A. The manufacturer's use of pool testing is not an acceptable substitute for a fully documented quality system. Despite the use of well-accredited viral inactivation steps, the manufacturer's limited ability to validate these is a deficiency. This product, despite its favorable price, should not be considered further.
2. Product B is singly inactivated using solvent-detergent treatment, the best method for eliminating the most highly infectious viruses. However, the lack of any other viral inactivation step is a problem, and NRAs should further consider other products.
3. Product C is very well manufactured and virally inactivated. Its cost-effectiveness against the other products is probably low. However, it is licensed for subcutaneous administration on the basis of evidence, which facilitates home administration and decreases hospital costs. This should offset much of the increased product costs for the relevant NRAs.
4. Product D has attractive features but the manufacturer should perform its own validation studies on the elimination of the infectious agents from which it claims product safety. The company's contract for plasma supply should be rigorously assessed for its adherence to the crucial features of the PMF requirement. Although a full clinical trial may not be required, some evidence of normal pharmacokinetics and efficacy would be desirable.



Summary

- NRAs must assess each product on its own merits and weigh carefully the relative features of each product in making a decision.

- To properly assess a product, NRAs must have information on:
 - Quality of the plasma raw material
 - Manufacturing process
 - Final product

- Certain minimum requirements should be met:
 - The manufacturer must have full confidence in the safety and quality of the plasma raw material.
 - Individual donations of plasma should be screened for serological markers of HIV, HBV, and HCV.
 - Manufacturing process must include deliberate, well-validated viral inactivation and/or removal steps.
 - Other safety measures to enhance safety from non-enveloped viruses, such as vaccination of people who receive plasma therapies on a lifelong basis and decreasing the viral load of the plasma pool, are recommended.



SECTION V

CONCLUSION

Choosing appropriate products for the treatment of PID is not an easy task. It depends on the resources and unique circumstances of each country. However, the principles and information given here can provide guidance to NRAs when making decisions about the purchase of IG treatment products.

IPOPI will be updating this guide regularly and welcomes comments for improving it. Please send any suggestions to:

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APPENDIX A

IG PRODUCTS AVAILABLE ON WORLD MARKET

The International Patient Organisation for Primary Immunodeficiencies has compiled a comprehensive country by country database of IG products available in many countries. It may be found at: www.ipopi.org

This document does not endorse any specific product but will reiterate the principles outlined, including the high level of assurance that may be gained through market approval by the established NRAs in North America, Europe, and Australasia.



APPENDIX B

MODEL PRODUCT ASSESSMENT QUESTIONNAIRE

This questionnaire includes the minimum information needed to assess a product with a view to allowing it on the market. The manufacturer should be asked to provide all the information requested before any assessment of products begins.

Information summary from candidate suppliers of IG plasma products						
1. Plasma raw material						
1. (a) Plasma supplier						
Name of supplier	Source or recovered				% first time donors	% repeat donors
(Insert rows for each supplier used by the manufacturer)						
1. (b) Donor epidemiology						
Name of supplier	HIV antibody positive donations		HCV antibody positive donations		HbsAg positive donations	
	per 10,000 repeat donors	per 10,000 new donors	per 10,000 repeat donors	per 10,000 new donors	per 10,000 repeat donors	per 10,000 new donors
(Insert rows for each supplier used by the manufacturer)						



1. (c) Regulatory status of plasma suppliers

Name	Frequency of internal audits performed by supplier, if any	Frequency of external audits performed by manufacturer, if any	Frequency of external audits performed by government authority, if any	Any other certification by a competent body
(Insert rows for each supplier used by the manufacturer)				

1. (d) Donor selection – exclusion criteria (whether checked for and what action)

2. Name	History of blood-borne infections (hepatitis/HIV, etc.)	IV drug abuse	High-risk sexual behaviour (male to male sex, prostitution, etc.)	Recipients of blood, tissues, etc.	Risky behaviour – tattoos, piercing, etc.	Medical procedures
(Insert rows for each supplier used by the manufacturer)						



3. (e) Blood/plasma screening					
4. Screening test	Name of kit – manufacturer		Regulatory status (USA/Europe)		
HbsAg					
HCV antibody					
HIV antibody					
HCV NAT (if any)					
HIV NAT (if any)					
(Insert rows for each supplier used by the manufacturer)					
5. (f) Quality assurance of test kits					
6. Describe any internal and external QA used by the collection agencies for their screening tests					
7. (g) Plasma measures by manufacturer					
Any Inventory hold measures, etc.	Maximum number of donations in plasma pool	Testing of the plasma pool – serology, NAT, etc.	Estimate of viral load in plasma pool from viral incidence data		
			HIV	HCV	HBV



2) Manufacturing process

The manufacturer is to include a copy of the licence to manufacture issued by the country where the facility is located and any other authority

8. (a) Critical steps

Here insert a flow chart of the manufacturing process, identify the crucial manufacturing steps and list their related in-process controls (IPCs)

9. (b) Viral reduction

List dedicated viral reduction steps

Validated log₁₀ elimination for

1. HIV (actual virus)
2. HCV (specify model, e.g., BVDV, etc.)
3. HBV (specify model)
4. HAV (actual virus or specify model)
5. B19 (specify model)

Estimated residual risk per vial of product from plasma pool viral load and validated viral elimination data, for

1. HIV
2. HCV
3. HBV



10.(c) Process consistency

List in-process controls (IPCs) identified in 2(a) for three chronologically sequential batches of the product manufactured at the scale used for the marketed form manufactured within the last 18 months.

In-process controls	Batch – 01	Batch – 02	Batch – 03
IPC-1			
IPC-2			
IPC-3			
IPC-4			
IPC-5			

11.(d) Batch release specification

List the batch release specification and the results for three chronologically sequential batches of product manufactured within the last 18 months.

Batch Release Parameter	Batch – 01	Batch – 02	Batch – 03
Batch release parameter 1			
Batch release parameter 2			
Batch release parameter 3			
Batch release parameter 4			
Batch release parameter 5			



12.(e) Stability and shelf life

Include the data for the levels of anticomplementary activity, IG dimers and aggregates of the product measured during the requested shelf life, at the temperatures sought in the application.

Aggregates (%)	At release	3 months	6 months	12 months	24 months
Should be $\leq 3\%$					
Anticomplementary activity (CH50/mg IG) Should be $\leq 1\%$					

3) Further product information

13.(a) Other Markets

List the other markets where the product is available, its history in these markets, volumes supplied, and related marketing authorizations from licensing bodies.

14.(b) Clinical studies

Summarize clinical trials used to demonstrate product efficacy, referring to the authorizations from other markets listed in 3(a). Manufacturers should comment on their endorsement or otherwise on the EMEA's *Guideline on the clinical investigation of human normal immunoglobulin for IV administration (IVIG)* available on http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500078472.pdf

15.(c) Adverse events

Describe manufacturer's system for receiving and reporting adverse events related to the product.



APPENDIX C

GLOSSARY

Batch release testing: Testing of end products by NRAs before official release to ensure that the product specification is met.

Characterization: Analytical measurements which allow detailed understanding of the composition and other attributes of a product.

Donor screening: Individual donations of blood are screened to ensure that blood-borne viruses do not enter the plasma pool. Screening is currently available for HBV, HCV, and HIV.

Donor selection: Procedures designed to identify and exclude donors at risk of being infected with viruses that can be transmitted by blood transfusion.

Enveloped/lipid enveloped viruses: The common transfusion transmitted viruses HIV, HCV, and HBV, which are all characterized by a lipid viral envelope and are highly infectious.

Finished product testing: Testing done on final product to allow manufacturers to characterize their products and to demonstrate compliance of every batch with the licensed specification.

Fractionation: The process of separating and processing human blood plasma into a range of products for therapeutic use.

Good manufacturing practices (GMPs): All the elements in established practice that will collectively lead to final products that consistently meet expected requirements as reflected in product specification. These include traceability, segregation of product manufacturing steps to avoid cross-contamination, training, documentation, change control, deviation reporting.



Inventory hold: The retention in storage of plasma for fractionation while processes designed to assure donor safety are undertaken.

Limit testing: Testing of the plasma pool using NAT in which a maximum level of viral contamination, rather than an absolute elimination, is the aim.

Lyophilization: The process of isolating a solid substance from solution by freezing the solution and evaporating the ice under vacuum. Freeze-drying.

Marketing authorization: The formal permit from a regulatory authority allowing a manufacturer to market a product following that authority's scrutiny.

Minipools: Plasma samples pooled from several donations, and then tested for viral markers.

Nanofiltration: A process whereby protein solutions are passed over small pore filters which can remove viruses while allowing therapeutic proteins to pass through.

Non-enveloped /non-lipid enveloped viruses: Pathogenic viruses (*e.g.*, HAV, B19) that lack a lipid envelope and therefore are not susceptible to viral inactivation techniques such as solvent-detergent treatment.

Nucleic acid testing (NAT): Testing for viral nucleic acid, thus allowing detection of a virus which may cause disease before the development of immunological markers of infection.

Pharmacokinetics: The action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation and excretion.



Plasma master file: A dossier of information compiled according to European guidelines, which allows the manufacturer of plasma derivatives to fully describe the source material.

Plasma pool: Plasma from a number of donors to be used to make one lot of product.

Plasmapheresis: A method of collecting plasma from donors whereby only the donor's plasma is removed. This method allows a donor to donate a larger volume of plasma per donation and donate more frequently than is possible when donating whole blood.

Potency: The biological activity which may be measured in the laboratory which is best related to a product's actual therapeutic effect.

Product specification: The properties of a product. They can be measured in the laboratory, allowing a manufacturer to assess and demonstrate fitness of purpose.

Purity: The proportion of the desired ingredient (e.g., factor VIII) in concentrates, relative to other ingredients present.

Quality assurance system: A mechanism for achieving, sustaining, and improving product quality.

Recovered plasma: Plasma collected as a by-product of donated whole blood. Recovered plasma is generally procured from unpaid donors.

Shelf life: The period of time during which a product may be stored under specified conditions and retain its characteristics.

Source plasma: Plasma collected from donors through a process known as plasmapheresis, which removes only the donor's plasma. The majority of this plasma is obtained from paid donors.



Spot plasma market: market for plasma available for purchase independently of any major regulated supplier or fractionator, with inadequate assurance of its source and quality

Validation: The action of proving that any material, process, procedure, activity, system, or equipment used in manufacture or control can and will reliably achieve the desired and intended results.

Window period: The period between when a donor is infected with a virus or disease-causing agent and when infection can be detected by an immunological marker. During this period the donor is infectious but the infection is undetectable. With NAT, the “window period” is shortened.



APPENDIX D

BIBLIOGRAPHY OF USEFUL REVIEWS ON IG PRODUCTS AND RELEVANT REGULATORY DOCUMENTS

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