Comment assurer l'autosuffisance de la Belgique en dérivés stables du plasma?

KCE reports 120B

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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PRÉFACE

Les médicaments sont généralement fabriqués à partir de substances que l'on trouve dans la nature en quantités quasi illimitées. Il n'en va pas de même pour la majorité des dérivés plasmatiques qu'il est impossible de fabriquer d'une autre manière que par fractionnement de plasma humain dont la quantité est limitée à ce qui a pu être collecté auprès de donneurs.

Comme les dérivés stables du plasma sont parfois les seuls remèdes possibles à des maladies graves, on comprend que les autorités de santé s'enquièrent des précautions nécessaires pour garantir un approvisionnement suffisant du pays compte tenu de ce facteur limitant à la source.

Interrogé à ce sujet, le KCE s'est rapidement rendu compte de la complexité du problème liée aussi bien aux conditions de collecte (volontariat et gratuité des dons) qu'aux problèmes d'équilibre financier des différents acteurs et au peu de transparence à ce sujet. Nous avons cependant pu repartir d'audits déjà effectués.

Nous remercions tous ceux qui nous ont aidés à y voir plus clair et en particulier les hôpitaux qui ont répondu massivement à notre enquête. Nous espérons avoir ouvert suffisamment de voies pour aider les décideurs à mettre en place des solutions à la fois sûres et coût-efficaces.

Jean-Pierre Closon

Directeur général a.i.

Résumé

CONTEXTE

Le sang assure le transport d'éléments essentiels à la vie chez la personne, mais il permet aussi de produire des dérivés qui interviennent dans le traitement d'affections particulières chez d'autres personnes tels que les immunodéficiences et l'hémophilie. Ces dérivés résultent d'un processus de fractionnement du plasma. Le plasma est la partie liquide du sang de couleur transparente et jaune, composée à 90 % d'eau et pour le reste d'immunoglobulines (à la consommation desquelles nous consacrons une partie de ce rapport), d'albumine, de facteurs de coagulation et de lipoprotéines. Ce plasma est obtenu soit par séparation des cellules sanguines à la suite d'un don de sang total, soit par plasmaphérèse, processus qui consiste à isoler le plasma du sang d'un donneur qui conserve ainsi ses cellules sanguines.

En Belgique, la totalité du sang et du plasma est collectée par la Croix Rouge et quelques petits centres indépendants. Les donneurs ne sont pas rémunérés conformément aux règles en vigueur dans l'Union Européenne. Le plasma collecté est vendu au Département Central de Fractionnement (DCF)[a], une entreprise qui en effectue le fractionnement.

La plupart des pays européens consomment une quantité plus grande de produits dérivés que ce que l'on peut extraire du sang et du plasma collectés auprès de leurs citoyens. Ils doivent donc s'approvisionner pour le surplus auprès de fractionneurs qui achètent du plasma à l'étranger. Si ce plasma étranger venait un jour à manquer ou à n'être plus vendu qu'à des prix exorbitants, les pays importateurs pourraient se trouver en difficulté. Difficulté d'autant plus importante que les dérivés plasmatiques sont indispensables pour soigner certaines maladies graves, D'où la question posée au KCE de l'auto suffisance de la Belgique en plasma et dérivés stables du plasma et des précautions à prendre pour réduire au maximum le risque de pénurie.

QUESTIONS DE RECHERCHE

Pour éclairer cette problématique, nous avons tenté de répondre aux questions de recherche suivantes:

A propos de l'offre:

- Comment et en quelles quantités le plasma est il collecté en Belgique et dans d'autres pays? Quelles sont les évolutions observées? Quels subsides sont accordés pour assurer une collecte suffisante?
- Comment se passe la transformation du plasma recueilli en Belgique en produits dérivés stables? Quelles sont les quantités produites? Comment le processus est-il financé?

A propos de la demande:

- Quelles sont les indications médicales traitées avec des dérivés stables du plasma ? Quelles quantités sont nécessaires pour traiter ces indications et quelles sont les quantités consommées en Belgique? Quelles tendances peut-on prévoir dans les prochaines années?

A propos de la sécurité de couverture de la demande :

- Que faut-il entendre par sécurité de couverture d'une manière générale ? Quel niveau de couverture cherche-t-on à atteindre en Belgique et dans d'autres pays?
- Quelles sont les différentes démarches possibles pour atteindre de façon optimale un niveau de couverture choisi?

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[a] En néerlandais: Centrale Afdeling voor Fractionering (CAF). Au départ, il s'agissait d'un département de la Croix Rouge. Aujourd'hui, il s'agit d'une entreprise commerciale multi nationale, dans laquelle la Croix Rouge n'est plus qu'un actionnaire minoritaire.

MÉTHODOLOGIE

Nous avons adopté des méthodologies spécifiques à chacun des trois thèmes traités dans ce rapport.

En ce qui concerne les questions relatives à l'offre :

Afin de déterminer les quantités de plasma collectées, nous avons recueilli des données auprès des collecteurs belges. Des données fournies par la Croix-Rouge et le CAF-DCF ont été recoupées avec des données issues d'un audit de ces deux institutions afin de déterminer les quantités de plasma vendues et achetées et leurs prix. Les données INAMI et une enquête auprès des hôpitaux nous ont permis de déterminer les quantités totales de produits dérivés vendues en Belgique, en distinguant celles fournies par le CAF – DCF et celles fournies par des firmes commerciales étrangères.

Nous avons étudié l'évolution des quantités de dérivés stables produites et vendues par le CAF-DCF et les avons mises en regard des quantités de plasma qu'il achète à la Croix Rouge. . Des documents internes de la Croix-Rouge ainsi que l'audit dont elle a été l'objet nous ont permis d'évaluer les coûts de ses activités et notamment de la plasmaphérèse qui constitue le mode de collecte de plasma dont la rentabilité était supposée insuffisante. Les prix perçus par la CR ont été comparés aux prix internationaux afin d'évaluer le gain potentiel pour la CR de vendre son plasma sur le marché international.

En ce qui concerne les questions relatives à la demande :

La recherche s'est concentrée sur les immunoglobulines (IG), qui représentent le dérivé plasmatique le plus déterminant de la demande. Les recommandations de bonne pratique en vigueur en Belgique et dans d'autres pays industrialisés ont été analysées. Une revue de la littérature, centrée sur les revues systématiques, s'est penchée sur l'efficacité des immunoglobulines pour les indications généralement reprises dans les recommandations nationales en vue de pouvoir expliquer et prévoir les quantités consommées. Les caractéristiques de consommation d'autres pays industrialisés ont été analysées pour déterminer quelles indications, pour lesquelles les IG ont montré une efficacité, représentaient la plus grande partie de la consommation en IG. En ce qui concerne la consommation en Belgique, trois domaines ont été examinés:

- Les données globales de consommation belge, basées sur les données de l'Inami (2004-2007) et sur une enquête auprès des pharmacies des hôpitaux belges (2008), ont permis d'étudier les consommations « réelles » en terme de quantités globales prescrites et/ou remboursées en Belgique.
- Les distributions des quantités prescrites par hôpital et par spécialité médicale, ainsi que les pratiques médicales en cours, ont été étudiées à travers l'enquête auprès des pharmacies et une deuxième enquête auprès de services universitaires d'immuno-hématologie.
- Une estimation théorique des quantités d'IG nécessaire pour traiter les 11 indications reconnues qui ont consommé 74% des IG dans les autres pays a été réalisée sur base des données épidémiologiques belges ou des pays voisins, ainsi que des pratiques dans les centres belges ou internationaux.

En ce qui concerne les questions relatives à la sécurité de couverture de la demande:

Les dispositions prises en Belgique pour assurer son auto suffisance en dérivés stables du plasma, ont été analysées. Une recherche dans la littérature grise et des contacts étrangers nous ont permis de décrire les systèmes d'approvisionnement, de la collecte à la consommation, dans plusieurs pays étrangers (France, Allemagne, Australie, Canada).

RÉSULTATS

En ce qui concerne le concept de sécurité de couverture

La réglementation belge ne définit pas la proportion de produits sanguins stables d'origine humaine qui doit être produite en Belgique pour garantir son auto suffisance. Un arrêté royal de 1998 précise seulement que pour garantir l'auto suffisance et la qualité de l'approvisionnement du pays en produits sanguins stables d'origine humaine, le prix du litre de plasma vendu par la Croix Rouge au CAF-DCF sera subsidié et qu'un Collège de réviseurs transmettra chaque année au SPF le nombre de litres vendus en vue de calculer correctement le subside. Dans les faits, ce Collège observe qu'une quantité équivalente à 60% de la consommation plus un stock de quarantaine de 180 jours sont subsidiables. On en déduit implicitement que la Belgique est ainsi auto suffisante mais nous n'avons trouvé aucune justification scientifique de cette proportion ni de la durée de la quarantaine (période pendant laquelle le plasma doit être conservé avant d'être fractionné). Celle-ci est passée de 50 à 180 jours entre 1998 à 2006 sans que rien ne justifie cette hausse d'un point de vue de la sécurité médicale. Au contraire, de nouvelles techniques d'analyse biologique permettent de réduire la quarantaine de façon drastique. Il semble donc que les concepts d'autosuffisance et de quarantaine n'ont jamais été vraiment réfléchis et définis en Belgique.

Au niveau international, on ne retrouve pas non plus de justification officielle précise de ce qu'il serait plus exact d'appeler un 'degré d'indépendance'. En Australie, l'indépendance complète semble être une finalité implicite même si il est accepté d'avoir recours aux firmes étrangères pour des besoins précis et ponctuels. En France, l'autosuffisance - définie comme la part représentée par le chiffre d'affaires de l'opérateur national LFB dans le chiffre d'affaires total de la branche considérée sur le marché national - représente 75% pour les produits plasmatiques mais avec des variations selon les produits considérés (par ex : 60% pour les IG). L'objectif fixé au LFB (Laboratoire Français de Fractionnement et de Biotechnologie) est d'atteindre un niveau de production capable de couvrir potentiellement 100 % des besoins des patients français en 2011. Toutefois, si LFB est le seul opérateur à fractionner le plasma livré par l'Etablissement Français du Sang, il ne détient pas pour autant le monopole de vente des produits plasmatiques et reste en concurrence avec les autres entreprises présentes sur le marché français.

En ce qui concerne la collecte du plasma

Chaque pays développe des stratégies particulières pour collecter le plasma en quantités suffisantes. En France et en Allemagne, afin de favoriser le don de plasma, l'accent est mis sur les 18-25 ans et la collaboration avec les universités ainsi que sur le suivi régulier des donneurs (très efficace) et la standardisation des dons de manière à augmenter le volume par don. L'Etablissement Français de Sang s'est engagé contractuellement à augmenter ses livraisons de plasma au LFB. En Allemagne, la logique commerciale prévaut (80% des dons) et les dons sont compensés financièrement (jusqu'à 25 euros / limite fixée par la loi). En Australie, la collecte, l'approvisionnement en produits dérivés et les contrats sont gérés par la National Blood Authority.

En Belgique, sur base des données disponibles, la plasmaphérèse est une activité en perte de vitesse à la Croix-Rouge qui a même fermé certains centres de plasmaphérèse. Peut être la plasmaphérèse n'est elle pas jugée suffisamment rentable ? Cette rentabilité est toutefois fonction, au moins partiellement, du mode d'affectation de coûts fixes à l'ensemble des activités.

Chaque litre de plasma issu de plasmaphérèse et vendu dans le cadre de l'autosuffisance donne droit à un subside de 24,79 euros versé à la CR, de façon à lui permettre de vendre ce plasma au CAF – DCF à un prix plus bas. La CR reçoit également un subside afin de couvrir le coût des tests NAT (Nucleic Acid Tests), effectués sur les prélèvements de sang, qui détectent la présence éventuelle de certains virus. Le paiement des consommables à la firme qui les commercialise est peu transparent et permet de facturer des tests qui n'auraient pas été effectués réellement.

En ce qui concerne la transformation du plasma en produits dérivés stables :

Le CAF – DCF assure le fractionnement de tout le plasma acheté sur le territoire en partenariat avec trois entreprises (allemande, française et hollandaise). Les conventions de partenariat ne sont pas rendues publiques. Nos calculs montrent que le rapport entre les quantités de dérivés produites et les quantités de plasma fractionné par le CAF-DCF, est très variable d'une année à l'autre. Cette variabilité semble liée aux modifications de la demande intérieure et à la part de marché du CAF-DCF. Pour certains dérivés et certaines années, le CAF-DCF dispose de plus de plasma qu'il n'est nécessaire pour produire les quantités qu'il parvient à vendre.

En ce qui concerne la consommation des produits dérivés stables :

Les immunoglobulines (IG) sont les dérivés qui nécessitent les plus grandes quantités de plasma pour répondre aux besoins thérapeutiques. Les IG représentent aussi la majorité des dépenses en dérivés stables (33.4 millions € ou 62% du total des dérivés stables en 2006), leur consommation augmente de manière continue et le nombre d'indications pour lesquelles les IG sont utilisées ne cesse d'augmenter. En Belgique, les IG sont actuellement remboursées pour 13 indications. Une analyse de la prescription d'IG dans les hôpitaux belges a été réalisée. Il en ressort que les prestataires de quatre spécialités ont prescrit 92% des IG en 2008 (médecine interne, neurologie, pneumologie et pédiatrie). On observe une grande hétérogénéité de la prescription entre les hôpitaux, en particulier en pneumologie. La prescription élevée d'IG en pneumologie (16% du total), prédominante dans quelques hôpitaux non universitaires, ne peut être reliée aux indications remboursées en Belgique, à l'exception de certaines déficiences immunitaires présentant des infections respiratoires bactériennes répétées qui seraient traitées par des pneumologues; ce phénomène a également été rarement observé dans d'autres pays. En ce qui concerne l'évolution future de la demande, aucun modèle n'a pu être défini : certains facteurs pourraient augmenter la demande, comme des nouvelles indications potentielles et l'augmentation de prévalence de certaines maladies affectant surtout les personnes âgées ; d'autres facteurs pourraient la diminuer, comme une limitation de la prescription aux indications reconnues et le développement de thérapies alternatives pour les indications actuelles des IG.

Les indications remboursées en Belgique ont été comparées à celles recommandées et/ou remboursées dans cinq autres pays (France, Royaume Uni (RU), Pays Bas, Canada et Australie), Table 1. Des recommandations belges sur l'utilisation des immunoglobulines sont actuellement en cours d'élaboration au Conseil Supérieur de la Santé (CSS/HGR).

Table 1: Indications pour lesquelles l'utilisation d'immunoglobulines est remboursée en Belgique, sous certains critères définis.

Indications remboursées en Belgique	Autres pays recommandant les IG dans le traitement de cette indication*
Syndromes d'immunodéficience primaire	France, RU, Pays Bas, Canada, Australie
Myélome et leucémie lymphoïde chronique (avec hypogammaglobulinémie secondaire sévère et infections récidivantes)	France, RU, Pays Bas, Canada, Australie
Purpura thrombocytopénique idiopathique	France, RU, Pays Bas, Canada, Australie
SIDA pédiatrique	France, Pays Bas, Canada, Australie
Syndrome de Guillain-Barré	France, RU, Pays Bas, Canada, Australie
Maladie de Kawasaki	France, RU, Pays Bas, Canada, Australie
Prévention des infections chez des patients subissant une transplantation allogène de moelle osseuse	France, RU, Pays Bas, Australie
Traitement de septicémie chez des prématurés	Pays Bas, Australie (prévention en France)
Traitement de septicémie pendant la période néonatale	France, Australie
Le traitement du syndrome du choc toxique d'origine streptococcique.	France, RU, Australie
La polyradiculoneuropathie démyélinisante inflammatoire chronique	France, RU, Canada, Australie
La neuropathie motrice multifocale	France, RU, Canada, Australie

*: Sources: Guidelines nationaux au Royaume Uni, Australie et Canada; liste publiée par l'Agence française de sécurité sanitaire des produits de santé (Afssaps) et la Haute Autorité de Santé en France; indications autorisées par le Medicine Evaluation Board aux Pays Bas.

Il existe des indications, pour lesquelles les IG ne sont pas remboursées en Belgique, mais pour lesquelles une revue de la littérature scientifique a montré que les immunoglobulines pouvaient apporter une amélioration. Cependant, d'autres thérapies efficaces existent pour la plupart de ces pathologies.

LIMITATIONS

La première des limitations de ce rapport est liée aux données que nous avons pu récolter. Nous n'avons pas pu recueillir de données sur les immunoglobulines non remboursées en 2004-2007. Pour 2008, les données rapportées par les pharmacies hospitalières sont plus complètes mais nous ignorons si l'utilisation d'immunoglobulines à usage compassionnel est inclue dans les données de tous les hôpitaux interrogés. Celles-ci pourraient représenter une proportion significative des consommations d'après certains experts, et nous amèneraient donc à sous-estimer systématiquement les consommations en IG et donc la demande réelle.

La deuxième limitation est liée à l'absence de vérification de l'affectation des coûts de structure de la Croix Rouge à l'activité de plasmaphérèse. Une autre forme de ventilation des coûts serait donc susceptible de réduire le déficit financier, voire de le supprimer.

La troisième limitation est liée à la variabilité du prix du plasma dans le temps et l'espace sur le marché international. Cette variabilité empêche de tirer des conclusions claires sur les gains potentiels en cas de vente du plasma sur le marché international

RECOMMANDATIONS

En ce qui concerne la définition de l'autosuffisance

- Le niveau implicite de couverture des besoins admis en Belgique entraîne une dépendance partielle à l'égard du marché international. Cette dépendance devrait résulter d'un choix politique conscient basé sur une analyse de risques tenant compte des prix internationaux, de l'offre et de la demande internationales et des capacités de la CR et du CAF – DCF à répondre positivement à une hausse éventuelle de la demande intérieure.
- Il est recommandé de revoir à la baisse le nombre de jours requis par la quarantaine pour sécurité biologique.

En ce qui concerne la collecte de plasma

- Si l'autorité publique décidait d'augmenter le degré d'indépendance de l'approvisionnement en produits dérivés, il serait utile de s'inspirer des nombreuses politiques mises au point à l'étranger et sur les réflexions existant au niveau de l'UE. Ainsi, il est recommandé :
  - de mieux cibler le recrutement notamment en termes de tranches d'âge et de cibler les jeunes adultes (18-25) en priorité ;
  - d'assurer un suivi régulier des donneurs, et de façon plus générale une bonne gestion de celui-ci par l'organisme de collecte ;
  - de procéder à des campagnes intensives de sensibilisation ;
  - sur le plan technique, de veiller à une véritable standardisation et optimisation des pratiques de collecte.
- Dans une optique d'équité, l'ensemble des donneurs et en particulier les travailleurs, devraient être traités de la même manière, notamment en uniformisant progressivement les avantages octroyés en cas de don de sang ou de plasma.
- En raison d'un système peu transparent relatif à la facturation des tests NAT (Nucleic Acid Tests) et à leur subsidiation, il est recommandé de procéder à une détermination des subsides qui tienne mieux compte des coûts réels supportés par la CR ou de vérifier la possibilité d'inclure le coût de ces tests dans le prix du sang.

En ce qui concerne la consommation de dérivés stables du plasma

- La variabilité des pratiques constatées - surtout dans des centres périphériques - invite à recommander
  - la production de guidelines au sujet de la prescription d'IG et de traitements alternatifs (une initiative en ce sens est en cours au CSS/HGR) ;
  - de privilégier une prescription et un suivi par des spécialistes et des centres de références pour le traitement par IG au long cours, comme cela est prévu pour l'usage du facteur VIII (convention pour les centres d'hémophilie).
- Il est recommandé aussi d'améliorer le suivi de la prescription par l'établissement par exemple d'un registre ou d'une base de données des patients traités par IG au long cours, et par la transmission de feedbacks aux prescripteurs avec l'utilisation de benchmarking.

En ce qui concerne la transparence des activités et des comptes des organismes subsidiés

Une autorité subsidiante doit pouvoir contrôler l'utilisation des subsides qu'elle octroie directement ou indirectement. Par conséquent:

- Il est recommandé de lier la poursuite de la subsidiation du prix du plasma vendu au CAF-DCF à une communication transparente
    - o des flux financiers et en volumes relatifs au plasma et aux produits dérivés qui transitent par le CAF-DCF et ses partenaires étrangers
    - o Des termes du contrat qui lie le CAF-DCF à ses partenaires concernant l'utilisation directe ou indirecte du plasma collecté en Belgique

  de manière à pouvoir vérifier l'utilité des subsides dans le cadre d'une politique d'auto suffisance clairement définie;
- Il est également recommandé de mener un audit approfondi des comptes de la CR afin de déterminer avec précision la structure des coûts de l'activité de plasmaphérèse et d'en déduire le subside minimal éventuellement nécessaire pour assurer que cette activité soit financièrement en équilibre, et ainsi soutenir la collecte du niveau souhaité de plasma source.

Scientific summary

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GLOSSARY

AD	Alzheimer's disease
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
ARCBS	Australian Red Cross Blood Service
BMT	Bone marrow transplantation
CAA	Coronary artery aneurysms
CAF-DCF	Centrale Afdeling voor Fractionering - Département Central de Fractionnement
CFS	Chronic fatigue syndrome
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CLL	Chronic lymphocytic leukaemia
CMV	Cytomegalovirus
CR	Croix Rouge
DRK	Deutsches Rotes Kreuz (German Red Cross)
EFS	Etablissement Français du Sang
FNAIT	Fetal or neonatal allo-immune thrombocytopenia
HAART	Highly active antiretroviral therapy
HSTC	Hematopoietic stem cell transplantation
IBM	Inclusion body myositis
IG	Immunoglobulins. In this report, IG is used to describe pooled polyvalent human immunoglobulin, that can be administered intravenously or subcutaneously; IG does not cover hyperimmune or specific immunoglobulins.
ITP	Idiopathic thrombocytopenic purpura
IVIG	Intravenous polyvalent immunoglobulins
LEMS	Lambert-Eaton myasthenic syndrome
LFB	Laboratoire Français de Fractionnement et de Biotechnologie
MG	Myasthenia gravis
MM	Multiple myeloma
MMN	Multifocal motor neuropathy
MS	Multiple sclerosis
NAT	Nucleic Acid Test
NBA	National Blood Authority (Australia)
NIHDI	National Institute for Health and Disability Insurance
PID	Primary immune deficiencies
PPMS	Primary progressive multiple sclerosis
PPTA	Plasma Protein Therapeutics Association
RCT	Randomized control trial
RP	Recovered Plasma
RRMS	Relapsing remitting multiple sclerosis
RSV	Respiratory Syncitial Virus
SCIG	Immunoglobulins for sub-cutaneous administration
SFS	Service Francophone du Sang
SID	Secondary immune deficiencies
SIPLA	Study on the Safety of Long-term Intensive Plasmapheresis in Donors (Germany)
SP	Source Plasma
SPMS	Secondary progressive multiple sclerosis

STC	Stem cell transplant
TFG	Transfusionsgesetz (German regulation on transfusion and blood-related issues)
VDB	Vlaamse Dienst voor het Bloed

1 INTRODUCTION

1.1 CONTEXT

Blood transports elements that are essential to life in individuals, but it can also be used to produce derivatives that are used in the treatment of specific disorders in others such as immunodeficiency and haemophilia. These derivates are produced by a process called plasma fractionation. Plasma is the transparent yellowish liquid part of the blood, composed of 90% water and the rest of immunoglobulins (a part of this report is devoted to their consumption), albumin, coagulation factors and lipoproteins. This plasma is obtained either by separation of the red blod cells following a whole blood donation, or by plasmapheresis, a process used to isolate the plasma from the blood of a donor, which retains the red blood cells.

In Belgium, all of the blood and plasma is collected by the Red Cross and a few independent centres. The donors are not paid, in accordance with the rules in force in the European Union. The collected plasma is sold to a company in Belgium, which performs the fractionation.

The majority of European countries consume a greater quantity of derivatives than can be extracted from the blood and plasma collected from their citizens. They must therefore obtain other supplies from fractionation companies that buy plasma abroad. If this foreign plasma should one day be in short supply or only be available at exorbitant prices, importing countries may find themselves in difficulty. This difficulty is exacerbated by the fact that plasma derivatives are vital for the treatment certain serious illnesses, hence the question posed to the KCE of self-sufficiency for Belgium in plasma and plasma derivatives and the precautions to be taken to reduce as far as possible the risk of a shortfall in supplies.

1.2 RESEARCH QUESTIONS

To clarify the issue, we intend to answer the following questions:

Concerning supply:

- How and in what quantities is plasma collected in Belgium and in other countries? What trends have been observed? What subsidies are provided to ensure that enough is collected?
- How are derivative products manufactured from the plasma collected in Belgium? What are the quantities produced? How is it financed?

Concerning demand:

- Which medical indications are treated with plasma stable derivatives ? Which amounts are required to treat these conditions and which amounts are consumed in Belgium? Which trends can we expect over the coming years?

Concerning security of coverage of demand:

- What it meant by security of coverage in general? What level of coverage do we seek to achieve in Belgium and in other countries?
- What different approaches could be used to achieve optimally the desired level of coverage?

2 SUPPLY OF PLASMA DERIVATIVES

2.1 COLLECTION OF PLASMA

2.1.1 Legal and ethical framework

Plasma donation and collection processes have to abide by specific rules, both from a sanitary and ethical point of view.

As a human product, collection and use of plasma are subject to specific rules, with a view to protecting patient safety, and also donor's security. Moreover specificity of plasma is that they stem from human donation. In the current state of science, artificial plasma as such cannot be produced, and the supply of plasma cannot be guaranteed. Therefore donation is of paramount importance.

However, one must clearly distinguish one the one hand donation and collection that remain in the hands of each national system and on the other hand the global market of plasma-derived products, that is subject to free competition between private firms.

For all these reasons, a very strict and specific legal and ethical framework has been defined. Given the high level of economic integration between EU economies in the field of plasma-derived products, but also the common expectations of EU citizens, these rules have been set out on the EU level.

2.1.1.1 European and international context: which impact?

EU regulatory framework on blood and blood products

More precisely, the key regulatory texts of the EU legal framework cover the following subjects:

QUALITY ISSUES: 2 DIRECTIVES

Directive 2002/98/EC (27 January 2003)[1] setting standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components and amending directive 2001/83/EC. This directive focuses on the following aspects: provisions for establishments, quality management, haemovigilance, quality and safety of blood (and blood components), reporting requirements, etc…

Directive 2004/33/ EC (22 March 2004) [2] implementing directive 2002/98 as regards certain technical requirements for blood and blood components. This directive is also of paramount importance, as the appendixes list the key requirements for the practical organization of blood donation: definition of terms and concepts, eligibility criteria for donors, storage and distribution conditions, quality/safety requirements.

TRACEABILITY REQUIREMENTS: 1 DIRECTIVE

Directive 2005/61/ EC (30 September 2005)[3] implementing directive 2002/98 of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse events reactions and events.

QUALITY SYSTEM FOR BLOOD ESTABLISHMENTS: 1 DIRECTIVE

Directive 2005/62/ EC (30 September 2005) [4] implementing directive 2002/98 of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments.

However, the issue of self-sufficiency as such has not been addressed by the EU regulation so far and has been left to each country's discretion. Besides, as far as plasma products are concerned, some further explanation is required, in terms of legal status. Indeed, it is a thorny and complex problem both from an intellectual and political point of view.

Focus: status of plasma products with regard to the EU legislation

Legal status of plasma-derived products remains a sensitive and delicate subject both from a legal and political point of view.

The main issue is to have a clear view on the legal nature of blood products, to be specific of plasma-derived products. Whereas these products are blood products or drugs might have far-reaching consequences, especially in terms of freedom of circulation.

Until now, no case law of the European Court of Justice has been identified on the legal status of blood or plasma products, as such.

The problem has really not been solved and the arguments listed below must be considered with great care, and might be challenged by the ECJ in the future. To some extent, one can rely on a body of legal evidence, considering the spirit of the existing EU legislation on blood and blood products.

Directive 2004/33/ EC (22 March 2004) mentioned above sets out in Annex I a long and precise list of what is considered as "blood" and "blood components", to which the directive's requirements are applicable.

Directive 2001/83 /EC (6 November 2001) on medicinal products: it is clearly stated in this directive that "medicinal products derived from human blood or human plasma" can resort to "albumin, coagulating factors and immunoglobulin of human origin". We can easily draw the conclusion that all these products are considered as medicinal products.

One can easily infer from the directives mentioned above that products that are listed in the Directive are blood products (and not pharmaceutical drugs) and are a matter for the EU Blood and Blood products legislation. Likewise, one can also infer that products resorting to human plasma (alone or combined with other substances) that are sold by pharmaceutical firms, after completion of the fractionation process, must be considered as drugs.

Nonetheless, plasma fractionation is an extremely long and complex process, and the range of plasma-derived products is very wide. Therefore, a "grey zone" can be identified between blood and blood-components and plasma-derived drugs as described in the previous paragraph. The main issue is to define accurate criteria to distinguish "blood components" and "pharmaceutical drugs" and to draw a border between both concepts. This is not an easy task, from a purely conceptual and legal point of view.

For lack of regulatory definition (or official case law of the European Court of Justice), several EU Directives on health-related subjects can provide us with interesting clues on that point, in several texts especially EU Regulation (EC) 1394/2007 on advanced therapies (13 November 2007) on advanced therapy medicinal products (amending Directive 2001/83 and Regulation 726/2004). The latter regulation deals with advanced therapies resorting to cells or tissues. One of the key issues of this regulation is to identify products that can be considered as "medicinal products". To this end, the regulation (Art.2 Definitions) resorts to the concept of "engineered products" (as opposed to non engineered products).

To be more specific only cells or tissues that undergo "substantial manipulations" can be considered as "advance therapy medicinal products". Given that clinical practice or scientific literature do not give a clear-cut definition of this concept, this regulation sets out a list of practices (Annex I) that are not considered as "substantial manipulations". In practical terms, such practices as centrifugation, sterilization, filtering, and freezing can be considered as "substantial manipulations" as such.

Then, a second criterion is used in the Directive, to be specific the volume of production: the scope of the regulation clearly refers to the routine industrial production of medicinal products (with a view to putting them on the market), and not to custom-made treatments. Thus, a product that is used within a hospital in compliance with a medical prescription and delivered to a patient is clearly excluded from the scope of the regulation, since it is not considered as a medicinal product.

In the light of these criteria, only products that comply with these two criteria should be considered as "medicinal products". However, one must remain cautious on that point, and keep this legal issue under scrutiny.

Apart from purely regulatory subjects, the EU level also plays a strategic role in the promotion of voluntary unpaid donation, in order to identify avenues worth exploring to improve EU countries' self-sufficiency, within the ethical and regulatory framework described above. This EU will play an important role over the next years.

EU policy and ongoing projects on promotion of voluntary unpaid donation

SURVEY OF THE EU COMMISSION (DG SANCO) ON PROMOTION OF UNPAID DONATION

One of the key issues for political decision-makers, but also for practical organization of blood and plasma donation is the lucrative or unpaid nature of donation. This takes us back to ethical notions, and to a philosophical and political debate.

Some countries like the United States clearly opted for remuneration of donation, whereas others - like Canada and EU countries - opted for non remuneration of donation. The EU level formally recorded that donation is unpaid. Within this ethical framework, the EU level organized an in-depth enquiry to learn more on existing practices on unpaid donation across Member States.

A Europe-wide survey has been launched by the EU-Commission (DG Sanco) [5] a few years ago on that subject, and a summary report has been issued on 17th May 2006. Across Member States, practices can vary on two points: Interpretation of the principle of "unpaid donation" and Promotion of donation itself.

Interpretation of the principle of "unpaid donation": from a political and ethical point of view, the principle of "unpaid donation" is the cornerstone of the donation systems, all over the EU. However, this principle does not exclude "financial compensation" for donors in some countries (or in specific institutions within these countries, depending on their own political options). The amount of this financial compensation is kept below a specific threshold set out by legislation, and the nature of expenses covered (and not covered) by this compensation (travel expenses, car park, etc..) is generally set out very precisely by the country's legislation.

Germany is a traditional example on that point: as explained further in the report, many German institutions involved in donation - especially private institutions involved in plasma donation- apply financial compensation as an incentive for donors. The amount of this compensation can reach € 25 for each donation (maximum amount set out by the German legislation).

As a result of this compensation mechanism and depending on the frequency of donation, regular donors are apt to receive a yearly amount of money, that is far from being nominal (around 1000 €).

Promotion of donation itself: a very wide range of media and institutions have been used or mobilised to support donation:

- Information campaigns resorting to traditional media (leaflets, posters, press) or modern media, especially internet.
- Special events on donation: World blood donor day or other events focusing on donation.
- Specific Student and secondary schools' pupils awareness: in many Member States, raising awareness of this age group is of paramount for further recruitment of donors.

FURTHER DEVELOPMENTS ON THAT SUBJECT ON THE EU LEVEL: SHARING BEST PRACTICES BETWEEN MEMBER STATES

In the light of these findings, the EU Commission decided to carry out a new study on best practices for promotion of voluntary unpaid, in order to share best practices between Member States. The findings of this new study should be available in early 2010.

Two technical European projects have been designed and implemented on donation:

"DOMAINE" / Donor Management in Europe focusing on recruitment, retention and long-term management of donors and "Optimal Blood Use" focusing on the clinical and technical use of blood components. These projects are all the more important as they will be completed in 2010 and should deliver helpful information on best practices on these subjects.

"DOMAINE": Donor Management in Europe: http://www.domaine-europe.eu/Home/tabid/36/Default.aspx

DOMAINE (Donor Management IN Europe) is a European project, in which blood establishments from 14 European member states and one patient-driven organisation join their forces on donor management. DOMAINE aims to create a safe and sufficient blood supply, by comparing and recommending good donor management practice. Even if 14 Member States play a leading role as partners countries, surveys obviously covers European practices, ie all EU countries**,** and a small number of European non-EU countries (as a whole 34 countries).

This project does not deal specifically with plasma donation. However, principles of donor management are apt to be applied to plasma donation as well.

The whole range of donor management issues will be addressed: donor recruitment strategies, donor retention strategies, deferral procedures and blood bank policy regarding patients requiring long-term transfusion.

Key points

- **The EU concept of unpaid donation, opposable to all EU countries, does not exclude financial compensation. Interpretation of this latter concept may vary across Member States. Exchange of best practices on unpaid donation will also be available over the next years.**
- **Noticeable discrepancies have been identified in donor's management but also in the use of blood and plasma across EU countries. The EU level's objective is to support harmonization of practices. As a result, a contribution is expected from 2010 onwards: Manual on donor management, Manual on the rational use of blood and plasma.**

2.1.1.2 Contribution to the ethical debate on donation

Over the last decades, blood and plasma donation has raised very specific ethical questions for the following reasons:

- Blood and plasma products are human products and not industry-produced drugs.
- Donation is based on a voluntary and individual act (at least in western countries).
- Donation does not meet supply/demand rules in the traditional economic sense.
- Specific ethical problems may appear both on the donor's and user's side.
- Ethical frameworks of donation systems have a major impact on self-sufficiency, as shown *inter allia* by the Canadian experience (see below).

Main ethical dimensions of blood donation

In Europe, many reflections have been conducted for several decades on blood and plasma donation and over the last years the University of Vienna in Austria (http://www.medicalethics.at/) , has conducted an in-depth reflection on that subject.

THE REFLECTION ON ETHICAL DIMENSION OF STEPS:

1. Main specificities of blood and plasma donation

The main traits of blood and plasma donation have been identified by Richard Titmuss and officially set out in the following article "Why give to strangers?" Lancet 16 January 1971[6] and his book titled "The gift relationship: from human blood to social policy" (last edition 1997) [7]. The most specific traits of this "Gift relationship" is its potentially one-sided and not rewarding dimension of this donation:

- Physically uncomfortable
- Anonymous and not rewarding (individually)
- Potentially one-sided dimension (donor can be excluded from a future donation)
- Absence of donation does not involve any sanction
- The use of donated blood depends on a large number of people
- For the donor, donation is no great or definitive loss whereas for the recipient, it can be a matter of life and death

For all the reasons mentioned above blood and plasma donation can be considered as a very specific kind of gift, not to be compared with other kind of donations or "gift relationships". Moreover blood and plasma donation as such entail specific symbolic dimensions (Myth of Blood). Further details: see Appendix

2. Main learnings

It is important to underline that hindering factors for donation must be considered in close connection with the individuals' past attitude towards donation (ie ever donors or non donors).

The collection regimes may have an impact on donors' motivation and donators' profiles. In practice, it often involves a split between two donors profile. Therefore, it is of key importance to bear in mind that such subjects as financial compensation cannot be considered separately from other subjects. in countries were compensation is applied, plasma donors are generally younger, more educated, and less involved in professional life than whole blood donors. Conversely, in countries where no financial compensation is provided any clear distinction, in terms of donors' profile, has been identified so far.

MAXIMIZATION OF THE USE OF THE DONATED BLOOD AS AN ETHICAL IMPERATIVE

Consensual prerequisites can be easily set out as follows, basically for purely practical reasons:

- Plasma is a scarce resource (plasma as raw material is not industry-produced)

- Plasma fractionation remains a complex and costly process. Therefore it involves very specific imperatives for stakeholders, more precisely:

- Facilitating plasma collection (bringing down actual or potential barriers to donation)
- Handling plasma and plasma-derived products cautiously
- Distributing burdens and benefits fairly to all participants of the collection and supply chain
- Needs of the population are not always easy to meet (self-sufficiency issue).

ETHICS OF THE PLASMA ORGANIZATION

Ethical dimension can work both ways: as clearly explained by Healy [8], "Collection regimes do not simply increase or decrease the donation rate along a sliding scale. They shape the kind of activity that blood donation is. How you organize a blood supply system not only affects how much you collect and who you get it from, it shapes the character of donation".

Therefore, it is of key importance to consider blood or plasma collection system not only from a technical point of view, but also from an ethical point of view, since each option – whatever it is- is apt to have a major impact on the ethical dimension on donation and thus on donors' behaviour and indirectly on donors' motivation as such.

Given this background, four options can theoretically be considered:

- A purely market-driven system: not affordable so far given the institutional European context described above. Besides it would require the fitting investments.
- A solidarity-driven system: requires a strong social bond and can be easily implemented in smaller communities. In fact only strongly bound communities whose members identify themselves with the same core values can perform such a system and rely on it..
- A purely-voluntary system: "gift-fetishism". However such a system does not seem to be reliable, as a matter of principle.

Using incentives but retaining the "gift-like" features of the donation: the latter option money as such is not an incentive, but this does not exclude financial compensation. The latter option which is used in Austria or Germany for plasma donation raises specific problems as they can be seen as "borderline systems" from a purely ethical point of view. Clear-cut distinction between of incentive Vs remuneration is not always easy to make.

The principle of voluntary unpaid donation

Over the last decades, all the key institutions involved in blood and plasma donation have reasserted that profit as such must not be a motive for donation. Step by step, the principle of unpaid donation has been ethical standard for the countries of the European Union. This principle is officially mentioned by foremost international institutions, and thus accepted by Member States of these institutions:

- International Red Cross and Red Crescent Societies / Core resolutions and guidelines on voluntary non remunerated blood donation: "Financial profit must never be a motive for the donors or those responsible for collecting the donation. Voluntary, non remunerated donors should always be encouraged"
- Council of Europe / Art 2 of the European Conference N. R (95) 14: "Donation is considered as voluntary and non remunerated" (even if small tokens, refreshments, and reimbursement of travel costs are compatible with voluntary non remunerated donation).
- World Health Organization: "Safe blood donors are the cornerstone of safe and adequate supply of blood and blood products. The safest blood donors are voluntary non remunerated blood donors from low-risk populations".
- Charter of Fundamental Rights of the European Union (Art 3): The right to the integrity of the person involves "The prohibition on making the human body and its parts as such a source of financial gain".
- Eventually, EU Directive 2002/98 Art 20 (opposable to all EU Member States) officially states that "Voluntary and unpaid blood donation are a factor which can contribute to high safety standards for blood and blood components and therefore to the protection of human health".

What emerges from all these statements is that blood and blood components are a subject of great ethical importance for the international and EU level. From an ethical point of view, the principle of voluntary unpaid donation is now accepted as the cornerstone of the donation policy in all EU countries. This is a key difference with other countries –especially the United States- where blood and plasma donation can be remunerated (even if it is not always remunerated).

The principle of unpaid donation is of key importance for the practical and technical organization of blood donation, as the main points of the EU ethical and regulatory framework should remain stable over the next years.

Key points

- **Principles underpinning blood and plasma donation are specific to this kind of donation. Making the best use of donated blood or plasma can be seen as an ethical duty.**
- **Ethical donation is not contradictory with a concept of compensation or other incentives, within strict limits.**
- **It must be borne in mind that in countries were compensation is applied, plasma donors are generally younger, more educated, and less involved in professional life than whole blood donors. Conversely, in countries where no financial compensation is provided no clear distinction, in terms of donors' profile, has been identified so far.**

2.1.2 Plasma collection in Belgium

2.1.2.1 Current legal framework

In Belgium, as in any country, blood and plasma donation can be considered as an individual gift or a good deed, based on personal motives and/or beliefs (altruism or any philosophical or religious belief) but also as a collective commitment, especially in a professional context.

For this reason, making public institutions and private firms (SMEs or bigger firms) aware of this problem and mobilizing their employees for blood donation has been one of the most important missions of the Red Cross over the last decades.

However, the situation of the employees is utterly different, whether they work in a private or a public context.

Private Law Contracts

The Belgian Private Work Contract Act (3rd July 1978) sets out all the key rules concerning the rights and duties of employers and employees. This Act addresses the different types of contract (worker's contract, employee's contract, sales representative, etc…) and covers the whole range of traditional work law issues.

However, it remains silent about possible leave or days off for blood or plasma donation. Legally speaking, specific provisions, measures or arrangements can be set out only in the policies and procedures of each firm, but actual implementation of these measures (or arrangements) is left to the employer's discretion.

The employees are generally allowed, in this exceptional case, to leave the office just for the time spent for donation, (generally between 1 and 2 hours) but may be requested to make up for the "time lost" ("lost" from the employer's point of view).

In practice, blood or plasma collection is often performed by the Red Cross's teams during or around a lunch pause, and employees hardly ever benefit from specific leave for donation.

Public Law Contracts

Virtually all the Belgian public law institutions have set out specific provisions, measures or arrangements in the employee's contracts to enable them to benefit from specific leave or days off for "philanthropic purposes" which covers, inter allia, blood and plasma donation (as well as bone marrow and tissue donation). However, regulatory rules vary widely across institutions and regions, as described below:

FRENCH-SPEAKING INSTITUTIONS

First Example – Wallonian Civil Servants [18 DECEMBER 2003 - Arrêté du Gouvernement wallon portant le Code de la fonction publique wallonne (Art 383)].

1. On the day of donation, one day off (blood donation) or one half day (plasma donation) is awarded to the employee.
2. One additional day (blood donation) or one-half additional day (plasma or platelet donation) is also awarded to the employee, whenever donation is performed during office hours and when the day after donation is a work day.

Second example – French-Speaking Community / Semi-public Institution [5 DECEMBER 2008 - Arrêté du Gouvernement de la Communauté française fixant le statut administratif et pécuniaire du personnel de Wallonie-Bruxelles International (Art 316)].

1. On the day of donation, one day off (blood donation) or one half day (plasma donation) is awarded to the employee.
2. One additional day (blood donation) or one half additional day (plasma or platelet donation) is also awarded to the employee, whenever donation is performed during office hours and when the day after donation is a work day.

Third example – French-Speaking Community / Governmental and Audiovisual Institutions [2 JUNE 2004. - Arrêté du Gouvernement de la Communauté française relatif aux congés et aux absences des agents des Services du Gouvernement de la Communauté française, du Conseil supérieur de l'Audiovisuel et des organismes d'intérêt public relevant du Comité de Secteur XVII (Art.42)].

On the day of donation, one day off for blood or plasma donation is awarded to the employee. If the donation takes place during off-duty hours (i.e. between the end of workday and midnight) the day off is awarded on the day following donation.

DUTCH SPEAKING INSTITUTIONS

Flemish Region [13 JANUARY 2006. - Arrêté du Gouvernement flamand fixant le statut du personnel des services des autorités flamandes (Art 79)].

Employees can be awarded a one day leave for blood, plasma or platelet donation, (within the limit of 1 day per month).

FEDERAL LEVEL

Federal level: "Day-Off or leave for philanthropic purposes" [9 December 1999. – Circulaire n° 487 relative à l'octroi d'une dispense de service pour le don de sang, de plaquettes et de plasma sanguin (Art.42)].

As a general rule, one day off for blood, platelet or plasma donation is awarded to the employee (Maximum: 4 days yearly). As far as plasma donation is concerned, employees are allowed to start the work day 1h54 later or to leave the office 1h54 sooner than usual.

Key points

- **From a purely legal point of view, there are no specific incentives to get private firms' employees involved into donation**
- **Conversely, regulatory framework is more favourable to public law employees, but rewards are utterly status-dependant.**

2.1.2.2 *Collected Quantities*

Ninety six percent of the blood and plasma donations in Belgium are collected by the Red Cross, which has been placed under the responsibility of the Belgian Red Cross since its inception in 1935. Four non Red Cross blood centres, at Charleroi Hospital and UCL Hospital Mont-Godinne, AZ Sint-Jan Brugge and the Service militaire du sang account for the remaining blood collections. All donations are made by voluntary non-compensated donors, although some donors (from public sector) may receive time off work in addition to the time for donation. Although the Red Cross collects donations by plasmapheresis (source plasma), the bigger part of plasma intended for fractionation is recovered plasma (from whole blood donations). This report focuses solely on the two organizations which form the "transfusion service": The SFS = le Service Francophone du Sang and the VDB = De Vlaamse Dienst voor het Bloed.

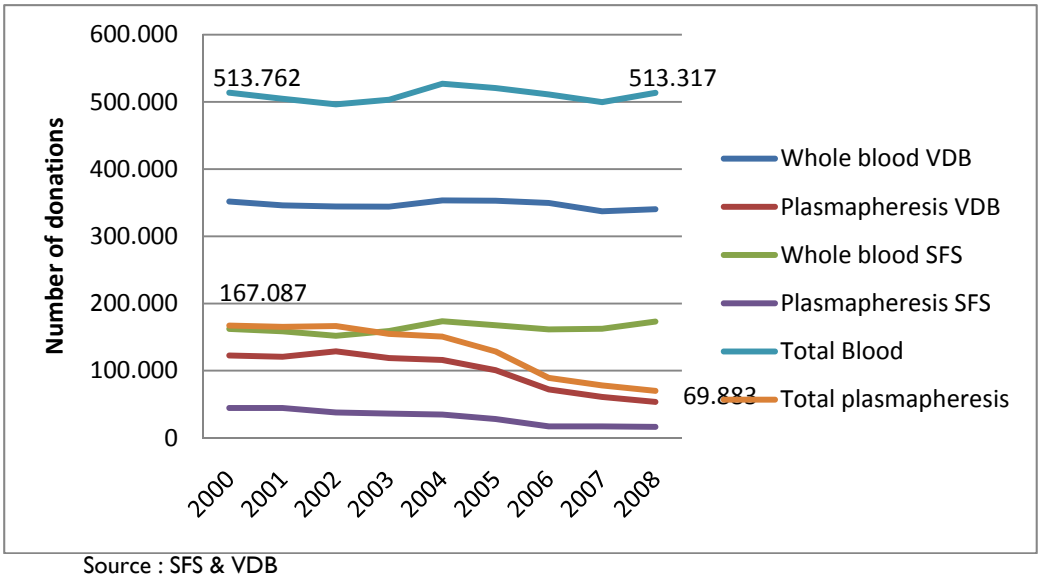
Table 1 and figure 1 show the trend in donations of whole blood and plasmapheresis from 2000 to 2008. We note that the overall number of donations of whole blood is very stable between the start and end of the period under review. However, this stability between these two dates (2000 and 2008) obscures the fall at the start of the period (from 513 762 donations in 2000 to 503 247 in 2003 and the strong growth (+ 4.7%) in 2004. Since then, the number of donations fell again before recovering in 2008. Comparing the trend in the French-speaking section of the Red Cross (SFS) with that of the Dutch-speaking section (VDB), we find a contrasting situation resulting in stability from a reduction of more than 11 000 units for the VDB offset by a rise of almost 11 000 units for the SFS, which is partially artificial as it follows the integration of two independent centres by the SFS (the transfusion centre in Brussels in 2003 and the Hustin centre in 2004) in the SFS activities. As for the number of plasmapheresis donations, the trend is clearly downwards, -56% for the VDB and -63% for the SFS over the period in question as a whole. It seems that the drop in the number of donations of source plasma is linked to the closure of plasmapheresis centres. Globally, the number of donors is quite stable during the last three years (+ 2%), resulting from a combination of a decreasing for the VDB (-1.5%) and a substantial increasing for the SFS (+9%).

Table 1: Number of donations collected by SFS and VDB and number of donors

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Number of donations whole blood SFS	162.101	155.083	151.835	159.083	173.602	167.902	161.499	162.474	173.083
Number of donations whole blood VDB	351.661	346.036	344.370	344.145	353.337	353.017	349.483	337.246	340.237
Total number of donations whole blood	513.762	501.119	496.205	503.228	526.939	520.919	510.982	499.720	513.320
Number of donations plasmapheresis SFS	44.569	44.515	37.791	36.106	34.691	20.538	17.013	17.021	16.315
Number of donations plasmapheresis VDB	122.518	120.653	128.727	118.700	115.898	100.654	72.167	60.962	53.568
Total number of donations plasmapheresis	167.087	165.168	166.518	154.806	150.589	121.192	89.180	77.983	69.883
Number of donations cytapheresis SFS	10.776	10.155	9.994	9.995	12.066	11.921	10.293	8.861	8.582
Number of donations cytapheresis VDB	7.768	8.623	8.884	7.403	13.662	13.489	12.512	13.107	13.164
Total number of donations cytapheresis	18.544	18.778	18.878	17.398	25.728	25.410	22.805	21.968	21.746
Number of donors whole blood SFS	91.422	91.009	98.953	89.767	85.654	82.972	80.628	82.353	87.875
Number of donors whole blood VDB	160.048	158.901	156.684	155.992	155.881	153.508	156.810	150.187	154.426
Total number of donors whole blood	251.470	249.910	255.637	245.759	241.535	236.480	237.438	232.540	242.301

Source : SFS & VDB

Figure 1: Number of donations collected by SFS and VDB



Source : SFS & VDB

In the following table we present the evolution of the volume of plasma collected by the SFS and the VDB during the period 2000-2008. The plasma from whole blood is decreasing in volume with 14.5% and the plasma from plasmapheresis is decreasing in volume with 41.4%. Globally, the total volume of plasma decreases with 24.6%

Table 2: Volume of plasma in litres collected by SFS and VDB

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Volume of plasma from whole blood SFS	36.148	38.643	35.304	39.529	36.762	35.350	34.565	35.461	37.164
Volume of plasma from whole blood VDB	89.326	86.014	88.061	84.639	79.393	73.340	70.526	70.533	70.139
Volume of plasma from whole blood SFS + VDB	125.474	124.657	123.365	124.168	116.155	108.690	105.091	105.994	107.303
Volume of plasma from plasmapheresis & cytapheresis SFS	16.662	18.428	17.339	14.932	23.814	17.825	13.642	13.499	13.255
Volume of plasma from plasmapheresis & cytapheresis VDB	60.390	59.380	57.526	52.983	70.362	60.243	43.583	36.626	32.069
Volume of plasma from plasmapheres. & cytapheres. SFS + VDB	77.052	77.808	74.865	67.915	94.176	78.068	57.225	50.125	45.324
Total volume of plasma collected by SFS + VDB	202.526	202.465	198.230	192.083	210.331	186.758	162.316	156.119	152.627

Source : SFS & VDB

It seems that the collection of plasma is a quite flexible activity. Indeed in 2004-2005, the demand has increased and SFS and VDB have collected more plasma from plasmapheresis to meet the increased demand.

Table 3: Rate of evolution of the volume of plasma during the period 2000 - 2008

	2000 - 2008
Volume of plasma from whole blood SFS	2,8%
Volume of plasma from whole blood VDB	-21,5%
Volume of plasma from whole blood SFS + VDB	-14,5%
Volume of plasma from plasmapheresis SFS	-20,4%
Volume of plasma from plasmapheresis VDB	-46,9%
Volume of plasma from plasmapheresis SFS + VDB	-41,2%
Total volume of plasma collected by **SFS + VDB**	-24,6%

Source : SFS & VDB

We have calculated the average volume of donation of plasma for the recovered plasma (RP) and the source plasma (SP). The first one shows a relatively constant trend, around 0.210 ml per donation for the SFS. This volume has lightly decreased for VDB (0.254 in 2000 and 0.206 in 2008). The average volume of plasma from plasmapheresis has strongly increased since 2004 for the two sections of the Red Cross.

We also noticed that the average number of donations of whole blood per donor is stable (Table 4), for the VDB and the SFS, during the 2003-2008 period (around 2.2) (The average number of donations was obtained by dividing the number of donations by the number of donors). Nevertheless, the evolution is different concerning the average number of plasmapheresis donations. Whereas this number remained stable for the SFS (5.7), it decreased for the VDB (7.0 in 2003 and 4.5 in 2008).

The figures presented do not make differences between the volume of plasma collected from plasmapheresis and the volume of plasma collected from cytapheresis. These two kinds of plasma are considered as source plasma and are sold to the CAF – DCF. Finally, we present the average volume of plasma per donation for the RP and the SP. For the VDB, we received directly these average volumes per year. For the SFS, we have calculated the average by subtracting the assumed volume of plasma collected by cytapheresis (hypothesis of 200 ml per donation) of the total volume of source plasma collected. The results are quite similar to those of the VDB. The increase in the average volume since 2004 is noticeable for the two sections of the Red Cross.

It seems that the substantial increase of SP collection in 2004 is the result of at least two factors:

- A switch of practices concerning the 'therapeutic plasma'
- A response to a increase of the international demand by a increase of the average volume per donation

Until 2004, the plasma used by hospitals for therapeutic purposes (used in the treatment of some bleedings) stemmed from plasmapheresis plasma, which was delivered by the Red Cross. From 2004 onwards, the Red Cross was authorized to manufacture this therapeutic plasma, straight from its own whole blood. As a result of this regulatory change:

- The corresponding volume of whole blood was tapped by the Red Cross (from the existing collected volume), in order to manufacture this therapeutic plasma.
- Likewise, the volume of plasmapheresis plasma, which was formerly delivered to hospitals for therapeutic purposes, was then transferred to the CAF-DCF.

This switch in practices is probably one of the factors explaining the sudden rise in the volume of plasmapheresis plasma delivered to the CAF-DCF, and simultaneously the sudden decrease in the volume of whole blood plasma delivered to the CAF-DCF in the year 2004. An other factor is the change in global demand, as shown for the 2004-2005 increase (Table 2).

Table 4: Average volume of plasma per donation and average number of donations per donor

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Average number of donations per donor of whole blood (SFS)	1,77	1,70	1,53	1,77	2,03	2,02	2,00	1,97	1,97
Average number of donations per donor of whole blood (VDB)	2,20	2,18	2,20	2,21	2,27	2,30	2,23	2,25	2,20
Average number of donations per donor of plasmapherese (SFS)					6,08	4,73	5,71	5,65	5,73
Average number of donations per donor of plasmapherese (VDB)	7,00	6,28	6,33	6,50	6,40	6,29	5,51	5,36	4,51
Average volume (ml) of plasma per donation of whole blood (SFS)	0,223	0,249	0,233	0,248	0,212	0,211	0,214	0,218	0,215
Average volume (ml) of plasma per donation of whole blood (VDB)	0,254	0,249	0,256	0,246	0,225	0,208	0,202	0,209	0,206
Average volume (ml) of plasma per donation of plasmapherese (SFS)	0,325	0,368	0,406	0,358	0,617	0,752	0,681	0,689	0,707
Average volume (ml) of plasma per donation of plasmapherese (VDB)	0,493	0,492	0,447	0,446	0,607	0,599	0,604	0,601	0,599

Source : SFS & VDB

Key points

- **The Red Cross collects 96% of all blood and plasma in Belgium**
- **The number of donors of whole blood is relatively stable for the Dutch-speaking community and slightly up in the French-speaking community**
- **The fall in the number of donations collected mainly affects source plasma (- 58% between 2000 and 2008)**
- **In 2008, the number of donations of whole blood showed a slight upturn for the Dutch-speaking community and confirmation of the rise in the French-speaking community**
- **The total volume of plasma has strongly decreased between 2000 and 2008, by - 24 % (- 14 % for RP and - 41 % for SP)**
- **If the number of donation of plasmapheresis per donor has decreased since 2000, the volume per donation has strongly increased since 2004**

2.1.2.3 The price of plasma

The plasma (from plasmapheresis, cytapheresis (SP) and whole blood (RP)) is sold by the Red Cross to a fractionation company – the CAF-DCF (Centrale Afdeling voor Fractionering - Département Central de Fractionnement) – at a mutually agreed price and quantity each year. This agreement, dating back to 26 February 1998, also sets out the technical criteria for delivery [a]. The price of the RP purchased by the CAF – DCF has remained unchanged since 1998 (53.30 euros). In 1998, the CAF – DCF was granted a price cut for the purchase of SP since 1998 (53.3 euros in place of 78.09 euros), in order to protect its competitiveness on the international market and to ensure the funding of the technological progress of its activities. In 2003, the price was increased.

[a] In compliance with the 5 July 1994 Law , it is a matter of confirming that plasma must stem, as a matter of principle, from voluntary and non remunerated donors

Table 5 shows the trend in the price of RP and SP from 1997 to 2007 with which we compare the trend in international prices found in an unpublished PPTA document. Over the years for which data are available (2002, 2003, 2004 and 2006, 2007), it appears that the price of RP sold by the Red Cross to the CAF-DCF (53.07 euros) represents a very competitive price compared with the prices being paid on the international market. As a corollary, this price represents a loss of potential revenue for the Red Cross. For SP, the situation prior to 2003 (given the international price in 2002) cannot have been profitable for the Red Cross. After the rise in price in 2003, from 53.30 to 78.09, the situation has improved: the amount received by the RC (price + subsidy, see next section) is systematically higher than the international price, according to the sources of Table 5.

In view of the small difference between the international price and the amount received by the Red Cross (price + subsidy), it is vital to confirm this analysis by comparing it with other sources of international prices. In Table 6, we show an average price of source plasma amounts to 106 euros.

As highlighted by Verhaegen,[9] the rise in price agreed in 2003 should correspond to re-establishing of the competitive position of the CAF-DCF, which had completed its investment in buildings (construction on the site at Neder-Over-Heembeeck). However, retaining the subsidy for the Red Cross was without doubts linked to the inadequate price paid by the CAF-DCF to cover the cost of plasma collection. The validity of the above results depends critically on international prices. During a meeting of external experts, we obtained different information that international prices were around 75 euros for RP and 90 euros for SP, including the price of the NAT test (see below). Other sources[10] appear to confirm that the price paid by the CAF-DCF for whole blood plasma is well below the international price and that the average price that the Red Cross could obtain for plasma from plasmapheresis is slightly higher than the price it currently receives, including the subsidy (Table 6).

Table 5: Plasma prices from 1998 to 2007

	Price of recovered plasma			Price of source plasma		
Year	**paid by CAF**	**received by Red Cross**	**International price (PPTA)**	**paid by CAF**	**received by Red Cross**	**International price (PPTA)**
1997	53.30	53.30		78.09	78.09	
1998	53.30	53.30		53.30	78.09	
1999	53.30	53.30		53.30	78.09	
2000	53.30	53.30		53.30	78.09	
2001	53.30	53.30		53.30	78.09	
2002	53.30	53.30	90.78	53.30	78.09	100.00
2003	53.30	53.30	70.04	78.09	102.88	100.00
2004	53.30	53.30	65.20	78.09	102.88	85.88
2005	53.30	53.30		78.09	102.88	79.00
2006	53.30	53.30	81.01	78.09	102.88	87.51
2007	53.30	53.30	60.65	78.09	102.88	98.55

1 Source: International Blood/Plasma News; June 2002
2 Source: International Blood/Plasma News; June 2003 – conversion: www.oanda.com
3 Source: International Blood/Plasma News; January 2004 – US-based suppliers, NOT Polymerase Chain Reaction (PCR) tested
4 Source: International Blood/Plasma News; April 2005 – not Nucleic Acid Test (NAT)
5 Source: International Blood/Plasma News; March 2006
6 Source: International Blood/Plasma News; January 2007 – NAT tested

Table 6: Price of plasma from whole blood and from plasmapheresis in 2009 (prices in euro using a conversion rate of 1 euro = 1.4 USD)

Type of plasma and country	Average price	Lower end	Upper end
Whole blood USA frozen within 120h (the most usual)	79 €	75 €	82 €
Whole blood USA frozen within 24h	86 €	82 €	89 €
Whole blood only Germany 8h and Austria	Significant variations depending on suppliers	95 €	110 €
Plasmapheresis USA	106 €	100 €	114 €
Plasmapheresis Germany (comparable figures)	106 €	100 €	114 €

(Source: [10])

Key Points

- **The Red Cross sells the collected source plasma to the CAF – DCF at a price determined in a contract between the two institutions**
- **We cannot determine if the price received is higher or lower than the price determined by the demand and supply of plasma on the international market**

2.1.2.4 Subsidy for source plasma

Since 1998, the Red Cross receives a subsidy of 24.79 euros per litre of source plasma (from plasmapherasis and cytapherasis) sold to the CAF-DCF. The subsidy is financed by a supplement of 0.10% paid on compulsory car insurance premiums.

These provisions therefore make a sometimes considerable distinction between the price on the Belgian market and the price on the international market. As showed in table 5, the Red Cross receives a fixed subsidy per liter of source plasma (plasmapheresis and cytapherasis plasma) sold to the CAF-DCF. The received subsidy had to offset a reduction in the sale price of the same amount.

Key points

- **Since 1998, the CAF – DCF benefits from a reduction of the price of source plasma**
- **To compensate this reduction, the Red Cross receives a subsidy from the State**

2.1.2.5 Subsidy for NAT testing

The transfusion establishments receive a budget that covers the cost of nucleic acid tests (NAT) HIV1 and HCV testing on whole blood donations. The budget takes the form of a provision that is subsequently topped up or clawed back depending on the number of tests actually performed. These budgets are determined by Royal Decrees. The establishments concerned are the two sections of the Red Cross, the non-profit organisation 'transfusion du sang' in Charleroi, the non-profit organisation 'Etablissement de transfusion de Mont-Godinne' and the AZ Sint-Jan in Bruges. The final balance of the subsidy granted, to be received or reimbursed, is calculated on the total number of successful samples collected, effectively carried out and tested using the NAT tests for HIV1 and HCV.

This number of units collected and testes must be justified by the invoices relating to these tests and certified by an internal or external auditor. The definitive balance of the institutions is calculated following the submission of the supporting documents, which are sent to the Federal Agency for Medicines and Health Products. In 2007, a sum of 14.00 EUR was paid for each test actually conducted. The Royal Decree states that the subsidies granted can under no circumstances exceed the real costs incurred.

The remuneration procedure defined for the NAT test licence is as follows: systematic collection of royalties for the test manufacturer - reflecting the number of **usable** results; for example if a single test is used for 10 pouches of blood (pool testing), the number of royalties will be equal to ten although only one test has been used if negative result). In addition, the subsidy depends on the number of units successfully collected and the number of tests certified in an invoice. As mentioned above, these are linked to the number of usable results and not necessarily to the number of units used as reagents. This means that if a pooling process is used (which seems to be the case for the Red Cross), the amount of the subsidies may be dissociated from the number of reagents purchased. For the Red Cross, the system of pool testing may lead to a saving in manpower.

Key points

- **The collectors of whole blood receive a specific subsidy for the NAT tests to detect HIV1 and HCV**
- **The Red Cross uses a system of pooling to carry out these tests, likely saving in manpower**
- **The firm selling these tests receives royalties in function of the number of usable tests (not necessarily of the number of tests carried out)**

2.1.2.6 Cost of plasmapheresis

We found the costs associated with the collection of plasma from plasmaphaeresis in an internal SFS report. Unfortunately, we did not have the opportunity to consult the same reports for the VDB.

Table 7: Costs SFS associated with the collection of 1 liter plasma from plasmapheresis

Year	Direct cost					Organisation	Total costs
	Donor manag	Collection	Labo	Distribution	Total direct		
1997	2.68	49.75	15.39	1.64	69.46	20.62	90.08
1998	4.04	50.25	13.76	0.77	68.82	17.75	86.57
1999	4.66	52.11	17.07	0.77	74.61	20.97	95.58
2000	5.97	53.69	15.02	0.92	75.60	20.15	95.75
2001	7.09	62.32	16.19	1.19	86.79	23.19	109.98
2002	3.37	65.49	19.03	1.37	89.26	17.94	107.20
2003	5.22	67.62	27.10	1.35	101.29	16.92	118.21
2004	7.53	67.29	27.30	1.06	103.18	24.79	127.97
2005	8.73	67.56	27.28	1.33	104.90	26.96	131.86
2006	10.25	72.72	28.85	1.42	113.24	31.40	144.64
2007	9.12	78.51	29.26	1.25	118.14	35.37	153.51

(Source: SFS – internal reports)

If we subtract the subsidies from the total costs, we can compare the SFS net cost to the price received.

Table 8: Comparison of total costs minus subsidies with prices of plasma from plasmapheresis

Year	Total costs	Subsidies	Total costs minus subsidies	Price received
1997	90.08	0.00	90.08	78.09
1998	86.57	24.79	61.78	78.09
1999	95.58	24.79	70.79	78.09
2000	95.75	24.79	70.96	78.09
2001	109.98	24.79	85.19	78.09
2002	107.20	24.79	82.41	78.09
2003	118.21	24.79	93.42	102.88
2004	127.97	25.19	102.78	102.88
2005	131.86	28.17	103.69	102.88
2006	144.64	30.35	114.29	102.88
2007	153.51	33.01	120.50	102.88

For the subsidies, we have taken the data from the internal reports of the SFS for the years 2004 to 2007. For the previous years, in the absence of such data in the above-mentioned reports, we have used the official data, which fix the subsidy at 24.79 euros. The headings for costs specific to plasmapheresis (donor management, collection and laboratory) are constantly rising. The organisation costs in 2007 constitute 23% of total costs; given that these costs are allocated to all organisation costs for 'plasmapheresis', a part of the negative result of the comparison between costs and prices for this activity may require discussion concerning this allocation. If a smaller part of the organisation costs was allocated to plasmapheresis, the total costs would be reduced accordingly.

Key points

- **The difference between the cost of a litre of plasma from plasmapheresis and the price received for this litre of plasma depends on the allocation of the structure costs on this activity**
- **We did not receive the cost structure used by the VDB**

2.1.3 Plasma collection in other countries

2.1.3.1 Plasma collection in Germany

General Points

Blood and plasma donation are organized within a strict legal framework defined by law. The Transfusion Act (Transfusionsgesetz- TFG) [11] sets out the key principles and rules that blood donation must follow: donor selection, information, blood tests and blood quality control, financial compensation, epidemiology data, data protection, follow-up of blood donations.

Principle of unpaid donation and financial compensation

Concerning financial issues, the key principle is that blood donation in general (full blood and/or plasma) must remain unpaid. However, financial compensation can be awarded to the donor ("may", as it is not mandatory), provided it is directly and clearly connected with donation-related costs, in practice: travel costs, car park, and time spent for donation.

The maximum amount of this financial compensation has been set out by the German legislation, ie 25€. However, as explained further in this report, each institution enjoys a complete freedom in this field: whereas some do reward donors (eg: Private Plasma donation centres), some other do not (eg: German Red Cross Institutions). The amount of the compensation is left to each institution's discretion, within the limit of 25€.

Free Competition between institutions of blood and plasma donation

Unlike in other countries, blood donation is not organized on a monopoly basis. Public and private institutions are allowed to compete with each other, in the field of blood donation and plasma donation alike. Three institutions have emerged in the field of donation: University-hospitals, German Red Cross Institutions, and Private Donation Centres.

However, it is also important to underline that these institutions, although competing with each other in day-to-day donation are required to cooperate with each other in case of shortage (mutual delivery of blood, plasma, or blood and plasma products).

This support service was already implemented on the field in 2007, when 300 000 pockets of Red Cells Concentrate have been shipped by the Red Cross to the University-Hospital donation centres.

In practice, as explained further in this report, plasma collection as such is largely performed by purely private or industry-driven institutions.

Clinical Issues: German Guidelines of 2005 on plasmapheresis and ongoing studies (SIPLA Studies)

Specific "Richtlinien" (mandatory guidelines) have been issued, and titled: "Guidelines for the Collection of blood and blood components and utilization of blood products (haemotherapy)" Established by the German Order of Doctors and agreed with the Paul-Ehrlich Institut, pursuant to the Transfusion Act [12].

These guidelines have been defined by the National Order of Doctors and the Paul Ehrlich Institut. However, in today's form, these guidelines are not considered as utterly satisfactory by most stakeholders, and a specific working group has been set out, and specific studies have been carried out ("Study on the Safety of Long-Term Intensive Plasmapheresis in Donors" also known as SIPLA I, and SIPLA II Studies"), in order to formulate new propositions on specific points, and to improve the volume of donations, while ensuring the protection of the donor's health.

Role of the German Red Cross (DRK) compared to private firms in the plasma collection industry

According to the German legislation, free competition is allowed between a large number of institutions, public and private alike. Today's picture of plasma collection in Germany is very specific as purely private firms or institutions have been more and more involved in this field, over the last years. These private firms resort to clearly customer-oriented and profit-centred strategies.

An in-depth survey conducted by Robert Koch Institute on distribution of plasma collection in 2006. This survey focused on the number of plasma repeat donors. It clearly showed that the number of donors from industry-driven centres and private centres amount for more than 81.6% of the total number of plasma repeat donors. The number of plasma repeat donors from the Red Cross is much smaller (10.4%). So is the number of repeat donors from Federal or municipal centres (8%).

Considering the volume of plasma delivered for fractionation, approximately half of this volume comes from plasmapheresis. This is of key importance, as private centres (industry-driven centres or private donation centres) design specific strategies targeting plasma donors, whereas the Red Cross did not (mainly for historical reasons).

All principles and rules detailed in the Appendix (see Appendix "Germany") relating to the German Red Cross – especially the campaign and information material – are in use both for full blood and plasma collection. Indeed, no specific campaign has been designed for plasma donation as such, unlike in the industry-driven or private donation centres.

Demographic dimension of plasma donation in Germany: survey of Robert Koch institute

The first objective of the survey was to conduct an in-depth analysis the demographic profile of plasma donors in Germany especially concerning distribution of age groups among plasma donors, in each type of institutions (Website: http://www.rki.de/).

The final objective of the survey was to analyze the possible impact of demographic changes of the German population on plasma donation over the next decades.

Distribution of age groups for blood donors highlights the crucial role of young people in plasma donation, ie people younger than 44 and among them those below 25. As shown on the graph below distribution of age groups is clearly uneven:

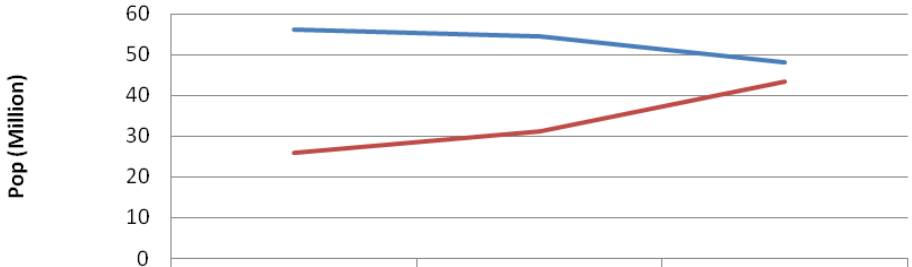
Table 9: Distribution of Donors 2006 Source: Robert Koch Institute

Age	18-24	25-34	35-44	45-54	55-68
New donors 2006 %	**51**	**24**	15	7	2
Repeat Donors 2006 %	**37**	**25**	21	15	2

Over the next decades, the German general population will undergo major changes, especially in terms of age structure. The objective of the survey was to make a quick synthesis on the main demographic trends and to analyze their impact on the donors population. In line with the German regulation and the guidelines mentioned above, the "Population within the donor age limits" is defined as people between 18 and 68.

Based on the data of the German statistical office (Destatis) the size of this population will evolve as below:

Figure 2: Demographic prospects in Germany 2006-2031 (Age distribution)



	2006	2016	2031
Pop 18-68	56,2	54,6	48
Pop>68	25,8	31,2	43,3

Source: German Federal Statistical Office

Divergence between these both trends has been clearly highlighted by Robert Koch Institute as an ageing population means an increase of potential recipients. On the long term, it could raise major problems in terms of supply/demand. In order to prevent shortfalls in plasma supply, it is clear that the number of donors should be raised over the whole population of potential donors (ie 18-68). Emphasis should also be laid on retention of donors. Private centres and industry-driven centres will face major difficulties unless they recruit a much large number of donors in higher age groups (above 35) than they do today.

Further information on donation campaign and demographic issues in Appendix "Germany"

Key points

- **Maximisation of individual donation volume is one of the key issues of ongoing studies in Germany.**
- **Considering plasma delivered for fractionation, plasmapheresis plays an important role, and is largely performed by private centres.**
- **Plasma donors' profile is quite specific: younger, more-educated, less involved in professional life, and less often married.**
- **"Real World" communication campaigns and practical follow-up of donors with modern techniques are of key importance to improve retention of donors. Interface with the education system is also of paramount importance.**
- **Great attention is paid to the demographic dimension to adjust recruitment and retention policy accordingly.**

2.1.3.2 Plasma collection in France

Historical Background

For historical reasons, collection and fractionation activities have been clearly split between two different institutions:

- Etablissement Français du Sang (EFS) for collection and vigilance activities (and other specific activities / see below)
- Laboratoire Français de Fractionnement et de Biotechnologie (LFB) for fractionation activities, marketing of plasma-derived products, and Biotechnology R&D.

In their own respective fields of activity, each of these institutions enjoys a monopoly. For practical reasons, both institutions have to work in connection under the supervision of public authorities. However, they are matters for different legal statuses.

Safety and security requirements

The AFSSAPS – Agence Française de Sécurité Sanitaire des Produits de Santé French Agency for the Safety of Health Products (Decision of 6 November 2006) is in charge of seting out security rules, defining and disseminating best practices, but also ensuring propoer monitoring of blood and plasma-derived products (see further).

EU legal requirements are obviously applicable in the field of blood donation, quality and safety, as described above in the report

Legal status and missions of the Etablissement Français du Sang -EFS

LEGAL STATUS

The EFS has been created in 2000, is a public-law body and comprises one national head office and 17 regional branches. Key members of its Board of Administration are representatives of the Department of Health, Ministry of Finance, and Ministry of Research. Representatives of the Health Care Insurance Funds are also members of the Board. While being a public institution one must notice that the EFS does not receive any public subsidy (most of its resources stem from the sale of labile products to hospitals) See website:

http://www.dondusang.net/rewrite/heading/1.htm?idRubrique=1) .

THE MISSIONS OF THE EFS

These missions have been set out by the French legislation as follows:

- Collection of blood and plasma: See also Appendix "France" on collection issues
- Ensuring self-sufficiency
- Vigilance activities: ensuring actual application of safety and quality requirements, especially good practices set out by the AFSSAPS mentioned above.
- Implementing highly-skilled technical and research activities in connection with blood/tissue: stem cells bank, bone marrow transplants, placental blood, etc…
- Delivery of labile products to hospitals for transfusion purposes
- Delivery of plasma to the LFB for fractionation purposes (official delivery targets)
- International cooperation activities

Legal Status and missions of the Laboratoire Français de Fractionnement et de Biotechnologie - LFB

LEGAL STATUS

In 2005, LFB (formerly public-law structure) has been transformed into a private-law firm (Edict of 28 July 2005) [13]. However, key members of the Board of Administration are representatives of public authorities (Department of Health, Ministry of Finance), and the majority of the LFB's shares remains in the hands of public stakeholders only.

In today's form, LFB is a holding company that controls two subsidiary companies:

- LFB Biomédicaments (specialized in plasma fractionation and marketing of plasma-derived products).
- LFB Biotechnologies (specialized in Biotechnology R&D)

THE MISSIONS OF THE LFB

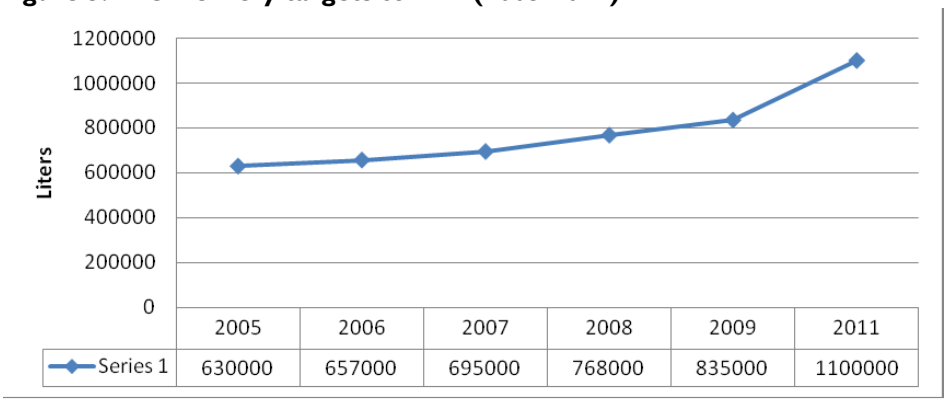
LFB is specialized in the following fields:

- Immunology: primary immune deficiency, secondary immune deficiency, Kawasaki disease, Guillain-Barré syndrome, etc..
- Hemostasy / Clotting factors: mainly von Willbrand and haemophilia
- Anaesthesia / Resuscitation products
- RD activities in the field of Biotechnology:
- International activities: as most private firms of this industry, LFB is also committed in international activities, especially in plasma fractionation. As described below in the report, it plays an important role on the Brazilian market, as it will assist Brazilian stakeholders in setting up plasma fractionation facilities, and a sustainable supply chain.

Connection between the EFS towards the LFB

As far as delivery of plasma is concerned, specific targets are fixed between EFS and LFB whereby, the volume of plasma to be delivered by EFS to the FFB is officially set out [14]. These targets are opposable to the EFS. Therefore, the key strategic objective of the latter is to keep up with the evolution of LFB supply needs. Delivery targets have evolved and will evolve as below (liters):

Figure 3: EFS Delivery targets to LFB (2005-2011)



Source: EFS Corporate data

This key driver for the EFS is basically to increase its plasma supply in order to meet the EFS needs, which thus involves an in-depth reflection on the whole collection strategy and processes. Besides, the sale price of the plasma is fixed nationally by the Department of Health. Over the last years, it was reduced from 155 € to 135€ in 2007, and to 105€ in 2008. For all these reasons, the EFS steadily needs to improve its productivity (in terms of process) and also the total volume of collected plasma.

In 2008:

- 73% of plasma delivered to LFB stems from traditional whole blood technique.
- 27% from other techniques: plasmapheresis, combined apheresis, and mixed platelets concentrates (MPC).

Cost control and EFS processes

Costs Issues

As mentioned above the EFS has to reach very demanding delivery targets, under strict constraints, especially unilateral sale prices fixing by the Departement of Health. Therefore, the EFS is compelled to deliver an increasing volume of blood to LFB 630 000 liters in 2006; 1,1 Millions liters scheduled for 2011.

The main problems for EFS managers are obviously to ensure overall financial balance of collection activities, but also to avoid discrepancies between the collection costs of blood and plasma. One of main driver for EFS's decision makers is to cut down apherese plasma production costs, step by step, thanks to an increased collection of actually collected plasma and a rationalization of collection techniques.

DISTRIBUTION BETWEEN APHERESE PLASMA AND RECOVERED PLASMA

In 2007, around 20% of plasma comes from apherese plasma whereas 80% remains recovered plasma. The objective of the EFS is to raise the share of apherese plama over the next year, for technical reasons (mainly increased frequency of donations). Frequency of donation is all the more important as the proportion of donors in the French population remains low (around 4% of the overall population). However, one must bear in mind that cost breakdown between apherese plasma and recovered plasma remains very different:

- Costs of Apherese Plasma
- 58% connected with collection step
- 42% connected with processing, vigilance, and quality-control
- Costs of Recovered Plasma
- 22% connected with collection step
- 78% connected with processing, vigilance, and quality-control

Hence, this policy will call for specific efforts and rationalization of the collection step itself as it accounts for the major part of the costs mentioned above. Rationalization can be understood as a systematic use of accurate processes and techniques, but also a better use of human resources, as described below.

CLINICAL PRACTICES AND HUMAN RESOURCES

Volume of individual donations

Across the country, clinical practices remain uneven, in the field of blood and plasma collection. As a practical matter, the volume of individual plasma collection may vary across donation centres and regions. Over the next years, one of the key issues (from a purely technical point of view) is to make sure that field practices are in line with official requirements set out by the EFS, and to standardize these practices. By doing so, the volume of individual collection could be raised significantly.

Plasmapherese techniques

Until now, 60% of apherese is performed is as a simple apherese and 40% is performed with an additive solution. Three measures will be implemented over the next years to maximize and to standardize the rentability of plasmapherese techniques:

- The more intensive use of MPC as additive solutions
- The automation of the production of the MPC

Human resources issues

The nurses' rate of activity is also a concern for the EFS: in practice, this rate is relatively low (in average around 55%), due to an inaccurate distribution of donation centres across the country and/or an inadequate organization of collection, especially considering the French sociological profile. In practice the use of donation rooms has not been rationalized yet, and the total amount of donor accommodation in donation rooms is often not fully used.

Principles on cost rationalization

Decision makers of the EFS have identified several key measures to improve cost efficiency of the donation system. All of these measures are not equally profitable for the donation system, but they all bring a helpful contribution to the smooth running of the whole process and to the best use of donated blood.

The following measures listed below have been ranked from the most profitable to the less profitable (from a cost / efficiency point of view) considering today's workforce.

- Rationalizing the use of donation rooms and raising the nurses' rate of activity: which involves a restructuring of donation facilities and a better distribution of donation. This will automatically raise the nurses' rate of activity
- Implementation of apherese with additive solution: this technique will improve individual rentability of blood donations
- Unifying and raising the volume of individual donation

Communication Campaigns: Further Information in Appendix "France : Plasma collection within the framework of EFS"

Key points

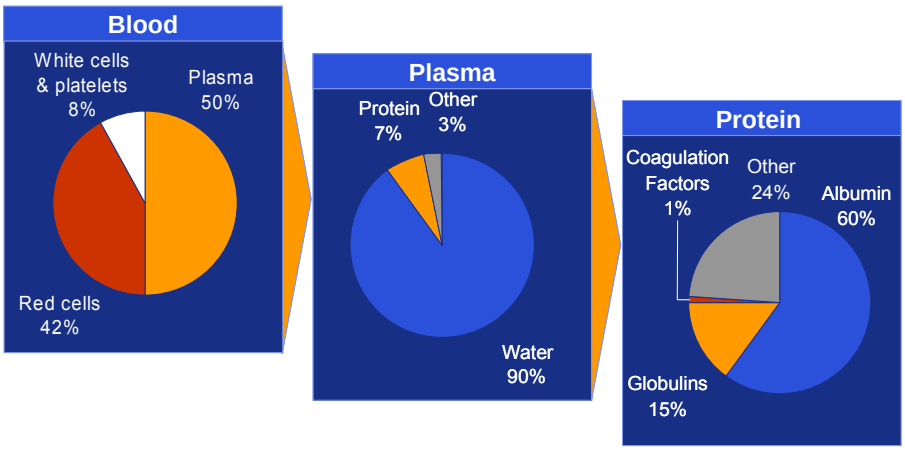
- **The French system combines public law and private law rules in the field of collection, fractionation and supply. Plasma collection is not supported by public subsidies, and the sale price of plasma is fixed by the national health authorities. Delivery targets of the EFS will be raised gradually over the next years.**
- **EFS's communication policy targets students and young adults.**
- **The main driver for the collection centres is to improve HR management, to increase individual collection volume, and to realize economies of scale.**

2.2 TRANSFORMATION OF PLASMA INTO PLASMA DERIVATIVES

2.2.1 Quick overview of fractionation process

Since the early 1940s the method of manufacturing plasma, initially developed by Pr Edwin J. Cohn, has been influenced by multiple factors, which over the years have forced the industry to adapt production in such a way that the optimal use of plasma – a human source - remains to be the leading objective. As already mentioned above, human plasma, is a unique biological material. Plasma fractionation, a "cracking" process (cf. petroleum "cracking") used to prepare therapeutic proteins, is and remains a complex process. Human plasma derived protein products have unique characteristics linked to the origin of the starting raw material. Human plasma exhibits a complex biochemical nature due to its high protein content, close to 60 g per litre, and to the diversity of its protein components.

Figure 4: Blood composition



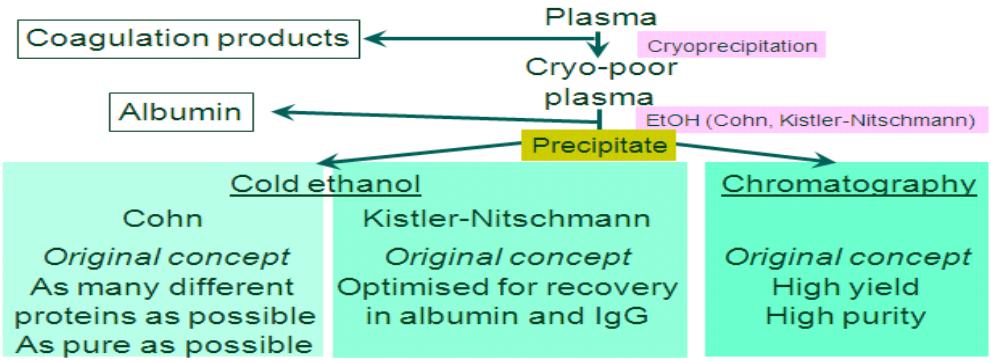
Below is a list of the best-known of those proteins which are commercially available, although one should note that the order does not reflect the relative importance of the proteins.

IVIG:	intravenous immunoglobulin
Albumin	
Factor VIII:	coagulation factor
Factor IX:	coagulation factor
AT-III:	anti-thrombin III
IMGG:	intra-muscular gammaglobulin
A1-AT:	alpha-1 anti-trypsin
Fibrin sealant	
IMGG anti-D:	intra-muscular gammaglobulin anti-Rh factor
Up to 25 others	

2.2.1.1 *Developmental nature of production*

Although the plasma derivatives industry continues to use the Cohn procedure, developed in the early 1940s by Professor E. Cohn, the products now obtained by this method bear little resemblance to those obtained during the early stages of the plasma derivatives industry. The Cohn procedure consists, fundamentally, of the precipitation of the various proteins by means of changes to pH and salt concentration levels, with the proteins being separated out by centrifugation. In order to prevent the proteins from being denatured, the work is conducted at low temperatures and ethanol is added at various concentrations. While this initial protein fractionation stage has been maintained, what has changed is the process of purifying the proteins in order to obtain a safer, purer end product.

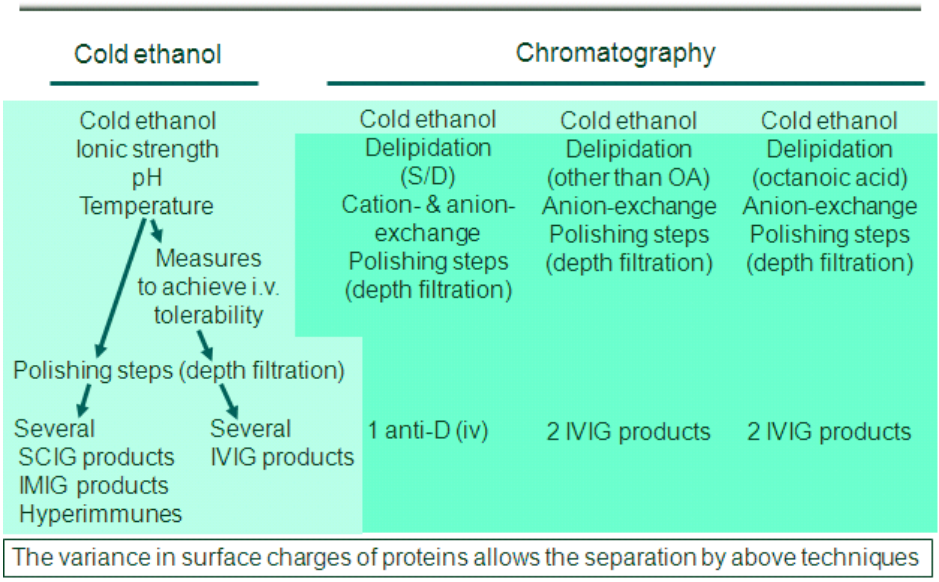
Figure 5: Schema of fractionation methods (Source: unpublished document of PPTA – Plasma Protein Therapeutics Association)



2.2.1.2 *Progress in purification*

The Cohn procedure does not produce therapeutic proteins in a pure state, and it has therefore been necessary to add purification stages which, in addition to purifying the proteins, eliminate the contaminants added during fractionation (ethanol and salts). These purification stages vary depending on the characteristics of the Cohn fraction to be purified and the nature of the product being obtained. In the case of FVIII or anti-haemophiliac factor, the development of affinity chromatography techniques (whether using monoclonal antibodies or heparin) has allowed the development of FVIII with far higher purity levels than the first FVIII used in the treatment of haemophilia. Another significant advantage is that the infusion volume of FVIII which now needs to be administered is considerably lower, with resulting improvements in patient comfort and quality of life.

Figure 6: Fractionation Techniques and Available Products (Source: unpublished document of PPTA – Plasma Protein Therapeutics Association)



Each of the affinity chromatography systems described above also requires 2 highly purified, but different, FVIII products. Purification using monoclonal antibodies (anti-FVIII antibodies produced in mouse cells and bound to the chromatography matrix) allows a very pure FVIII to be obtained. In contrast, if affinity chromatography with heparin is used, both FVIII and von Willebrand Factor are obtained. VWF protects the FVIII molecule and is used in the treatment of immuno-intolerance in haemophiliacs who have developed anti-Factor VIII antibodies, and can also be used to treat patients with von Willebrand Factor deficit.

Immunoglobulins are another group of products where the new purification techniques have led to unforeseen therapeutic progress. Originally, immunoglobulins could only be administered intramuscularly, but this method hindered the administration of sufficient quantities of immunoglobulins, thereby bringing into question their therapeutic utility.

The use of different purification stages – precipitation with polyethylene glycol, glycine etc. – and different affinity chromatography systems has made it possible to obtain intravenous immunoglobulins (IVIG). This has meant that sufficient therapeutic doses can be administered to patients, allowing not just patients with primary immunodeficiency's to benefit from such treatments (patients suffering from immunoglobulin production deficit), but also other patients with auto-immune illnesses, together with some who have neurological diseases.

2.2.1.3 Progress in safety

Because the plasma fractionation industry uses plasma as its raw material, many viral illnesses carried in the plasma can be transmitted through transfusions of the end product. In order to prevent the risk of further viral transmission, the industry developed a series of safety procedures which covered the donor, the plasma and the product. An interesting example in the development in viral safety can be found in the technical and scientific advances in the field of viral DNA detection (NAT techniques) which complement and improve upon the old viral marker techniques which used ELISA technology. The old techniques were based on detecting antibodies to different viruses. However, as there is a variable time period (known as the 'window period') between initial infection and the production of antibodies depending on the virus type, there is a danger that plasma with a low viral load which has tested negative using ELISA techniques can still be used in plasma fractionation.

NAT technology for viral DNA detection has dramatically reduced this window period. Negative results from the subsequent application of NAT technology to the plasma pool for a range of viruses (HCV, HIV, Parvo B19, HBV, etc.) provide assurance that the initial viral load in the plasma pool is zero or very low.

2.2.2 The worldwide supply of plasma products

2.2.2.1 Corporate structure of the market of plasma products

Restructuring of the sector of plasma products

Considering the increasing and vital needs of plasma products in most western countries, and simultaneously the uncertain level of donation, purchasers of plasma products – ie hospitals, and more generally health care institutions – can feel in an inferior position towards the plasma fractionation industry.

The evolution of medical practices and also the political pressure of patient associations on health authorities do not leave them much room for manoeuvre. Therefore it is important to analyze the recent evolution of this industry to have a clear idea on the purchasers' actual negotiation power.

MAIN SPECIFICITIES OF THIS INDUSTRY SINCE THE NINETIES: FUSIONS AND MARKET CONSOLIDATION

In 1996, the number of global stakeholders in the nineties was relatively high: almost 40 companies (or non profit organisations) were identified worldwide in the plasma fractionation industry. Following several merger waves, only 20 companies still exist today.

Among these 20 companies some of them do not play a noticeable role on the global market because of their size or because of regulatory barriers that still isolate their domestic market from the international market. Hence, only a very small number of companies can be considered as real "global players" in terms of economic weight: and market share.

CURRENT SITUATION (2003-2005)

Worldwide, only five private companies still play an important role (>5%) on the global market. Non profit organizations are also important stakeholders; however some of them enjoy a monopoly, based on a specific national regulation.

Table 10: Global firms on the plasma product industry

	2003	2005
Baxter	18.4%	19.5%
State ruled or on Profit Organisations	23.1%	16.5%
CSL-Behring	15.8%	17.1%
Talecris / Bayer	14.2%	13.8%
Octapharma	5.7%	7.1%
Grifols	7.6%	6.1%
CSL/ZLB / Bioplasma	6%	1.6%
Other	9.1%	18.2%
Total	100%	100%

GEOGRAPHICAL DIMENSION OF THIS INDUSTRY:

Table 11: Geographical dimension of the plasma product industry

'MM US$	Oceania	Africa	South America	Middle East	Asia-Pacific	Europe	North America	World Total
Baxter	13.22	8.77	174.12	26.31	74.81	557.20	1230	2084.4
CSL-Behring	116.54	13.08	72.4	39.2	191.54	539.98	929.74	1902.47
Talecris	0	5.12	19.3	15.37	55.58	128.65	925.79	1149.81
Octapharma	24.5	32.25	98.78	96.75	23.07	382.98	205.75	864.08
Grifols	0	1.53	40.59	4.60	16.66	413.59	270.65	747.63

Leaving aside non profit or public organisations (the strategy of which is largely connected with specific national regulations), private companies' strategies is obviously guided by financial prospects and expected profits on each geographical area. In that respect, the North-American area remains the most attractive geographical area for plasma fractionation firms.

Therefore, European buyers are apt to compete with American ones, and a harsh competition could arise at any time between them with two possible consequences: punctual supply shortage and/or sharp increase in the prices of plasma-derived products.

Capital structure: Four profiles identified

As far as capital structure is concerned, one must notice that four profiles of capital structure have emerged, generally due to specific and deliberate corporate strategies. In other cases, (public institutions or other structures commissioned by public authorities) capital structure is closely connected with the monopoly status of the institution or specific national regulations.

PROFILE 1: PRIVATE OWNED FIRMS (OCTAPHARMA AND GRIFOLS)

These two firms are relatively close situations from this point of view: Octapharma is as a private-owned firm, and so is Grifols. In both cases, other stakeholders (especially banks) can play an important role in capital structure. However, private and family stakeholders remain the key investors in both cases and key stakeholders often remain deeply connected with the national or even regional economy (Switzerland / Catalonia).

PROFILE 2: NATIONAL STATE-CONTROLLED FIRMS OR INSTITUTIONS (LFB)

In several western countries, fractionation firms enjoy a monopoly as defined by a specific regulation (generally for historical or cultural reasons). In this case, the firm is either owned or controlled by public stakeholders, ie governmental institutions or institutions commissioned by the government.

LFB in France is a traditional example: it enjoys a monopoly in plasma fractionation based on a French specific regulation. Before 2005, LFB used to be a public-law institution. Since then, it has been transformed into a private law holding company (legally a Ltd company) divided into two subsidiary companies: one focusing on Biotechnology, one focusing on Plasma fractionation. The capital of both subsidiary companies is state-controlled. Key members of the Board of Administration are government's representatives (Ministry of Finance, Ministry of Health).

PROFILE 3: FOREIGN-OWNED FIRMS (CSL-BEHRING)

CSL-Behring is a very specific case: it was originally a German firm, CSL Behring became a subsidiary of CSL Limited, a biopharmaceutical company headquartered in Melbourne, Australia. From a financial point of view, about 90% of the shares are now controlled by Australian stakeholders. Therefore, even if CSL-Behring's main facilities and RD centres are still located in Europe, it is under the control of foreign-based institutions.

PROFILE 4: TRADITIONAL PRIVATE FIRMS (US FIRMS: BAXTER, TALECRIS)

These firms' capital structure is more traditional, as their capital is owned by private stakeholders (eg: Telecris is owned by private equity groups Cerberus Partners and Ampersand Ventures).

In may 2009, CSL tried to take over the US firm Talecris mentioned above. However, the US Federal Trade Commission recommended legal actions to block the purchase of Talecris by CSL, on antitrust grounds. US public authorities**,** especially the new American administration, seems to keep a vigilant eye on this industry, especially on merging of business, whenever it is apt to have an impact on the American

Main learnings for decision-makers:

- The capital ownership of the leading global firms of the plasma fractionation industry is unlikely to evolve over the next years and this industry, in today's form, seems to be blocked.
- Restructuring of the plasma fractionation industry: the recent merging of businesses and the increasing weight of each firm (considered individually) can be seen as a rather negative evolution for the purchasers' negotiation power.

Key points

- **The recent merging of businesses has involved a high concentration of fractionation activities. Given this context, the negotiation power of purchasers (disregarding public or private status) is getting weaker.**
- **In the context of a global fractionation industry, any change in the prescription habits or authorization of drugs of one country is apt to have an impact on the production flows of any other country. Great attention must be paid to the US policy on that point.**

2.2.3 The supply of plasma stable derivatives in Belgium

2.2.3.1 Who are the suppliers

The plasma collected by the Belgian Red Cross Blood Services - source plasma (SP) as well as recovered plasma (RP) - is sent to CAF-DCF for fractionation[b]. CAF-DCF is the exclusive manufacturer of plasma derivatives based on plasma collected in Belgium. All locally produced derivatives are intended to be used within the country. The CAF-DCF was historically an integral part of the Belgian Red Cross up to the 23 December 1997. From that date, the independent CAF-DCF was set up as a cooperative company with limited liability. Today the owners of the shares are:

- the Sanquin Bloodsupply Foundation (Nl) 50.02%,
- the Laboratoire français du fractionnement et des biotechnologies, LFB (Fr), a limited company created in July 2005 and fully owned by the French State 24.99% and
- the Belgian Red Cross 24.99%.

Besides that, CAF-DCF has signed a cooperation contract with the German company Biotest for the fractionation of intermediate plasma products into immunoglobulins. CAF-DCF also fractionates for international firms, its total fractionation capacity is centered between 500.000 and 550.000 kilo of plasma

b Except for a limited amount that is transformed into fresh frozen plasma, used to treat specific hemorrhagic situations and some coagulation disorders

It is surprising to find that the capital of the company with a monopoly on the fractionation of plasma collected in Belgium is mainly in the hands of foreign partners. Granting a monopoly to an enterprise only makes sense if, in exchange for this monopoly, the enterprise in question fulfils a mission of collective interest, and if the authority that granted this monopoly can control what use is made of it. In this particular case, control of the CAF-DCF by the public authorities is difficult, verging on the impossible, given the minority stake held by the Belgian partner. In addition, it seems that there is no agreement or norm binding the CAF-DCF in terms of the organisation and intended use of its output.

It should also be noted that the Board of Administration of CAF-DCF consists as well of suppliers (CR) as clients (e.g. Sanquin), having diverging interests.

2.2.3.2 Quantities fractionated by CAF-DCF

The following table presents the quantities of plasma (RP & SP) purchased by CAF-DCF from all collectors, as well as the quantities really used for fractionation each year by the CAF-DCF.

Table 12: Purchased and fractionated quantities (2000-2008)

in litres	2000	2001	2002	2003	2004	2005	2006	2007	2008
Plasma purchased by CAF (source: Federal Agency for Medicines)	219.552	218.200	213.869	205.578	220.163	195.945	179.553	167.634	163.089
Plasma fractionated by CAF (source: CAF-DCF)	190.964	192.648	206.015	212.827	210.578	178.249	182.149	170.497	159.421
Differences (calculated by KCE)	28.588	25.552	7.854	-7.249	9.585	17.696	-2.596	-2.863	3.668

CAF-DCF reported a quite strait competition on the Belgian market and the underlying reduction of plasma collection to explain the constant reduction of fractionated plasma.

It must be noted that, overall, CAF-DCF fractionates a smaller volume than the actually purchased volume. Strategic stocks are then constituted, which can prove helpful whenever quantities of collected plasma are not sufficient to fulfill the demand. In 2003, 2006 and 2007, we observe that stocks had to be tapped. This tapping of the stock is confirmed by the audit reports of Verhaegen[9] and PWC[15].

Availability of strategic stocks at the end of each year have been communicated by CAF-DCF and recorded on the first line of the table below. If we add to the yearly recorded strategic stock, the volume of plasma bought to the Red Cross the following year - but not fractionated, and if we subtract the strategic stock recorded at the end of the following year, we calculate a yearly balance, shown on the last line of the table below.

Table 13: Stocks and balances (2000-2008)

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Stategic stock	78.010	81.095	86.684	83.170	76.673	90.819	58.588	48.342	34.803
Purchased - fractionated	28.588	25.552	7.854	-7.249	9.585	17.696	-2.596	-2.863	3.668
Balances		22.467	2.265	-3.735	16.082	3.550	29.635	7.383	17.207

Calculated by KCE and based on CAF-DCF data

According to CAF-DCF, it is normal that the yearly variations in the volume of the strategic stock do not correspond to the differences between the volume of purchased plasma and the one of fractionated plasma. Indeed, losses may occur along the process e.g. when testing reveals that a batch of plasma is infected, as well as production losses - or even volumes of plasma put into quarantine for testing purposes, and thus not recorded onto the strategic stock. However the volume of « lost » quantities may greatly vary from a year to another. No precise element could be collected concerning the origin of these variations.

2.2.3.3 *Produced and sold quantities*

Based on the availability of volumes of plasma fractionated by CAF-DCF, volumes of derivatives manufactured from this plasma, and yearly volume of sales, we can make the following analysis.

The first finding is the bearish trend for the sale of specific derivatives. The risk of (and fear for) disease transmitted by plasma derivatives has probably contributed to the variations in the amounts of derivatives sold. For instance, the risk for Creutzfeld Jacob or other transmissible disease has contributed the increasing use of recombinant coagulation factors to treat hemophilia, and subsequent decreasing use of plasma derived factors. Indeed in 2004, the Belgian authorities have reported that Belgian hemophilic patients had received coagulation factors prepared from a European plasma pool that could have been contaminated with prions.[c]

We will focus the following analysis on albumin and immunoglobulins.

Albumin

The first calculus consists in dividing the number of litres of fractionated plasma by the number of actually produced grams of albumin. This ratio is decreasing since 2001 even if the level of 2008 shows a weak increase.

Table 14: Calculation of number of grams obtained from 1 litre of plasma (2000-2008)

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Plasma fractionated by CAF-DCF in litres	190.964	192.648	206.015	212.827	210.578	178.249	182.149	170.497	159.421
Albumin produced by CAF-DCF in Belgium in kg	4.679	4.873	4.755	4.873	5.005	4.264	2.419	2.607	3.085
Albumin sold by CAF-DCF in Belgium in kg	4.640	4.860	5.040	4.780	4.730	3.570	2.740	2.450	2.750
Number gr produced albumin for 1 litre plasma (calculated by KCE)	24,50	25,29	23,08	22,90	23,77	23,92	13,28	15,29	19,35

Source: CAF-DCF for the three first lines of the table

As from 2003 the intermediate albumin rich fraction is sent to Sanquin ([9] p. 12) for refining and packaging. According to Verhaegen[9], the overall cost of this processing totals 3.1 million euros in 2003 and 4.6 million euros in 2004. We calculated the volume that could have been produced, if the albumin/plasma ratio had remained identical to the one of 2001 for the reviewed years.

Table 15: Calculation of the potential production of albumins (2000-2008)

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Production of albumin if the yield equals 25,29 gr/litre	4.829	4.872	5.210	5.382	5.326	4.508	4.607	4.312	4.022
Albumin produced by CAF-DCF in Belgium in kg	4.679	4.872	4.755	4.873	5.005	4.264	2.419	2.607	3.085
Differences	150	0	455	509	321	244	2.188	1.705	1.272

Thanks to this calculus, we observe that between 0,15 and 2,18 supplementary tons of albumin per year could have been produced, technically speaking. However, line 3 of table 14 shows that no purchasers could be found for such volumes on the Belgian market. Hence, CAF-DCF had no interest to produce more albumins. The production of albumin follows the demand on the Belgian market. The real yield for fractionation of albumins ivaries between 24,6 and 25,6 gram per kilo of plasma.

[c] Service public fédéral Santé publique. Communiqué de presse du 23 novembre 2004.

This Belgian demand is function of the nature of the competition between firms present on the market and of an international underlying reduction of albumin demand. This is confirmed by a recent Australian Report of CSL where we can read that 'In Australia the amount of albumin issued per annum over the period 1994-95 to 2004-5 has increased by an average annual growth rate of ca. 1.4%, as shown in, although in the last five years this value has been higher at ca. 2.3%. In contrast, the growth in plasma collections has been ca. 6% per annum over the same period and if all of this plasma had been converted into product then Australia would have accumulated a substantial excess of albumin over requirements. Recognizing this situation, CSL was instructed to limit the production of albumin from 1999-00 onward in order to balance supply with demand. As a consequence of this policy the latest data from 2004-05 indicates that Australia can meet demand for albumin by converting only about 60% of the available plasma into finished albumin product'.[16] The same phenomenon occurred in Belgium and a proportion of collected plasma is then sold to foreign firms under the form of intermediate products.

The case of immunoglobulins

The trend identified for IG is opposed to the trend for albumin: it shows that since 2004 the quantities of IG sold by the CAF-DCF follow a rising path despite the fall in collection. This rise in sales volume might be partly explained by the desertion of the Belgian market by one firm around 2004.

Table 16: Calculation of number of grams obtained from 1 litre of plasma (2000-2008)

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Plasma fractionated by CAF	190.964	192.648	206.015	212.827	210.578	178.249	182.149	170.497	159.421
IG produced by CAF-DCF in Belgium in gr	171.000	185.000	118.000	340.000	379.000	456.000	455.000	531.000	636.000
IG sold by CAF-DCF in Belgium in gr	122.000	151.000	170.000	298.000	393.000	389.000	462.000	490.000	543.000
Number of gr of produced IG for 1 litre plasma	0,90	0,96	0,57	1,60	1,80	2,56	2,50	3,11	3,99

Source: CAF-DCF for the tree first lines of the table

The calculated ratios present a constant increase since 2000. These ratios are calculated as if all the fractionated plasma was used to produce immunoglobulins. CAF-DCF reported that the quantities of fractionated plasma used for a given derivative is always determined by the demand. The reported technical yield by the CAF-DCF is 2,7 gr/L plasma for the period 2000-2002. Since 2003, the CAF-DCF used a very performing technology to produce the Multigam. During the period 2003-2007, the yield was equal to 4,2 gr/L. In 2008, the use of the nanofiltration caused a light reduction of the yield to 3,9 gr/L. In 2008, the ratio is exactly the same as the reference mentioned in an unpublished document of PPTA (3.98 g/L). Nevertheless it seems that the world's best fractionation operators should obtain a constant yield of 5.3 g/L (CSL reference). However, as we do not have at our disposal the right data to determine the precise content of the yields identified in other countries, this comparison must be considered with care.

This evolution shows CAF-DCF's responsiveness to demand and also its capacity to raise its production at a faster pace than the one of demand.

Key points

- **The production of plasma derivatives is not carried out only by the CAF-DCF, which has concluded agreements with foreign firms to carry out a part of the process**
- **Relatively large volumes of plasma purchased by CAF-DCF do not contribute at all to the fractionation process. These volumes seem to vary greatly over the years, and this phenomenon has not been clarified.**
- **The CAF-DCF seems to experience overcapacity for specific stable derivatives. In spite of the decrease of the volumes of purchased plasma, it produces more than it actually sells on the Belgian market. A proportion of collected plasma (under the form of intermediate product) is sometimes dedicated to the production for foreign markets.**
- **Trading as well as production agreements, concluded between CAF-DCF partners, are not transparent towards the public authority, although this financially supports CAF-DCF through subsidized plasma prices.**

2.2.3.4 Position of CAF-DCF on the international market

The investments made by the CAF-DCF, notably in a new building in Neder-Over-Hembeek, enable the company to manufacture quality products that have resulted in foreign companies taking holdings in the capital of the CAF-DCF. Nevertheless, the CAF-DCF remains a very small enterprise on the world stage and its financial situation is precarious, despite the indirect subsidies it receives through the price that it pays for plasma to the Red Cross.

An audit carried out in 2006 had already highlighted the difficult financial situation of the CAF-DCF. [9] According to this audit, the results of this enterprise in Belgium were in the red for the entire period under review (2000 – 2005) and the positive results of foreign operations were not enough to offset the losses made in Belgium. As from 2003, the purchases column saw a substantial increase due to the rise in the price of plasma from plasmapheresis (+37%). Two other cost headings were also to blame for the deterioration in the financial situation of the CAF-DCF during the period in question: 'special orders' and 'purchases of stable derivatives'. The rise in the heading 'special orders' follows the closure of the former CAF fractionation factory in Ixelles. As from 2004, the plasma was fractionated into intermediate products in the factory at Neder-Over-Heembeek. The intermediate products are then sent to foreign partners for finer fractionation. Since 2002 the preparation of factor VIII has been carried out by the French company LFB. Since 2003 the albumin has been produced by Sanquin in the Netherlands. As for the rise in the heading 'purchases of stable derivatives', it results from a combination of two factors: the purchase of PPSB by Sanquin following the rise in demand for this product and the manufacture of Multigam (immunoglobulins) by the firm Biotest, which receives the intermediate products from the CAF-DCF and sends them back as the finished product.

According to the audit conducted by F. Verhaegen, this negative financial situation should improve significantly with the removal of the compulsory levy on the pharmaceutical firms.

Key points

- **The CAF-DCF is a high technology firm but rather small on the world-wide scale.**
- **The financial situation of the CAF-DCF, structurally negative between 2000 and 2005, recovered thanks to the removal of the levy on pharmaceutical products, from which plasma derivatives are currently exempt**

2.3 LIMITATIONS

The subject we are dealing with is sensitive in more than one respect. Firstly, the products in question constitute, for a number of medical conditions, the only possible therapy at the present time. In addition, the data concerning the price and the quantities collected and produced concern actors that play an important role in this sector. It is therefore essential to have validated data in order to be able to draw relevant conclusions. It is also essential to identify the reasons why caution is necessary in the formulation of certain findings and conclusions, and we present here the limitations of our analysis.

The first limitation concerns the cost of plasmapheresis. We have seen that the allocation of organisation costs to this activity, compared with the other activities of the Red Cross, could have a decisive effect on the real cost of the activity in question.

The second limitation is related to the profitability of plasmapheresis. We are not in a position to establish with certainty the price at which the Red Cross could sell, or could have sold, plasma on the international market. The various data collected show that we cannot be sure of the profitability of such an approach because of the variability of prices in time and space.

3 DEMAND FOR PLASMA DERIVATIVES: THE CASE OF IMMUNOGLOBULINS

This chapter aims at describing the quantities of plasma derivatives used in Belgium, how they are used and what are the future trends in consumption. The purpose is to subsequently compare quantities used and quantities supplied.

Since polyvalent immunoglobulin (IG) is the plasma derivative considered as the market driver for plasma procurement, we have focused most of our research on IG.[17] In a first phase, we have studied the indications for IG use: we have compared the recommendations for IG use in Belgium and in other industrialized countries and reviewed the scientific evidence on IG effectiveness. In a second phase, we have analyzed the quantities of IG that are used in Belgium and in other countries, the amounts that would be required to treat the main indications and how can IG consumption be rationalized and reduced.

3.1 USE OF PLASMA DERIVATIVES IN BELGIUM

We collected data on the use of plasma derivatives in Belgium to determine the quantities and expenses involved in the recent years, as well as to identify recent trends.

3.1.1 Methods

The National Institute for Health and Disability Insurance (NIHDI or INAMI/RIZIV) provided us with national data on reimbursed plasma derivatives for the period 2004-2006 with the following relevant information: hospital, ward (inpatient or outpatient), trimester, category of reimbursement, ATC code 5 (J06BA01 et J06BA02), number of packages and price. These data have been checked for consistence between the number of items and the expenses. The yearly quantities of each derivative have been computed in grams or international units (IU) by year and by type of producer, categorized in CAF-DCF (Centrale Afdeling voor Fractionering - Département Central de Fractionnement) or non CAF-DCF.

We had no access to data on non-reimbursed plasma derivatives and derivatives used for compassionate use.

3.1.2 Results

The yearly amounts of the main reimbursed derivatives are presented in Table 17. Recombinant coagulation factors, obtained using recombinant DNA technology, are also mentioned (in italic). Though they are not derived from plasma, their evolution influences the trends in plasma derived factors.

Over the period 2004-2006, the following trends in consumption are observed: human factors VIII and IX are decreasing by more than half (-61% and -56% respectively), parallel to an increase in recombinant factors; von Willebrand factors are doubling; the use of FEIBA and sub-cutaneous immunoglobulins are emerging; and intravenous immunoglobulins have increased by 11%. The consumption of CAF-DCF products has been compared to those from other producers on the Belgian market: all CAF-DCF products show a sharp decrease in quantities, except for immunoglobulins (+18%) and PPSB (+16%). This decrease can not be exclusively explained by the increase in recombinant product use.

Table 17: Main plasma derivatives and recombinant factors reimbursed by the National Institute for Health and Disability Insurance (NIHDI) in kU or grams

Plasma derivatives and equivalents	2004	2005	2006
PPSB CAF	5.193 kU	5.825 kU	6.013 kU
Fact VIII	43.606 kU	52.153 kU	58.148 kU
Fact VIII-human CAF	4.049 kU	3.404 kU	1.598 kU
Fact VIII-recombinant	*39.557 kU*	*48.749 kU*	*56.550 kU*
Factor Eight Inhibitor Bypassing Activity (FEIBA)	65 kU	206 kU	839 kU
Factor IX-human	2.069 kU	1.293 kU	908 kU
Factor IX-human CAF	1.921 kU	1.045 kU	602 kU
Factor IX-human not-CAF	148 kU	248 kU	306 kU
Factor IX-recombinant	*1.825 kU*	*3.537 kU*	*4.789 kU*
Fact VII-human CAF	101 kU	110 kU	24 kU
Factor VIIa-recombinant	*375.324 kU*	*265.866 kU*	*127.588 kU*
Von Willebrand +/- Fact VIII	2.011 kU	3.978 kU	4.605 kU
von Willebrand +/- Fact VIII CAF	1.226 kU	1.001 kU	829 kU
von Willebrand +/- Fact VIII not-CAF	785 kU	2.978 kU	3.776 kU
Factor XIII-human	13 kU	11 kU	9 kU
Alb & SSPP	4.599.557 gr	4.904.672 gr	4.224.990 gr
Alb & SSPP CAF	4.416.990 gr	3.543.800 gr	2.479.800 gr
Alb & SSPP not-CAF	182.568 gr	1.360.873 gr	1.745.190 gr
SC Immunoglobulins polyvalent	0 gr	115 gr	3.604 gr
IV Immunoglobulins polyvalent	749.559 gr	773.486 gr	828.546 gr
IV Immunoglobulins polyvalent CAF	353.058 gr	356.314 gr	416.363 gr
IV Immunoglobulins polyvalent not-CAF	396.501 gr	417.172 gr	412.183 gr
Antithrombine III	803 kU	1.112 kU	721 kU
Fragmin	0 kU	0 kU	0 kU
C protein	0 kU	0 kU	0 kU

Table 18 presents the national expenses in plasma derivatives and recombinant factors by year, the changes in expenses over the 3 year period (in percent increase compared to 2004) and the proportion of each product expense related to the total expenses for all derivatives (recombinant included). The cost of human derivatives stayed relatively stable over the 3 years, while the cost of recombinant increased by 35% (mostly due to an 43% increase in Factor VIII recombinant). The trends in human derivative expenses follows the same patterns than the trends in quantities reimbursed. All together, plasma derivatives and recombinant factors represented in 2006 3% of all drug expenses from the health budget.

In 2006, the cost of recombinant products represented 52% of total expenses, with recombinant Factor VIII alone representing 48% of all expenses. Among human derivatives, the highest expense was due to intravenous immunoglobulins (33.4 millions € or 62% of human derivatives), followed by albumin and SSPP (12.2 millions € or 23% of human derivatives).

Table 18: Plasma derivatives and recombinant factors reimbursed by the NIHDI in euros

Plasma derivative	2004	2005	2006	Increase (%) from 2004 to 2006	% of total (2006)
PPSB CAF	**3.085.617**	**3.460.927**	**3.538.650**	**+15%**	**3%**
Fact VIII	**40.985.245**	**49.261.250**	**55.007.814**	**+34%**	**49%**
Fact VIII-human CAF	3.641.669	3.346.896	1.529.897	-58%	1%
Fact VIII-recombinant	*37.343.576*	*45.914.354*	*53.477.916*	*+43%*	*48%*
FEIBA	**44.564**	**141.977**	**578.834**	**+1199%**	**1%**
Factor IX-human	**1.300.125**	**804.461**	**541.869**	**-58%**	**0%**
Factor IX-human CAF	1.220.440	671.533	378.548	-69%	0%
Factor IX-human not-CAF	79.685	132.928	163.321	+105%	0%
Factor IX-recombinant	***1.482.492***	***2.866.969***	***3.639.488***	***+145%***	***3%***
Fact VII-human CAF	**47.712**	**52.041**	**11.280**	**-76%**	**0%**
Factor VIIa-recombinant	***4.606.335***	***3.262.395***	***1.565.229***	***-66%***	***1%***
von Willebrand +/- Fact VIII	**838.996**	**1.246.384**	**1.335.818**	**+59%**	**1%**
von Willebrand +/- Fact VIII CAF	651.254	531.557	439.080	-33%	
von Willebrand +/- Fact VIII not-CAF	187.741	714.826	896.738	+378%	
Factor XIII-human	**3.941**	**4.751**	**4.034**	**+2%**	**0%**
Alb & SSPP	**13.578.166**	**14.248.444**	**12.200.319**	**-10%**	**11%**
Alb & SSPP CAF	13.061.558	10.499.273	7.416.617	-43%	7%
Alb & SSPP not-CAF	516.470	3.749.154	4.783.694	+826%	4%
Other plasma protein fractions	**138**	**17**	**8**	**-94%**	**0%**
SC Immunoglobulins polyvalent	**0**	**5.231**	**165.310**	**-**	**0%**
IV Immunoglobulins polyvalent	**30.448.581**	**31.498.645**	**33.450.863**	**+10%**	**30%**
IV Immunoglobulins polyvalent CAF	14.137.200	14.262.430	16.485.695	+17%	15%
IV Immunoglobulins polyv. not-CAF	16.311.381	17.236.216	16.965.168	+4%	15%
Antithrombine III	**446.735**	**566.246**	**377.277**	**-16%**	**0%**
Total all products	**96.868.647**	**107.419.738**	**112.416.793**	**+5%**	**100%**
Total human derivatives	**53,436,244**	**55,376,020**	**53,734,159**	**+1%**	**48%**
Total recombinant factors	***43,432,403***	***52,043,718***	***58,682,633***	***+35%***	***52%***

3.1.3 The case of immunoglobulins

The remaining of this chapter focuses on polyvalent immunoglobulins (IG). Demand in immunoglobulins is the highest among all derivatives when considering the amount of plasma required to produce it. Its use continues to grow as the number of clinical indications for IG keeps increasing. This increased demand resulted in severe product shortages in the late 1990's in the US and a number of other countries, impacting IG supply in Belgium. In addition, IG is important in terms of amounts involved and budget impact in Belgium, representing 62% of expenses in human plasma derivatives in 2006.

In this chapter, IG is used to describe pooled polyvalent human immunoglobulin, that can be administered intravenously or subcutaneously; IG does not cover hyperimmune or specific immunoglobulins.

Polyvalent IG are used to treat a wide range of diseases due to three major therapeutic properties: IG can replace or supplement antibodies in immunodeficiency diseases, in order to restore normal humoral immune function; IG has an immunomodulatory action in various autoimmune conditions and inflammatory diseases; and IG may be used as prophylaxis or therapeutic adjunct against some infectious agents in patients with normal immune humoral function. After IG was shown to be effective in the treatment of auto-immune and inflammatory disorders, the list of disease for which it is used has grown rapidly.

3.2 INDICATIONS FOR IMMUNOGLOBULINS

This section aims at identifying the diseases requiring significant amounts of immunoglobulins, to enable interpretation of IG amounts consumed or calculation of amounts required. We describe and compare the recommendations for IG use in Belgium and in five other industrialized countries. Based on the indications that are included in at least one country (29 indications), we present a review of the scientific evidence on IG effectiveness to date.

Warning: In this document, the term indication is used to refer to a disease or syndrome for which immunoglobulin (IG) is used or considered to be used. It does not stand for "authorized indication" or "licensed indication", which refers to the indications proposed by the manufacturer and authorized by the drug regulatory authority.

3.2.1 Recommendations for the use of immunoglobulins

The recommendations on which diseases can be treated with polyvalent immunoglobulins vary per country, as well as the status of the recommendations.

A few countries have developed full evidence-based guidelines, such as Canada and the United Kingdom (UK), extending recommendations beyond the labelled indications; other countries, such as Belgium, did not develop guidelines yet but have legally defined a list of reimbursed indications; for others countries, such as the Netherlands, a list of "labelled" indications is presented (i.e. indications approved by the regulatory drug agency). As a consequence, the legal status of these recommendations differs per country.

3.2.1.1 Recommendations in Belgium

In Belgium, official recommendations for IG use have not been yet published, but guidelines for IG use are currently under development by the Health Council (CSS/HGR). The only sources for guidance on IG use are the list of indications that are authorized in Belgium for each IG brand product (labelled indications) and the list of reimbursed indications and criteria for reimbursement for each indication, stated in the law (Table 19):

- The authorized indications vary per brand product and over time.
- The indications and criteria for which IG are reimbursed by the INAMI/RIZIV are described in the Royal Decree from 21 December 2001, with last modification stated in the Ministerial Decree from 15 July 2008.[d]

Intravenous immunoglobulins

In Belgium, several brands or pharmaceutical specialities of intravenous immunoglobulins (IVIG) are registered. Though reimbursed indications vary per brand product, the following pathologies are considered in the decree and summarized in Table 19:

1. Haematological indications
   - Primary immune deficiency conditions: agammaglobulinemia; hypogammaglobulinemia with specific criteria; congenital deficiency in anti-polysaccharidic antibodies (providing specific criteria are met)
   - Secondary immune deficiency:
     - Multiple myeloma and chronic lymphocytic leukaemia with severe hypogammaglobulinemia and recurrent infections
     - Prevention of infections in patients having an allogenic bone marrow transplant
     - Paediatric AIDS
     - Treatment of septicaemia in preterm infants and neonates

[d] Arrêté ministériel du 18 juillet 2008 modifiant la liste jointe à l'arrêté royal du 21 décembre 2001 fixant les procédures, délais et conditions en matière d'intervention de l'assurance obligatoire soins de santé et indemnités dans le coût des spécialités pharmaceutiques (MB 18 JUILLET 2008 DEUXIEME EDITION).

- Idiopathic thrombocytopenic purpura: in children and in adults presenting a high risk of bleeding or for those awaiting surgery

2. Neurological indications
   - Guillain-Barré syndrome, with specific criteria
   - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), with specific criteria
   - Multifocal motor neuropathy (MMN), with specific criteria
3. Other indications
   - Kawasaki disease
   - Treatment of the toxic shock syndrome (TSS) due to streptococcal infections

Table 19: Indications and reimbursement by pharmaceutical specialty of intravenous immunoglobulins, Belgium, as of October 2008

Indications / brand product of immunoglobulin	Sandoglobulin ®	Multigam®	Gammagard®[a]	Octagam® Nanogam®
Primary immune deficiency conditions (specified)	I, R	I, R	I, R	I, R
Multiple myeloma and chronic lymphocytic leukaemia	I, R	I, R	I, R	I, R
Paediatric AIDS	R	I, R	I, R	I, R
Idiopathic thrombocytopenic purpura	I, R	I, R	I, R	I, R
Guillain-Barré syndrome	I, R	I, R	I, R	I, R
Kawasaki disease	R	I, R	R	I, R
Allogenous bone marrow transplant	I, R	I, R	I, R	I, R
Treatment of septicaemia in preterm and neonates	R		I, R (2002)	
Treatment of toxic shock syndrome due to streptococcal infection	I, R			
Chronic inflammatory demyelinating polyradiculoneuropathy	I, R (2002)	I, R (2003)		
Multifocal motor neuropathy	I, R (2002)	R (2008)		
Rheumatoid polyarthritis		I		
For humoral immune deficiency following cytostatic treatment	I (R for above indications)		I (R for above indications)	

I: included in indications
R: reimbursed indication (date of introduction of reimbursement)
a: interpretation of the indications that are labelled in these general terms: "used in the substitution treatment of primary and secondary immune deficiencies, as for the prevention of infections resulting from these immune deficiencies. Used in the aim of modifying or controlling the immune response in many diseases."

The list of reimbursed indications per brand product has also evolved over time. The neurological indications CIDP and MMN have been added in the list of reimbursed indications in July 2002 for Sandoglobulin® and later for Multigam® (CIDP in 2004 and MMN in 2008). For each patient with CIDP or MMN, there is a maximum reimbursement of 9 g/kg per patient every 6 months, after a positive clinical evaluation.

Subcutaneous immunoglobulins

Sub-cutaneous immunoglobulins, Subcuvia® and Vivaglobin®, are reimbursed for the following indications:

- Primary immune deficiency conditions: agammaglobulinemia, hypogammaglobulinemia with specific criteria, congenital deficiency in anti-polysaccharidic antibodies with specific criteria
- Multiple myeloma and chronic lymphocytic leukaemia.

3.2.1.2 Recommendations in other countries

The recommendations for IG use in terms of which clinical indications can be treated with IG are presented for five other industrialized countries and compared to Belgium in Table 20.

In Canada, the UK and Australia, guidelines are clearly stating that "IG therapy is not indicated" for specific conditions, described as "No" in the table, when applicable.

The sources of these recommendations on IG use are described below:

1. In Canada, detailed national guidelines covering the haematological and neurological indications have been published in four articles in the journal Transfusion Medicine Reviews in 2007.[18-21] They have been elaborated by a special committee, based on scientific evidence and using expert panels.
2. In the United Kingdom, evidence-based guidelines from the Department of Health have been elaborated and the most updated version is dated May 2008.[17] Besides a list of recommendations on IG use, a list of "grey indications" has been established: grey indications are those "for which the evidence base is weak, in many cases because the disease is rare, and for which IVIG treatment should be considered on a case by case basis, prioritised against other competing demands". This comprehensive list of grey indications is not included in the table unless the disease was listed in other country recommendations, and grey indications are indicated with a "(3)", see Table 3 legend. This guideline also includes a short list of indications for which IVIG is not recommended (indicated as "No" in the table).
3. In the Netherlands, labelled indications are described in a document for prescribers from the Medicines Evaluation Board (2003).[e]
4. In France, full recommendations have not been yet established at national level. Each IG specialty has a limited list of authorized indications; in addition, a wider list of diseases for which IG is recommended has been published by the "Commission de la Transparence", "Haute Autorité de Santé" (HAS) for specific products, and from the Drug Agency (AFSSAPS) for IG in general in its document «Proposition de hiérarchisation des indications des immunoglobulines humaines intraveineuses (IgIV) en situation de tension forte sur les approvisionnements pour le marché français, 06/05/2008 ».f Clinical indications have been categorized per level of priority in several groups, to identify patients that should receive IG in a context of shortage. On one hand, the indications included in the marketing authorizations (Autorisation de Mise sur le Marché or AMM) have been classified in priority groups: priority indications; indications to keep for vital emergencies or after failure of alternative treatment; and non-priority indications (that can wait till shortage end). On the other hand, a list of diseases non included in the AMM

e Medicines Evaluation Board. http://db.cbg-meb.nl/IB-teksten/h16942.pdf

f AFSSAPS. Proposition de Hiérarchisation des indications des IgIV reconnues dans l'AMM, disponible dans la circulaire DGS/PP/DHOS/E2/AFSSaPS/2008/92 du 14/03/2008 relative à la surveillance des approvisionnements en immunoglobulines humaines normales et à la gestion des situations de tension. 6 June 2008. Available on http://www.afssaps.fr/Infos-de-securite/Autres-mesures-de-securite/Proposition-de-hierarchisation-des-indications-des-immunoglobulines-humaines-intraveineuses-IgIV-en-situation-de-tension-forte-sur-les-approvisionnements-pour-le-marche-francais2 Accessed January 2009.

has been classified in 5 groups and published by the AFSSAPS, based on the expert recommendations.[g] In total, 8 groups of diseases are defined, and how to apply these priority levels is not clearly described.

5. In Australia, the "Criteria for the clinical use of intravenous immunoglobulin in Australia" has been issued by the Australian health Ministers' conference in December 2007.[22] It is intended to be regularly updated, and revisions are periodically issued on http://www.nba.gov.au/ivig/pdf/criteria-revisions.pdf (last update February 2009). It also set up several groups of diseases for priority setting: 1. Conditions for which IVIg has an established therapeutic role; 2. conditions for which IVIg has an emerging therapeutic role: 3. conditions for which IVIg is used in exceptional circumstances; 4. conditions for which IVIg use is not indicated.

As previously said, the legal status of these recommendations differs per country, due to the difference between sources describing them.

Based on the comparison of national recommendations (Table 20), the following conclusions on indication for IG can be drawn:

- IG is recommended in all countries for a number of diseases, in a consistent way: primary immune deficiencies, multiple myeloma and chronic lymphocytic leukaemia for selected situations, idiopathic thrombocytopenic purpura, Kawasaki disease and selected neurological diseases such as Guillain Barré syndrome. It should be noted that the recommendations published in the Netherlands include only a limited number of indications because only reimbursed indications are listed; this does not precludes that IG use is accepted for other diseases.
- In many indications, IG is only recommended in "selected" cases of a given disease, according to specific criteria described by each country. Criteria include clinical variables, severity or level of disability, age, biological criteria (e.g. serum Ig levels) or therapeutic response to other treatments. For instance, IG is only recommended for multiple sclerosis and dermatomyositis cases showing failure or contra-indications to standard treatment.
- However for many other diseases, recommendations for the use of IG are not consistent across countries. In most of these diseases, the available evidence on IG effectiveness is either not available, of low level, inconsistent across studies, or only show a marginal benefit.

Key points

- **In these six industrialized countries, IG is recommended for a defined number of diseases in a consistent way.**
- **In many indications, IG is only recommended in "selected" cases and the criteria for IG treatment vary per country.**
- **In a number of diseases, IG is not recommended on a consistent way across countries. This mostly concern diseases with an auto-immune component, for which the available evidence is either of low level or only shows marginal benefit.**

g Comité d'Evaluation et de Diffusion des Innovations Techniques" (CEDIT) of the "Assistance Publique des Hôpitaux de Paris. Proposition de Hiérarchisation des indications hors AMM des IgIV réalisée par le Comité d'experts IgIV du Cedit de l'AP-HP, dans l'attente de la publication par l'Afssaps prévue d'ici fin Juin 2008 des référentiels de bon usage sur les IgIV, qui définiront les situations temporairement acceptables justifiant la mise en place d'un protocole thérapeutique temporaire. Available on http://www.afssaps.fr/Infos-de-securite/Autres-mesures-de-securite/Proposition-de-hierarchisation-des-indications-des-immunoglobulines-humaines-intraveineuses-IgIV-en-situation-de-tension-forte-sur-les-approvisionnements-pour-le-marche-francais2

Table 20: Recommendations for intravenous immunoglobulins use in six selected countries

Indications	Belgium[a]	Canada[b]	The UK[b]	Netherlands[c]	France[d]	Australia[b]
Immuno-haematological indications						
Idiopathic thrombocytopenic purpura	Yes, selected (1)	Yes (1)	Yes, selected	Yes (1)	Yes, selected (1)	Yes, selected
Primary immune deficiency conditions	Yes, selected (1)	Yes (1)	Yes, long term	Yes, selected (1)	Yes (1)	Yes, selected
Secondary immune deficiencies: - in general	Not mentioned	Yes (1)	Yes (3)	Not mentioned	Yes (1)	Yes in general, for selected conditions
- multiple myeloma, chronic lymphocytic leukaemia	Yes, selected (1)	Yes, selected (2)	Yes, selected	Yes, in CLL (1)	Yes, selected (1)	Yes, selected
- Allogenous bone marrow transplant	Yes (1)	No but labelled	Yes if low IgG	Yes (1)	Yes (1)	Yes, selected
- paediatric HIV/AIDS	Yes (1)	Yes, selected (2)	No	Yes (1)	Yes, selected (1)	Yes, selected
- in solid organ transplant	Not mentioned	NA	For CMV pneumonitis For rejection (3)	Yes, kidney (1)	Yes (kidney) (3)	Yes, selected
- septicaemia in neonates	Yes treatment (1)	NA	No	Not mentioned	Yes (3)	Yes but (3)
- infections in preterm and/or low birth weight	Preterm, to treat septicaemia (1)	NA	NA	Yes (<1500g) (1)	Preterm, prevention (3)	Yes if hypogammaglobulinemia
Isoimmune haemolytic jaundice in neonates	Not mentioned	Yes, selected (2)	Yes, selected	Not mentioned	Yes (3)	Yes but (3)
Alloimmune thrombocytopenia, foetal and neonatal	Not mentioned	Yes (2)	Yes, selected for neonatal	Not mentioned	Not mentioned	Yes, selected
Neurological indications						
Guillain-Barré syndrome	Yes, selected (1)	Yes, selected (2)	Yes, selected	Yes (1)	Yes, selected (1)	Yes, selected
CIDP	Yes, selected (1)	Yes (2)	Yes, selected	Not mentioned	Yes (3)	Yes, selected
Multifocal motor neuropathy	Yes, selected (1)	Yes (2)	Yes, selected	Not mentioned	Yes, selected (1)	Yes, selected
Multiple sclerosis (RRMS)	Not mentioned	Yes, selected (2)	No	Not mentioned	No	Yes, selected
Neuromyelitis optica	Not mentioned	Not mentioned	Not mentionned	Not mentioned	No	Yes but (3)
Paraprotein-associated neuropathy	Not mentioned	No	Yes, selected	Not mentioned	Not mentioned	Yes, selected
Lambert-Eaton myasthenic syndrome	Not mentioned	Yes (2)	Yes, selected	Not mentioned	Not mentioned	Yes, selected

Myasthenia gravis	Not mentioned	Yes, selected (2)	Yes, selected	Not mentioned	Yes (3)	Yes, selected
Dermatomyositis	Not mentioned	Yes, selected (2)	Yes, selected	Not mentioned	Yes (3)	Yes, selected
Inclusion body myositis	Not mentioned	No	No	Not mentioned	Yes, selected (3)	Yes, selected
Stiff person syndrome	Not mentioned	Yes, selected (2)	Yes, selected	Not mentioned	Yes (3)	Yes, selected
Other indications						
Kawasaki disease	Yes (1)	Yes (1)	Yes	Yes (1)	Yes, selected (1)	Yes
Treating septic shock and/or necrotizing fasciitis	Yes, streptococcus (1)	NA	Yes, selected	Not mentioned	Yes, streptococcus (3)	Yes, streptococcus staphylococcus
Viral myocarditis in children	Not mentioned	NA	Not mentionned	Not mentioned	Not mentioned	Yes but (3)

Yes: Immunoglobulin use is recommended
No: recommendations state that IG is not indicated for that disease
Selected: Immunoglobulin use is recommended or reimbursed for this indication in selected cases; criteria have been established for recommendation or reimbursement.
NA: non available, meaning that recommendations on this indication have not been published yet
Not mentionned: this indication is not mentionned in exhaustive guidelines or list of indications
RRMS: relapsing remitting multiple sclerosis

a: reimbursed indications
b: from national guidelines
c: from labelled indications, according to the Medicine Evaluation Board
d: from the "Commission de la Transparence », "Haute Autorité de Santé" (HAS), Avis 19 juillet 2006 and from AFSSAPS « Proposition de hiérarchisation des indications des immunoglobulines humaines intraveineuses (IgIV) en situation de tension forte sur les approvisionnements pour le marché français, 06/05/2008 ».

(1): Labelled use (or registered use or use included in the marketing authorization)
(2): Off-label use (i.e. not included in the registered indications) but IG use is recommended for this disease in the guidelines
(3): Use of IG is only recommended for this disease in specific cases: after failure of other therapies or in vital emergencies (France); considered on a case by case basis in the UK, prioritised against other competing demands (grey indications); or in exceptional circumstances - urgent or life-threatening circumstances, or in circumstances in which significant morbidity would be expected and other clinically appropriate standard therapies have been exhausted or are contraindicated (Australia).

3.2.2 Evidence review on immunoglobulin effectiveness

3.2.2.1 Background

The mechanisms of action of polyvalent immunoglobulins (IG) are complex and not totally elucidated today, aside of their use in correcting immunodeficiencies. In immunodeficiency diseases, polyvalent IG is given to restore normal humoral immune function by increasing antibody levels. In autoimmune disorders and some inflammatory diseases, it is assumed to have a rapid immunomodulatory action, by neutralizing circulating auto-antibodies, modulating the production of inflammatory cytokines, interfering in complement activation, and a few other mechanisms. In the long term, it also regulates the production of antibodies and cytokines. This evidence review does not cover the IG mechanisms of action but it reviews the effectiveness of IG in treating a number of diseases.

3.2.2.2 Methods

Scope

As more than 100 indications have been considered for IG use, this literature review focuses on the indications that contribute to address the research question. We selected indications for which IG are reimbursed or recommended by national authorities and/or likely to consume significant amounts of IG and/or have been covered in systematic reviews. We included the following diseases (see Table 21):

- indications reimbursed in Belgium
- diseases for which IG is recommended in five comparable industrialized countries (France, Netherlands, UK, Canada and Australia)
- other diseases covered by Cochrane systematic reviews including IG effectiveness
- diseases under investigation that may consume high amounts of IG

Twenty-nine indications have thus been selected for this literature review:

Haematological diseases

1. Primary immune deficiency conditions
2. Secondary immune deficiencies:
   - Multiple myeloma and chronic lymphocytic leukaemia
   - Allogenic bone marrow or stem cell transplant
   - Prophylaxis in solid organ transplant
   - Suspected or proven infections in neonates
   - Preterm and/or low birth weight infants
   - Paediatric HIV/AIDS
3. Idiopathic thrombocytopenic purpura
4. Isoimmune haemolytic jaundice in neonates
5. Fetal allo-immune thrombocytopenia

Neurological and neuro-muscular diseases

1. Guillain-Barré syndrome (and variants)
2. Chronic inflammatory demyelinating polyradiculoneuropathy
3. Multifocal motor neuropathy
4. Paraprotein-associated peripheral neuropathies
5. Multiple sclerosis
6. Lambert-Eaton myasthenic syndrome (LEMS)

7. Myasthenia gravis
8. Dermatomyositis and polymyositis
9. Inclusion body myositis
10. Stiff person syndrome
11. Neuromyelitis optica

Other diseases

1. Kawasaki disease
2. For treating sepsis and septic shock
3. Viral myocarditis
4. For treating respiratory syncitial virus infection

Diseases under investigation

1. Chronic fatigue syndrome
2. Alzheimer disease

Search strategy

The search for evidence synthesis was focused on systematic reviews. Systematic reviews identified were subsequently updated with original RCT published in Medline or Embase, after the last literature search. For diseases not covered by a systematic review, published randomized controlled trials (RCT) were considered. The date of search was November 2008 and an update was performed in June 2009.

Databases used were the Cochrane review database, the database of abstracts of reviews of effects (DARE) in the Centre for Reviews and Dissemination database (CRD) (http://www.crd.york.ac.uk/crdweb/), Medline and Embase. Search terms are described in appendix.

Selection of studies

Evidence synthesis studies were eligible if they reviewed the literature systematically on the clinical efficacy of polyvalent immunoglobulins (administrated intravenously or subcutaneously), on clinically relevant outcomes regarding morbidity / mortality / disability due to these diseases.

Original studies were eligible if they were randomised controlled trials published after the last systematic review search, or after 1998 if no systematic review was found. Studies published in English, Dutch, French and Spanish were considered. When no systematic reviews or randomized controlled trial were found on the disease of interest, observational studies covering the effectiveness of IG published after 1998 were described for information. Cost-effectiveness studies were also included.

Controlled trials on other interventions such as specific immunoglobulins, oral or intra-muscular administration, and on other health conditions than those listed under "Scope" were excluded.

In addition, the eligible references or related articles of the systematic reviews were searched for any missing publication, when evidence was lacking or conflicting.

Search results

COCHRANE SYSTEMATIC REVIEWS

Nineteen Cochrane Systematic Reviews (last versions) were found on the effectiveness of immunoglobulins in treating the following diseases: multiple myeloma, chronic lymphocytic leukaemia, bone marrow/stem cell transplant, isoimmune haemolytic jaundice in neonates, fetomaternal alloimmune thrombocytopenia, CMV prophylaxis in solid organ transplant, severe infections in neonates, for preventing infection in preterm and low birth weight babies, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, multiple sclerosis, paraprotein-associated peripheral neuropathies, Lambert-Eaton myasthenic syndrome, myasthenia gravis, dermatomyositis, Kawasaki disease, treating sepsis and septic shock, viral myocarditis and treating respiratory syncitial virus infection.

CRD DATABASE

We found 105 references on immunoglobulins, including 30 which focused on polyvalent immunoglobulins. These included 28 systematic reviews (including the 19 Cochrane reviews), 1 guideline and 1 report which fitted the selection criteria.

Appraisal of evidence

Relevant papers were reviewed to identify the best evidence to answer the key clinical questions. This process involved selection of relevant studies; assessment of study quality; synthesis of the results; and grading of the evidence.

The critical appraisal was done for systematic reviews and additional studies. A level of evidence (high, moderate or low) was assigned to each body of evidence according to the GRADE methodology, as described by the GRADE working group (see Appendix).[23]

Table 21: Summary of evidence findings and evidence levels per disease

Disease / syndrome	Main findings	Evidence level	Comment on level of evidence
Primary immune deficiency conditions	Large reduction in infection severity and incidence in XLA, CVID and agammaglobulinemia. No clear benefit in specific antibody deficiencies.	Moderate	Observational studies and 1 RCT showing dose-response gradient
Secondary immune deficiencies:			
- multiple myeloma and chronic lymphocytic leukaemia	IG significantly decreased documented infections and may be considered in patients with hypogammaglobulinemia and recurrent infections. No impact on mortality.	High	Meta-analysis of 10 RCT
- in stem cell/bone marrow transplant (BMT/HSCT)	IG prophylaxis significantly reduced the risk for interstitial pneumonia after BMT/HSCT in two meta-analyses. IG also significantly reduced the incidence of CMV pneumonia in one meta-analysis.	Moderate	Two meta-analyses of >30 RCT, old RCT, different results, poor directness (BMT treatment evolved)
- in solid organ transplant	Reduction in CMV deaths but no significant reduction of CMV disease and overall mortality. Antivirals are effective. In highly sensitized patients, RCT showed some benefit of IG after transplant but no significant reduction in rejection rates	Moderate	- Meta-analysis of 37 RCT with poor study quality - 3 small RCT, inconsistent results across RCT
- for suspected or proven infection in neonates	IG given to neonates with proven infection reduced overall mortality in 5 meta-analyses. Reduction in mortality in neonates with suspected infections is less clear.	Moderate	Meta-analysis of 9 RCT but sparsity and inconsistent results with the former Cochrane meta-analysis
- in preterm / low birth weight	IG given to in preterm and/or low birth weight infants only marginally reduced sepsis and serious infections (by 3-4%), and had no effect on mortality.	High	Meta-analysis of 19 RCT, 5000 infants, confirm 3 previous meta-analyses
- in paediatric HIV/AIDS	IG decreases incidence of infections and hospital admissions. But limited use due to HAART and AB prophylaxis.	Moderate	Several RCT before HAART, lack directness
Idiopathic thrombocytopenic purpura (ITP)	- In children with acute ITP, IG has higher and quicker effectiveness than no treatment or steroids. IG role in chronic childhood ITP could not be established. - In adult ITP, IG may be more effective than steroids in the short term. For chronic ITP, the advantage of IG over other therapies is not established.	Moderate	Meta-analysis of 28 RCT but low quality and sparsity
Isoimmune haemolytic disease in neonates	IG significantly reduced the need for exchange transfusion and phototherapy.	Moderate	Meta-analysis of 3 small not blinded RCT
Fetal allo-immune thrombocytopenia (FNAIT)	Observational studies suggest a benefit of IG in FNAIT. IG added to prednisolone has no higher effectiveness than IG alone	Low	26 observational studies, 2 RCTs of IG added to steroids
Guillain-Barré syndrome (and variants)	In severe GBS, IG hastens recovery as much as plasma exchange, but no RCT compared IG with supportive care or placebo. In children, limited evidence suggests that IG hastens recovery compared with supportive care alone.	Moderate for adults, low for children	In adults, meta-analysis of 5 RCT comparing IG to PE; directness questioned. 3 small trials in children

CIDP	IG improves disability for up 24-48 weeks compared to placebo, but is not more effective than plasma exchange and prednisolone. Unclear which treatment is more effective.	High	Meta-analysis of 5 RCT vs. placebo, 2 RCT vs. other treatments.
Multifocal motor neuropathy	IG showed a significant effect on muscle strength and a non-significant improvement in disability	Moderate	Meta-analysis of 4 RCT, but small size and sparse data
Paraprotein-associated peripheral neuropathies	In IgM associated neuropathies, IG may produce some short-term benefit. In IgG and IgA disease, evidence on IG effectiveness is insufficient.	Moderate Low	Review of 2 small RCT, but quality problems Small observational studies
Multiple sclerosis - Relapsing remitting (RRMS) - Primary progressive (PPMS) - Secondary progressive (SPMS)	In RRMS, IG reduced disease progression and MRI lesions. IG delayed disease progression in PPMS. No effect on disease progression in SPMS. IG reduced the rate of relapses in the post-partum period.	Moderate	Several meta-analyses, 15 RCT. Inconsistent results in the last and larger multinational RCT on RRMS.
Lambert-Eaton myasthenic syndrome	IG improved functional capacities and muscle strength in a small RCT	Low	Review but 1 small RCT
Myasthenia gravis	IG is more effective than placebo or as effective as other treatments for severe exacerbation and worsening, but this benefit was not shown in mild and moderate disease.	Moderate	Review of 6 RCT but one had inconsistent results
Dermatomyositis and polymyositis	IG improved symptoms and muscle strength and was more effective than placebo	Moderate	Review w/ 1 RCT, 1 non controlled trial, observational studies
Inclusion body myositis	IG did not improve muscle strength in IBM patients but significantly improved swallowing functions in one study	Moderate	3 small RCT (N=47)
Stiff person syndrome	IG improved stiffness and sensitivity scores	Moderate	1 small RCT
Neuromyelitis optica	The effectiveness of IG in neuromyelitis optica has not been shown.	Low	Few case series
Kawasaki disease	IG showed significant decrease in new coronary artery abnormalities, fever and hospitalization compared to placebo.	High	Meta-analysis of 16 RCT
Viral myocarditis in children and adults	Limited evidence does not show a benefit of IG over placebo for the management of presumed viral myocarditis in adults. There is no evidence for paediatric cases	Moderate for adults	Review with 1 RCT, results inconsistent with open studies
Treating sepsis and septic shock	IG used as an adjuvant therapy reduces mortality compared to placebo or no adjuvant therapy in 3 recent meta-analyses.	High	3 meta-analyses (11-20 RCT each)
Treating RSV infection	No significant benefit of IG treatment added to supportive care, compared with supportive care alone.	Moderate	Review of 4 RCT, heterogeneity of outcomes
Alzheimer disease (AD)	Evidence is lacking on the effectiveness of IG	Low	2 small case series
Chronic fatigue syndrome	No conclusion can be drawn on the effect of IG in CFS as the evidence is conflicting. The larger trial showed no effect, with 70-80% of adverse events.	Moderate	3 RCT but inconsistent results

3.2.2.3 Immuno-hematological diseases

A summary of evidence findings and levels of evidence for IG use is presented in Table 21.

Primary immune deficiencies

Primary immunodeficiency disorders (PID) result from intrinsic defects of the immune system, in contrast to immune disorders that are secondary to infection, chemotherapy or immunosuppressive therapy. Individuals with PID are prone to recurrent bacterial infections, typically in respiratory and gastro-intestinal tracts, or protozoal, fungal and viral infections, of varying severity. Deficiencies of various components of the immune system have been identified, and more than 200 different PID are currently recognized by the WHO. In Europe, the PID requiring IG replacement that are the most commonly diagnosed are: the common variable immunodeficiency (CVID) - revealed at adulthood, X-linked agammaglobulinemia (XLA), other agammaglobulinemia, Wiskott-Aldrich syndrome, severe combined immunodeficiency, hyper-IgM syndromes and severe hypogammaglobulinemia with recurrent and severe bacterial infections.[24] In most of the cases with severe antibody deficiency (IgG<200mg/dL), IG replacement is indicated, and on a lifelong basis for many of them. Patients with IgG subclass deficiencies and impaired polysaccharide responsiveness may also present with recurrent infections and deficient response to appropriate vaccines, but the definition of quantitative defect and its correlation with clinical status is often problematic.[25]

A systematic review on PID was found, which assessed the effectiveness of IG.[26] No controlled trial compared IG with placebo or no treatment in PID patients, as it was considered unethical to withhold IG in these patients; indeed, those treated with IG had dramatically better outcomes than historical controls.[27] Most available evidence on IG effectiveness consists of observational studies. A reduction in infection severity and incidence, when comparing outcome before and after IG treatment, were observed in observational studies involving patients with CVID,[28,29] XLA,[30] and agammaglobulinemia.[31] In addition, an RCT involving 43 patients with primary hypogammaglobulinemia showed that a high dose of IG (600mg/kg every 4 weeks in adults) significantly reduced the number and duration of infections, compared with a standard dose.[32]

The effectiveness of IG in IgG subclass deficiencies is unclear and subject to debate, as no RCT was conducted and there are few published studies documenting its efficacy.[33] Conservative treatment, based of early antibiotic treatment, supportive therapy and prophylactic antibiotic treatment in selective individuals, is considered as the first line treatment in these patients.[25, 34]

Several studies have investigated the subcutaneous administration of IG in PID cases.[35] One trial, involving 22 PID adult patients, compared the intra-venous and subcutaneous administration of IG.[36] There were no significant differences in the number of infections between the two treatments or in adverse reaction rates. In addition, four open studies have compared the two administration routes, studying the same patients over time, and showed similar findings.[37, 38,39,40]

In conclusion, IG reduces the number and the severity of infectious episodes in patients with agammaglobulinemia and severe hypo-gammaglobulinemia. Although evidence is limited due to ethical concern, IG represents the mainstay of treatment for these patients. Effectiveness of IG in milder hypogammaglobulinemia, IgG subclass deficiency and impaired polysaccharide responsiveness is unclear and treatment decision based on specific criteria. The route of administration - intra-venous or sub-cutaneous - did not influence treatment effectiveness.

- **IG reduces the incidence and severity of infection in patients with agammaglobulinemia and severe hypo-gammaglobulinemia.**
- **Effectiveness of IG in milder hypogammaglobulinemia, IgG subclass deficiency and impaired polysaccharide responsiveness is unclear.**
- **The route of administration (IV or SC) does not influence treatment effectiveness.**

Secondary immune deficiencies

In many patients, the immune deficiency is a direct consequence of a decreased antibody production due to cancers of the haematopoietic system, such as multiple myeloma or chronic lymphocytic leukaemia, cytotoxic chemotherapy, immunosuppressive therapy to prevent transplants rejection, very low weight etc.

The effectiveness of IG in treating the conditions leading to secondary immune deficiency varies per pathology. It has only been well studied for specific pathologies, such as multiple myeloma, chronic lymphocytic leukaemia and stem cell transplants (see below). For hypo-gammaglobulinemia related to other diseases or drug therapy, no evidence on the benefit of IG treatment was found. However, most guidelines recommend the use of IG – besides antimicrobial prophylaxis – to decrease the risk of infection in cases with the same criteria than those set for PID requiring IG supplementation: IgG levels under reference range and severe or recurrent bacterial infections that are unresponsive to prophylactic antibiotics etc.[17, 22].

Multiple myeloma and chronic lymphocytic leukaemia

Multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL) are rare proliferative disorders that lead to a higher incidence of serious bacterial infections, such as pneumonias and urinary tract infections. Factors underlying the increased susceptibility to infections are many and complex. A major factor is the decreased capacity to produce potent immunoglobulins, often reflected by a certain degree of hypo-gammaglobulinemia observed in the majority of patients. In MM, the immunodeficiency is mainly caused by abnormal Ig production and impairment of the primary immune response.[41] Infections and its consequences (including renal failure) are the major cause of morbidity and mortality in both diseases. Up to 65% of CLL patients die from infection-related events and MM cases have a fatality rate of 30%. Many treatment strategies exist for MM and CLL; IG is mainly used as prophylactic agent to prevent infections, mostly in recurrent life threatening infections.[42]

A Cochrane review updated in 2009 included ten RCT involving MM or CLL patients with hypogammaglobulinemia and recurrent infections, and the meta-analysis combined studies from both diseases.[43] It showed that no benefit of IG could be demonstrated in terms of mortality, but IG significantly decreased the risk of clinically documented infections by 51% (RR 0.49, 95% CI 0.39-0.61), and significantly reduced the occurrence of microbiologically documented infections as compared to controls (RR 0.71, 95% CI 0.53-0.95). Authors concluded that IG use may be considered in MM and CLL patients with hypogammaglobulinemia and recurrent infections, for the reduction of clinically documented infections.

Another systematic review, conducted by the same group, included nine of the 10 RCT involving CLL and MM patients, and presented similar findings and conclusions.[44]

A 2005 systematic review on the cost of disease included cost-effectiveness studies.[45] It only found one cost effectiveness study on IG, published in 1991, thus excluded from this review.[46]

IG significantly decreased documented infections in CLL and MM patients but had no impact on mortality. IG is considered in patients with documented hypogammaglobulinemia and recurrent infections.

Bone marrow transplantation and hematopoietic stem cell transplantation

Bone marrow transplantation (BMT) and hematopoietic stem cell transplantation (HSCT) compromise the immune system of patients due to the administration of high doses of chemo-radiotherapy prior to infusion of the donor stem cells.[44] Multiple immunological deficiencies, including T- and B-cell abnormalities and hypogammaglobulinemia, predispose patients to a high risk of developing infections. As the incidence of CMV seropositivity in the general population is high, CMV reactivation and subsequent disease becomes a significant prognostic factor of morbidity and mortality in BMT/HSTC. Even though antiviral agents can inhibit the viral replication in vivo, they have not been able to treat CMV interstitial pneumonia effectively. This period of immunological incompetence usually lasts from six to 12 months. These abnormalities are less prominent in autologous than in allogenic transplantations.

Systematic reviews of evidence are contradictory, despite numerous RCT on this area, as many of them have divergent findings.

On one hand, the Cochrane review published in 2008 included 30 RCT with 4223 patients receiving prophylaxis after BMT/HSCT.[43] Twenty-one RCT evaluated polyvalent IG or compared it to CMV hyper-immune IG. The analysis did not distinguish between allogenic or autologous transplantation. When polyvalent IG was compared to control, there was no difference in all-cause mortality. IG significantly reduced the risk for interstitial pneumonia but increased the risk for veno-occlusive disease and adverse events. This review concluded that routine prophylaxis with IG is not supported by available evidence for these patients.

On the other hand, a meta-analysis of 12 RCT involving 1282 patients was conducted in 1993 and showed that IG reduced all cause mortality (though with borderline significance), CMV pneumonia and non-CMV interstitial pneumonia.[47] Three of the trials were not RCT and the Cochrane review excluded several of them for methodological reasons; however, this review allocated a quality weight for data analysis.

A major limitation of both reviews is that the majority of RCTs are old (patients treated in the 80's and 90's) while techniques and treatment for patients undergoing transplantation for haematological malignancies have changed considerably over the last two decades, such as the use of non-myeloablative treatment. This may explain the divergence in conclusions between the two meta-analyses. In addition, several RCT concluded that IG was not found to be beneficial in autologous BMT recipients. Despite the controversy about the benefit of IG in HSCT/BMT, this agent is still recommended in most transplantation protocols in many countries. Some authors suggest that IG should be reserved for patients who are hypo-gammaglobulinaemic after BMT.[48]

IG prophylaxis significantly reduced the risk for interstitial pneumonia after BMT/HSCT in two meta-analyses. IG also significantly reduced the incidence of CMV pneumonia in one meta-analysis.

Solid organ transplant

IG may be indicated for two main problems encountered in solid organ transplant (SOT) recipients:

- On one hand, immunosuppression after SOT is associated with increased risk of opportunistic infections, particularly during the 6-month post-transplant period when viral infections are most prevalent.[49] Cytomegalovirus (CMV) is a major cause of disease and death in SOT recipients during this period, with an overall incidence of 30% to 50%. CMV also has the propensity to establish lifelong 'latency' infection in the host after the initial infection has resolved. Therefore, SOT recipients may be infected either by exogenous virus or by reactivation of latent virus if they were CMV positive pre-transplant. Those at highest risk of symptomatic CMV disease are thus CMV sero-negative patients who receive organs from CMV sero-positive donors, and CMV sero-positive patients on heavily immunosuppressive regimens. CMV is also associated with increased risk of allograft injury and rejection, opportunistic infections and late onset malignancies. Two main strategies to prevent CMV disease exist: prophylaxis of all organ recipients with antiviral medications and/or immunoglobulins called 'pre-emptive therapy' for high-risk groups, such as patients receiving anti-lymphocyte antibody preparations.
- On the other hand, one-third of patients awaiting renal allograft transplant have high levels of pre-formed anti-HLA antibodies, and are called highly-sensitized patients.[50, 51] If transplanted, these patients experience an increase number of rejection episodes and have poorer graft survival. Over the past several years, high doses of IG have been used to help improve transplantation rates in this group.[52]

A Cochrane review published in 2007 included 37 RCT on the effectiveness of IG on CMV risk and disease.[53] Studies looking at the efficacy of polyvalent IG and CMV hyperimmune IG were combined as no difference between the two groups could be detected. There was no significant difference in the risk for CMV disease, CMV infection and all-cause mortality with IG compared with placebo/no treatment. However, IG significantly reduced the risk of death from CMV disease (RR 0.33, 95% CI 0.14-0.80). Adding IG to antiviral medication did not affect the risk for CMV disease, CMV infection or all-cause mortality, compared to antivirals alone. The authors concluded that there are currently no indications for IG in the prophylaxis of CMV disease in SOT recipients, considering that the efficacy of several antiviral medications (valganciclovir, ganciclovir, acyclovir, valganciclovir) have been demonstrated in reducing CMV disease, CMV infection, all-cause and CMV related mortality and opportunistic infections.

In highly sensitized patients, no systematic review was found, but three RCT involving kidney transplants in patients at risk for rejection were retrieved. A first RCT was conducted in 41 patients having received a second kidney transplant and treated with immunosuppressant.[54] Daily IG was added to the treatment of 21 patients on the first 5 days after transplantation. The number of acute rejection episodes and incidence of CMV infection were similar but the 5-year survival rate was significantly higher in the IG group compared to the control group. A second RCT, involving 30 patients with confirmed steroid-resistant rejections, compared the effectiveness of IG versus monoclonal anti-CD3.[55] The incidence of rejections after treatment was lower in the IG group compared to the other group but not significantly (46% vs. 75%, p=0.4). Patient survival rates and graft survival were not significantly different in the two groups.

A third RCT, conducted in 101 patients with end-stage renal disease and involving 27 kidney transplants, showed that IG was effective in reducing anti-HLA antibody levels, improving kidney transplant rates in highly sensitized patients compared to placebo, and decreased waiting time to graft.[51] There was however no significant decrease in graft survival rates and patient survival in the IG group compared to placebo and allograft rejection was significantly higher in the IG group. The authors concluded that IG pre-treatment should improve the transplant potential for highly sensitized patients with end-stage renal disease awaiting kidney transplantation, especially those resistant to other therapies.

- **IG, used alone or with antivirals, for the prophylaxis of CMV disease in SOT recipients did not decrease the risk of CMV disease and overall mortality compared to placebo, or to antivirals alone, in a meta-analysis of 30 RCT. IG reduced the risk of death from CMV disease compared to placebo. Antiviral medications are effective.**
- **In highly sensitized patients, three RCT suggested some benefit of IG treatment after transplant but failed to show a significant reduction of transplant rejection.**

Suspected or proven infection in neonates

As endogenous synthesis of immunoglobulins does not begin until about 24 weeks after birth, neonates are at high risk for morbidity and mortality from infections acquired in utero, as well as from exposure to infectious sources in neonatal intensive care units.[56] Sepsis is an important cause of neonatal death and brain damage. Though effective antibiotic treatment is essential for sepsis, adjuvant therapies such as IG may offer an additional strategy. The rationale for IG treatment for neonatal infections is based on the evidence that it provides IgG that can bind to cell surface receptors, provide opsonic activity, activate complement, promote antibody dependent cytotoxicity and improve neutrophilic chemoluminescence.

A Cochrane review published in 2004 included 9 RCT involving 553 neonates with suspected infection.[57] Six studies reported on mortality and results showed a reduction in mortality following IG treatment in cases with suspected infection of borderline statistical significance. Treatment with IG in cases of subsequently proven infection did result in a statistically significant reduction in mortality (RR 0.55, 95% CI: 0.31-0.98). However, the authors points that these findings are in contrast with a previous Cochrane meta-analysis (from the same author) that showed the reverse relationship (significant reduction in mortality in suspected infections and non significant reduction in proven infections).[58] The review also mentions that four former meta-analyses showed statistically significant reductions in mortality following IG treatment for neonatal sepsis, up to a six-fold decrease (p=0.007) when IG is administered in addition to standard therapies.

IG given to neonates with <u>proven</u> infections reduced overall mortality in five meta-analyses. However, the effectiveness of IG to reduce mortality in neonates with <u>suspected</u> infections was not always significant.

Preterm / low birth weight infants

As maternal transfer of IG to the foetus occurs mainly after 32 weeks of gestation and endogenous synthesis does not begin until about 24 weeks after birth, the preterm infant is especially vulnerable to infectious sources.[57] Indeed, nosocomial infections continue to be a significant cause of morbidity and mortality among preterm and/or low birth weight infants. Due to the mechanisms above described, IG was considered to have the potential of preventing or altering the course of nosocomial infections.[59]

A Cochrane review on IG for preventing infections in preterm (<37 weeks) and/or low birth weight (<2500g) infants was published in 2004.[57] It included 19 RCT involving around 5000 pre-term infants. It revealed that IG administration results in a marginal but significant 3% reduction in sepsis and 4% significant reduction in one or more episodes of any serious infection. IG is not associated with reductions in other important outcomes such as necrotizing enterocolitis, intraventricular haemorrhage or length of hospital stay and did not have any significant effect on mortality from any cause or from infections. The authors concluded that a 3-4% reduction in nosocomial infections without a reduction in mortality or other important clinical outcomes is of marginal importance from a clinical perspective and the decision to use prophylactic IG will depend on the costs and the values assigned to the clinical outcomes. No further RCT was found after 2004. It should be noted that a benefit as marginal as a 3-4% reduction in outcome did only reach statistical significance because of the large number of trials and subjects.

The use of IG for the prevention of infections in preterm and/or low birth weight infants only marginally reduced sepsis and serious infections, and had no effect on mortality

Paediatric HIV/AIDS

Paediatric cases of HIV infection often have early and significant humoral immunodeficiency, which can manifest as high levels of non-specific antibodies with decreased specific antibody formation and resulting bacterial infections.

Several large RCT in children with HIV have shown that IG prophylaxis can decrease the incidence of infections and hospital admissions.[60,61] However, all these trials were conducted before the use of highly active antiretroviral therapy (HAART), which had dramatically reduced the occurrence of opportunistic infections. One trial showed benefit only for patients not receiving prophylactic cotrimoxazole.[60] This suggests that IG benefit in HIV paediatric infections is limited, and would only benefit to patients with severe hypogammaglobulinemia, or those suffering from recurrent or severe infections, even after cotrimoxazole prophylaxis.

Prophylaxis with IG in HIV patients can decrease the incidence of infections and hospital admissions. However, its benefit is limited after highly active antiretroviral therapy and antibiotic prophylaxis have shown to be effective.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP), also called immune thrombocytopenic purpura, is an auto-immune disorder characterized by an auto-antibody induced destruction of platelets by the reticuloendothelial system, especially the spleen. It is defined by a low platelet count, a normal blood marrow and the absence of other causes of thrombocytopenia.[62] Approximately 50% of the cases are children. A high proportion of these patients will have spontaneous resolution of the disease in the absence of therapy. Because the natural history of ITP differs in children and adults, literature is reviewed separately. ITP may present with an acute and/or a chronic form, and the traditional cut-off point used to define chronic ITP is disease duration above 6 months.

- In children: Acute ITP in children is characterized by a low platelet count and mucocutaneous bleeding (petechiae, purpura). Several thresholds for platelet count are described and no consensus has been found. Between 15 and 20% of children with acute ITP, particularly those above 10 years, may develop a chronic form of ITP. The most serious complication of ITP is a life-threatening intracranial haemorrhage, which is estimated to occur in 0.1% to 1% of children with acute ITP. ITP can be treated with steroids, IG, splenectomy and drugs stimulating thrombopoiesis. The goal of the treatment is to prevent serious and potentially fatal bleeding. Criteria to initiate treatment widely vary per country: in settings such as in France, Italy or Canada, treatment is based on the platelet count as a surrogate marker for bleeding risk (platelet count < 10 or 20×109/L), regardless of

bleeding occurrence. In some countries, IG is used as the first line treatment (e.g. France) and in other countries as a second line or as one of the treatment options.

- In adults: Adult ITP usually has an insidious onset and is typically a chronic disease. Its incidence increases with age. IG is usually recommended in cases with risk of serious bleeding, as part of a multi-modal therapy. Other treatments include intravenous steroids, anti-D immune globulin, vincristine, platelet transfusions and factor VIIa. However, recommendations for chronic ITP widely vary per guideline.

A systematic literature review was published in 2008 as part of a health technology assessment undertaken by the Canadian drug agency.[62] It included 28 RCT: 15 RCT among children with acute ITP, 4 RCT among children with chronic disease, 7 RCT among adult ITP and 2 RCT among mixed populations. IG was compared with steroids, anti-D immunoglobulin, modified or different doses of IVIG, or close observation. The review only included English language publications.

- In children: In one trial that compared IG with close observation, IG was associated with earlier improvements in platelet counts. IG also showed higher effectiveness compared with steroids for early recovery of thrombocytopenia in acute ITP. The advantage of IG over anti-D immunoglobulin is uncertain due to sparse evidence. The optimal dose of IG has not been established. There was insufficient evidence to determine if specific subgroups of children with acute ITP may receive preferential benefit from IG treatment. The role of IG in chronic childhood ITP could not be established, because evidence from scant, poorly designed, and poorly reported RCT could not be synthesized.
- In adults: Two RCT compared IG with steroids in adults with newly diagnosed ITP: in one, no advantage for IG was found; in the other study, IG was more effective than steroids for the short-term improvement of thrombocytopenia and gave a more rapid and sustained response.[63] IG was associated with more severe adverse events that prolonged hospitalization. The review concluded that sparse evidence indicates that IG may be more efficacious than high dose corticosteroids in improving platelet counts in the short term, though its effect on clinical outcomes remains indeterminate. Limited evidence could not demonstrate the superiority of a 2 g/kg dose of IVIG over a 1 g/kg dose; a dose of 1 g/kg, however, may be better than a dose of 0.5 g/kg. For the long-term management of adult ITP, data were insufficient and studies were heterogeneous, preventing any conclusion on whether IG has an advantage over other treatments.

A US study compared the cost-effectiveness of IG, anti-D, methylprednisolone and prednisone.[64] Therapies with IG and methylprednisolone were less effective and more expensive than anti-D and prednisone, respectively. However, this analysis has been debated by many authors, as it is based on several questionable assumptions; for instance, they assumed that all ITP patients received treatment, all children responded to the initial management strategy, and IG is not more effective than steroids.[65, 66]

A more recent Chinese systematic review of studies published between 1990 and 2007 showed that the use of steroids provided additional life years and was more cost-effective compared with IG, but that transferability of results to other countries was low.[62]

- **In children with acute ITP, evidence suggests that IG improves more rapidly platelet counts than no treatment or steroids. The role of IG in chronic childhood ITP could not be established.**
- **In adult ITP, sparse evidence indicates that IG may be more efficacious than steroids in improving platelet counts in the short term, though its effect on clinical outcomes is unclear. For long term treatment of chronic ITP, studies did not allow to determine the benefit of IG and its advantage over other treatments.**

Fetal/Neonatal allo-immune thrombocytopenia

Fetal or neonatal allo-immune thrombocytopenia (FNAIT) accounts for 27% of cases of severe foetal and neonatal thrombocytopenia and is the most frequent cause of foetal/neonatal intracranial haemorrhage.[67] FNAIT occurs when the mother produces antibodies against fetal platelet-specific antigens that the foetus has inherited from the father. These antibodies may easily cross the placenta as early as the 14th week of gestation and cause fetal thrombocytopenia. Transfer of antibodies increases as gestation progresses, until a maximum level is attained in the late third trimester. Its incidence is estimated to be one in 1000-2000 births. The recommended antenatal therapy, aiming at preventing intracranial haemorrhage, mainly consists of maternal infusions of IG, with or without steroids, or intrauterine transfusion of antigen compatible platelets.[68] Steroids are often used in the management of refractory cases.

A Cochrane review published in 2005 identified one RCT involving 54 pregnant women. However, this trial only compared intravenous IG plus steroids with intravenous IG alone, thus not covering the research question.[68] A systematic review published after the Cochrane search period identified an additional RCT, published in 2007, comparing again the effectiveness of IG plus prednisone to IG alone in 73 women.[69] No RCT comparing IG to placebo has been found, likely because IG is currently the first line treatment in most settings. However, 26 observational studies on IG efficacy have suggested an improvement in clinical outcome and probable reduction in risk for intracranial haemorrhage. Though no meta-analysis wad performed and in spite of the drawbacks of observational studies, most of current practice is based in their findings.[68]

Though no RCT have been conducted to study the IG effectiveness in fetal/feonatal allo-immune thrombocytopenia, data from observational studies suggested a benefit of IG.

Isoimmune haemolytic jaundice in neonates

Both rhesus factor and ABO incompatibilities between maternal and fetal or neonatal cells can result in autoimmune haemolytic disease of the new-born. The use of anti-D prophylaxis in rhesus negative women has led to a marked decline in haemolytic disease of the newborn. However, anti-D immunoglobulin does not always prevent sensitization as a high proportion of haemolytic disease of the newborn is caused by antibodies to antigens other than D.[70] Exchange transfusion and phototherapy have traditionally been used to treat affected newborn infants. However, exchange transfusion is related to increased mortality and morbidity. New therapies, aiming at reducing the need for exchange transfusion, include IG.

A Cochrane review published in 2002 included three RCT, involving 189 term and preterm infants with rhesus and ABO incompatibility. The use of exchange transfusion decreased significantly in the IG treated group, with a lower mean number of exchange transfusions per infant. None of the studies assessed long term outcomes. Authors considered that the applicability of the results is limited. A more recent systematic review published in 2003 included 4 RCT to compare neonatal IG plus phototherapy to phototherapy alone.[71] It also found that fewer infants in the IG group required exchange transfusion. The IG group also required lower duration of phototherapy and shorter hospital stays than the control group.

In isoimmune haemolytic disease in infants, IG reduced the need for exchange transfusion and phototherapy and lead to shorter hospital stays.

3.2.2.4 Neurological and neuro-muscular disorders

A summary of evidence findings and levels of evidence for IG use is presented in Table 21.

Guillain-Barré syndrome and variants

Guillain-Barré syndrome is an acute disease of the peripheral nerves. It causes the rapid development of weakness and usually numbness of the limbs and often the facial, swallowing and breathing muscles. Between 3.5 and 12% patients die of complications during the acute stage. Recovery takes several weeks or months. One year after onset, 12% patients still require aid to walk and 62% still notice its effect on their or their carers' lives three to six years later.[72,73]

A Cochrane review, updated in 2004, has shown that plasma exchange significantly hastens recovery.[74] A Cochrane review on IG, updated in 2006, did not find any trial comparing IG with placebo in adults.[73] It included 6 RCT comparing IG with plasma exchange. A meta-analysis of 5 of these RCT, involving 536 patients (mostly adults) with severe disease and using disability grades, showed that IG started within two weeks from onset hastens recovery as much as plasma exchange. Treatment with IG was significantly more likely to be completed than plasma exchange. Giving IG after plasma exchange did not confer significant extra benefit. One study showed a trend toward higher improvement with high-dose (2.4g/kg) compared to low-dose IG (1.2g/kg).

Three trials compared IG to supportive care or steroids in children, involving 75 participants. Results suggested that IG hastens recovery compared with supportive care, but this was only found significant in two studies, including an open trial in which the further analysis of raw data a found significant association when using disability grade (outcome not selected by the trial). The third study involved only 18 participants and lacked power. This suggests that IG hastens recovery in children, compared with supportive care alone.

A 1999 study compared the cost-effectiveness of plasma exchange and IG in the treatment of Guillain Barré disease.[75] Trials comparing the effectiveness of plasma exchange and IG for the treatment of acute Guillain-Barré syndrome showed insufficient evidence that one therapy was more effective than the other. The study determined that plasma exchange was almost $4,000 less costly per patient than IG but that further research is required to determine the impact of patient and physician preferences. No recent cost-effectiveness analysis has been found.

- **In adult Guillain Barré cases, IG hastens recovery as much as plasma exchange - which has been shown to be more effective than supportive care alone.**
- **In paediatric cases, limited evidence suggests that IG hastens recovery compared to supportive care alone.**

Chronic inflammatory demyelinating polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) causes progressive or relapsing weakness and numbness of the limbs, developing over at least two months. It may cause prolonged disability and even death. It is often considered to be a chronic variant of GBS. CIDP can occur at any age, with a peak prevalence in the sixth and seventh decade and a lower prevalence among children.[76] Three therapies have demonstrated beneficial effect in RCT: corticosteroids, plasma exchange and IG.

A Cochrane review updated in 2009 included 7 RCT with 287 participants.[76] These trials were homogeneous and the overall quality was high. In the 5 RCT comparing IG against placebo, a significantly higher proportion of participants improved in disability within one month after IG treatment as compared with placebo (RR 2.4, 95% CI 1.7-3.4). One large RCT included in this review had a long-term follow up and indicated that IG improves disability more than placebo over 24 and 48 weeks.[77]

Two small trials compared IG with prednisolone and plasma exchange respectively, and showed no difference in improvement in disability in the IG group compared to the other therapy. There were no statistically significant differences in frequencies of side effects between the three types of treatment. Based on this evidence, the authors concluded that IG improves disability for at least two to six weeks compared with placebo, with a number needed to treat of 3. Since IG, plasma exchange and prednisolone seem to be equally effective, it is currently uncertain which of these treatments should be the first choice.

Cost-effectiveness studies comparing the alternative treatments were also retrieved. A multinational study (including Belgium) aimed at analyzing incremental cost-effectiveness of IG compared to prednisolone to treat CIDP.[78] IG was shown to be substantially more expensive than prednisolone (3754€ over a 6 week period) and did not reduce disability substantially compared to prednisolone. But IG did result in greater improvement in health-related quality of life. The probability of IVIG being cost-effective in comparison with prednisolone was 50% or above only if one QALY was valued at over 250,000€. The impact of later side-effects of prednisolone on long term costs and quality of life are likely to reduce the cost per QALY of IG treatment.

In patients with CIDP, IG improves disability for at least two to six weeks compared with placebo, but showed no difference in effectiveness compared to plasma exchange and prednisolone. Further cost-effectiveness studies are required.

Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) is a rare disease marked by a slow progression of motor weakness, often distal, asymmetric and involving the forearms, without sensory impairment. Consensus statements assert that IG is the only safe treatment for MMN patients. Steroids and plasma exchanges are not effective and may even exacerbate the disease.

A Cochrane systematic review published in 2005 included 4 RCT involving 34 patients.[79] Strength improved in 78% of patients treated with IG and only 4% of placebo-treated patients. Disability improved in a higher proportion of patients treated with IG (78%) than with placebo (14%) but the difference was statistically not significant. Authors concluded that limited evidence from RCT shows that IG has a beneficial effect on strength. IG has been so far the only therapy showing significant improvement in MMN.

In patients with multifocal motor neuropathy (MMN), IG showed a significant effect on muscle strength and a non-significant improvement in disability in small trials. No other treatment has proven effective for MMN.

Paraprotein associated polyneuropathy

The paraprotein associated polyneuropathy is another auto-immune neuropathy with demyelination, characterized by a slow progression and a sensory predominance. However, it may produce eventual disabling motor symptoms. The condition is associated with a monoclonal paraprotein, an immunoglobulin molecule produced by bone marrow cells, that is present in excess and is often non-functional.[80,81] This paraprotein may belong to one of these three classes: IgG, IgA or IgM.

A Cochrane review on IgG and IgA paraproteinemic peripheral neuropathy, published in 2007, included only one RCT on plasma exchange.[80] This review also identified several small observational studies showing a beneficial response in some of the patients treated with IG. Another 2006 Cochrane review examined the efficacy of immunotherapy in IgM paraprotein-associated demyelinating neuropathy.[81] It included two RCT comparing IG with placebo and concluded that IG may produce some short-term benefit: a trial involving 22 participants showed a significant improvement in overall disability with IG over placebo at four weeks;[82] a small trial of 11 patients showed a modest improvement in strength in 18% of patients.[83] As other therapies such as steroids have been shown beneficial in this disease in open trials, some reviews recommend that IG be considered but not continued if acute benefit is not observed.[27]

- **In patients with IgM paraprotein-associated demyelinating neuropathy, IG produced short-term benefit, such as reduced disability and improved muscle strength.**
- **In IgG and IgA paraproteinemic neuropathy, evidence on IG effectiveness is insufficient.**

Multiple sclerosis

Multiple sclerosis (MS) is a disorder of the central nervous system with progressive deterioration of neurological functions caused by autoimmune, inflammatory and neurodegenerative mechanisms. The course of the disease is relapsing remitting (called RRMS) initially in 80-85% of all MS patients. A minority of patients (10-15%) have a chronic progressive course from the beginning, without typical relapses and remissions, termed primary progressive MS or PPMS. In most patients, the disease progresses to a stage with steady deterioration, known as secondary chronic progressive MS or SPMS.[84,85]

A Cochrane systematic review included only 2 RCT out of the 10 RCT on RRMS cases that were eligible, due to methodological issues or studies being in progress, and did not perform any meta-analysis.[86] Another review was published in 2008 and performed a meta-analysis based on 4 RCT.[87] Nine additional RCT published after the last Cochrane review update (Jan 2003) have been retrieved. All findings are relatively consistent across studies and are presented below by type of MS.

1. RRMS: The two literature reviews have evaluated IG effectiveness compared to placebo in treating RRMS, and three additional RCT have been published.
   - The 2008 review included four RCT, involving 265 RRMS patients.[87] A meta-analysis of the 4 RCT showed a significant reduction in relapse rate, proportion of relapse-free patients and changes of disability scores in the groups treated with IG compared to placebo.[88,89,90] A small RCT comparing two doses to placebo also found a significant reduction in groups treated with IG.[91] A small RCT assessing Magnetic Resonance Imaging (MRI) impact on 26 patients showed a significant reduction in MRI lesions.[90]
   - The 2003 Cochrane review was based on two of these RCT, involving 168 RRMS participants, and found a significant reduction in relapse rate and an increased time to first relapse during IG treatment.
   - One recent multi-national RCT, published after the two reviews and involving 127 patients from 30 European and US sites, showed no beneficial effect of IG at doses of 0.2 to 0.4g/kg as compared to placebo in RRMS patients after a year period.[92] Authors could not explain why these results contrast with other findings, except for an overly optimistic sample size calculation.
   - Two RCT involving 19 and 76 patients with MS and acute relapses found that IG combined to prednisolone was not more effective in the treatment of relapses than prednisolone alone.[93,94]
2. PPMS: A small RCT published after the search period of the two reviews and involving 34 patients with PPMS showed that IG significantly reduced disease progression as measured by clinical indicators, compared to placebo.[84]
3. SPMS: Three RCT, involving a total of 585 SPMS patients, consistently showed no significant effect of IG on disease progression, relapses or MRI lesions compared to placebo.[84,95,96,97] No meta-analysis was performed as only one RCT was included in the 2008 review (though no exclusion criteria was stated).
4. Post-partum relapses: The risk of MS relapses is increased in the post-partum period and the other available therapies are not recommended during pregnancy or lactation. Several non-controlled trial or retrospective studies on IG treatment suggested that the exacerbation rate in the treated group

was lower than in a reference population.[98, 99] A multi-national RCT in 9 EU countries including Belgium, comparing two doses in the 6 months post-partum (but not to placebo), did not show significant differences in outcome between the two doses.[100] Despite the lack of RCT comparing IG to placebo, many authors conclude that IG can be considered as an optional treatment to reduce the increased rate of relapses in this period, because no alternative treatment with proven efficacy is available.

5. In patients with clinically isolated syndrome: An RCT evaluated the occurrence of a second attack in 91 MS cases after a first neurological event suggestive of demyelinating disease. Among patients in the IG group, the incidence of a second attack and disease activity as measured by brain MRI significantly reduced compared to placebo.[101]
6. Dosage: all RCT but one used a dose ranging 0.15-0.4g/kg monthly. A single study used 2g/kg but did not yield higher efficacy rates.[90] A study comparing two dose treatment (0.2 and 0.4g/kg/month) for the treatment of RRMS could not show any significant differences between the effects of the two doses.[92]

A systematic review searched clinical and cost effectiveness studies on immunomodulatory drugs for MS, but did not find any cost-effectiveness study including IG.[102]

- **In RRMS disease, IG has shown beneficial effects on disease progression and on magnetic resonance imaging (MRI) lesions (moderate). Combined to prednisolone, IG was not more effective in the treatment of relapses than prednisolone alone (high). The ideal dose and the effect on long term disability have not been well studied. IG is considered as one of the options for the treatment of RRMS.**
- **In PPMS patients, IG delayed disease progression in one RCT (moderate).**
- **In SPMS disease, IG had no significant effect on disease progression or MRI lesions (high).**
- **IG reduced the increased rate of relapses in the post-partum period in open studies and is considered as an optional treatment (low).**

Lambert-Eaton myasthenic syndrome

Lambert-Eaton myasthenic syndrome or LEMS is a rare autoimmune disorder of neuromuscular transmission, most commonly seen as a paraneoplasic syndrome (60% of patients). It is characterized by proximal muscle weakness, ocular symptoms, bulbar symptoms and autonomic dysfunction. LEMS often responds to steroids or other immunosuppressant.

A Cochrane review published in 2005 included only 1 RCT assessing the use of IG in LEMS cases.[103] Significant improvement in limb muscle strength, vital capacity and drinking time was observed compared to placebo, but was short term and declined after 8 weeks. The review concluded that IG can be considered as an alternative treatment to steroids and immunosupressants for LEMS.

A small RCT showed that IG improved functional capacities and muscle strength in Lambert-Eaton myasthenic syndrome on the short term

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease, characterized by weakness and fatigability of muscle changing over shorter or longer periods. Acute exacerbations (or crisis) may be life-threatening because of swallowing difficulties or respiratory failure.[104] Prevalences tend to increase with time, partly due to ageing of the population combined to higher prevalence in the elderly, and better diagnosis.[105] Current treatment includes anticholinesterase drugs, thymectomy, steroids, immunosupressants, plasma exchange and IVIG.

A Cochrane review updated in 2008 included 6 RCT.[106] A placebo controlled trial involving 51 patients provided evidence for the effectiveness of IG in MG worsening, while another small study involving 15 mild or moderate MG cases found no significant difference in efficacy after six weeks compared to placebo. Two studies, one involving 87 participants with exacerbation and another small study involved 12 participants with moderate or severe MG, showed no significant difference between IG and plasma exchange, after two and four weeks respectively. No significant difference in the efficacy of IG and methylprednisolone was shown in a study including 33 patients with moderate exacerbations. A large RCT showed no significant difference in efficacy between two doses for MG exacerbations (1 and 2g/kg). An open study of 10 severe MG patients unresponsive to common treatment showed that IG induced and maintained remission with sparing of the dose of immunosuppressive treatments. Gajdos et al. concluded that there is no convincing evidence to support the routine use of IG as maintenance therapy. Several reviews recommend IG for myasthenic crisis that are unresponsive to other agents, for severe exacerbations until other immunosuppressive treatments achieve stabilization, or as an option to stabilize patients before surgery.[107,108] The best IG dose in MG remains unclear, ranging 1-2g/kg.

IG is more effective than placebo and as effective as other therapies (plasma exchange and steroids) for severe MG exacerbation and MG worsening, but this benefit was not shown in mild and moderate disease. Most RCT studied MG with exacerbations.

Dermatomyositis and polymyositis

Dermatomyositis and polymyositis are idiopathic inflammatory myopathies, characterized by chronic inflammation of skeletal muscle which can result in persisting muscle weakness with significant disability.[109] Dermatomyositis also affects the skin, results in skin abnormalities, while polymyositis may have occasional pulmonary involvement. Both diseases generally responds to steroid or immunosuppressive drugs but the optimal therapy remains unclear, and a number of patients are resistant or only partially responsive to these therapies.[110]

A Cochrane review published in 2005 included one small RCT on IG compared to placebo, involving 15 patients with dermatomyositis.[109] It showed that IG was significantly superior to placebo in improving muscle strength, neuromuscular symptoms and skin rash.[111] Other therapies did not show clear benefit. The RCT concluded that IG is an effective second-line therapy for patients with dermatomyositis that incompletely respond to steroids and immunosupressants. A non-controlled trial and several observational studies confirmed the IG benefit in dermatomyositis and polymyositis.[112,113]

IG improved symptoms and muscle strength in dermatomyositis.

Inclusion body myositis

Inclusion body myositis (IBM) is the most common inflammatory myopathy in elderly patients. It is characterized by a slow chronic progressive and painless asymmetric weakness, with involvement of distal muscles with atrophy. Corticosteroids and immunosupressants are not successful. Treatment remains difficult as there is no or very little response to immunotherapy.[108]

Three RCT involving 47 patients showed similar results.[108] A placebo controlled RCT involving 19 patients showed an improvement in muscle strength in the group treated by IG compared to placebo, but the differences were not statistically significant, except for the muscles used for swallowing.[114] A second study showed similar results.[115] A third study compared IG (2g/kg) added to prednisolone to prednisolone alone.[116] After 3 months of treatment, there was no significant difference in muscle strength between the two groups. Despite these negative findings, many reviews recommend a short course of IG (2g/kg) as trial because no other treatment is effective.[27,107]

IG did not improve muscle strength in patients with inclusion body myositis patients but significantly improved swallowing functions in one study

Stiff person syndrome

The stiff person syndrome is a rare disorder of the nervous central system characterized by severe and episodic muscle rigidity and spasms. The cause is unknown but most patients are associated with high levels of antibodies directed against a specific enzyme, the glutamic acid decarboxylase, which is responsible for the synthesis of a major neurotransmitter (gamma amino butyric acid).

A single RCT conducted in 1996-99, involving 16 patients with Stiff person syndrome comparing IG to placebo, showed that IG significantly reduces muscle stiffness and occurrence of spasms in this disease compared to placebo.[117] The duration of the beneficial effect of IG varied from 6 weeks to one year. Three open studies have suggested the same effectiveness and improvement in quality of life.[118],[119],[120] IG is now considered to be the treatment of choice in many countries because other therapies only produce modest improvement in symptoms.

IG significantly reduced muscle stiffness and occurrence of spasms in Stiff person syndrome

Neuromyelitis optica

Neuromyelitis optica is a demyelinating disease of the spinal cord and optic nerves that manifest by recurrent attacks, and tends to have a poor prognosis. There is no proven effective treatment, although relapses are commonly treated with steroids; patients with recurrent attacks may be managed with immunosupressants.[121] IG has been considered as a possible treatment because the disease is antibody mediated.

There are a few case studies, involving 1 to 2 cases, suggesting that monthly IG may be effective in preventing relapses.[121,122] However, no RCT or other observational studies were found. More recent studies have rather focused on the effectiveness of rituximab, as it appears to reduce the frequency of attacks, with subsequent stabilization or improvement in disability.[123,124]

There is no evidence on the effectiveness of IG in neuromyelitis optica, and limited evidence suggested the effectiveness of rituximab

3.2.2.5 Evidence on other medical conditions

Kawasaki disease

The Kawasaki syndrome is an acute vasculitis affecting infants and young children, involving the coronary arteries. Its aetiology is unknown. The main complications are coronary artery aneurysms (CAA) that may occur from the second week of illness during the convalescent stage.

A Cochrane review published in 2003 included 16 RCT involving children with Kawasaki disease.[125] Results of the meta-analyses of IG versus placebo showed a statistically significant decrease in new CAA in favour of IG plus salicylate over salicylate alone, in favour of a single high dose regime over 4 or 5 day low dose regime. There was also a significant decrease in duration of fever and duration of hospitalization in cases treated with IG, with no statistically significant increase in adverse events.

Authors concluded that children fulfilling the diagnostic criteria for Kawasaki disease should be treated with high dose IG within 10 days of onset of symptoms. An RCT published after the Cochrane search period, comparing the effectiveness of IG at different doses, showed that a lower dose (1g/kg) was as effective as the standard 2g/kg dose.[126]

A Canadian study compared the cost-effectiveness of aspirin, low doses of IG (0.4g/kg/day for 4 days) and high doses of IG (2g/kg single dose).[127] It concluded that a single high dose is preferred because it results in both lower costs and lower rates of new CAA. A study in Japan came to the same conclusion, though it limited the high dose therapy to patients with specific criteria (Harada score).[128]

In Kawasaki disease, IG showed a significant decrease in new coronary artery abnormalities, fever and hospitalization, compared to placebo. A lower dose (1g/kg) is as effective as a high dose (2g/kg). A high single dose (2g/kg) is more cost-effective than a lower dose (0.4g/kg/day) for 4 days.

Viral myocarditis in children and adults

Acute myocarditis is a disease that occurs in all age groups. In young patients, it is the most common cause of heart failure requiring cardiac transplantation.[129] It is presumed to usually start as a viral infection, although autoimmune and idiopathic forms also occur. It remains unclear if the primary problem is most the ongoing damage from a virus, a post infectious inflammatory reaction, or a combination of both. However, immunosuppressive therapy was not shown efficacious in previous RCT. As IG has both antiviral and immunomodulatory effects and is an important therapy for Kawasaki disease, IG has been used in children with new-onset myocarditis.

A Cochrane systematic review published in 2005 included only one RCT involving 62 adult patients with presumed viral myocarditis.[129] Clinical improvement and incidence of death were not significantly different in patients receiving IG compared with the placebo group, due to the high rate of spontaneous recovery. The favourable prognosis with conventional therapy may explain the apparent improvement reported in uncontrolled studies.[129] These findings contrast with case series and a study comparing cases treated with IG to recent historical controls, which reported significant improvements in left ventricular function in cases treated with IG.[130,131,132] Authors concluded that evidence from this trial does not support the use of IG for the management of adults with presumed viral myocarditis. There are no randomized paediatric trials.

Evidence from one trial did not show a benefit of IG for the management of presumed viral myocarditis in adults. There is no evidence for paediatric cases.

Treating sepsis and septic shock

Despite the development of new antibiotics and advances in the management of critically ill adults with severe infections, the mortality rate from septic shock remains very high, ranging from 21 to 72%.[133,134] Because of its broad and potent activity against bacterial products and host cytokines, polyclonal intravenous immunoglobulin has been investigated as an adjunctive therapy for treating severe infections.

Several Cochrane systematic reviews have been published on this topic. The most recent one (2002) included 11 RCT involving 492 patients treated with polyvalent IG.[133] Overall mortality was reduced in patients who received polyclonal IG compared to placebo or no intervention (RR=0.64; 95% CI 0.51-0.80). Polyclonal IG also reduced mortality from septic shock in a pooled analysis from 3 RCT. Several other systematic reviews and meta-analyses have been published after this Cochrane review. The two most recent meta-analyses searched literature till March and May 2006 and included 14 and 20 RCT respectively, comparing IG for the adjunctive treatment of severe sepsis and septic shock with placebo or no treatment.[134,135] Though only 5 RCT were common to the three reviews, the two meta-analyses found similar and significant reduction in mortality in patients treated with IG compared to placebo or no intervention (RR=0.66; 95% CI 0.53-0.83 and RR=0.74; 95% CI, 0.62-0.89).[134,135]

Severe sepsis or septic shock cases receiving a higher dose (total dose 1g/kg or more) and treated for longer than 2 days were strongly associated with this survival benefit.[134,135]

IG used as an adjuvant therapy in patients with sepsis and septic shock reduced mortality compared with placebo or no intervention. This survival benefit was consistently observed in three large meta-analyses.

Treating Respiratory Syncitial Virus infections

Infection with the Respiratory Syncitial Virus (RSV) is a common cause of childhood bronchiolitis and pneumonia, and can cause severe disease in children between two to eight months. In older age groups, RSV may cause simple upper respiratory tract illness. Nearly all children have had at least one infection by the age of 3 years. No cure exists for RSV infections. Prophylactic use of IG products with high anti-RSV antibody titres or monoclonal anti-RSV antibody have proved beneficial when given monthly in selected high-risk infants,[136] but are not discussed in this section on polyvalent IG. Several studies have also assessed the effectiveness of providing IG for children admitted to hospital for severe RSV infection as treatment.

A Cochrane review published in 2006 evaluated the treatment of RSV infections with several types of IG, including polyvalent IG, IG with high anti-RSV antibody titres and humanised monoclonal antibody to RSV.[137] It included four publications, and no RCT demonstrated statistically significant benefit of IG treatment added to supportive care, compared with supportive care alone. No meta-analysis was possible due to the wide heterogeneity of the outcomes assessed. No RCT published after the review period were found. The available evidence thus does not support a role of IG for the treatment of RSV infection, with the doses used in the studies.

No significant benefit of IG treatment added to supportive care has been shown for the treatment of RSV infections, compared with supportive care alone.

3.2.2.6 Medical conditions under investigation

Alzheimer disease

Alzheimer's disease (AD) is the most common cause of dementia and accounts for more than half of the dementia cases. One of the major manifestations of AD is the presence of abundant plaques in the brain tissues of the affected individuals, due to deposits of an amyloid-beta peptide (AbP). The dominant theory states that overproduction of AbP, or failure to clear this peptide, leads to the neuronal damage.[138]

Preliminary studies have suggested that IG therapy has several positive effects on patients with AD, by lowering the level of soluble AbP in the brain.[139] However, no RCT was found; IG was only shown to have positive effect on AD patients in two small and non-controlled trials. The first trial involved 5 AD patients with IG monthly for six months and showed a drop in CSF AbP (by 30%) and an increase in plasma AbP (by 23%), together with a stabilization in cognitive decline in all the patients.[140] Another 18-month study in 8 patients with mild AD receiving IG led to transient increases in plasma levels of AbP.[141] The CSF AbP levels decreased after six months of IG therapy and, after three months without IG, increased to their pre-treatment baseline levels. These findings indicate that no definite statement on the effects of IG in AD can be made. Many other agents for passive immunotherapy are under study, mostly monoclonal antibodies against Ab or investigative vaccines. A phase III trial of pooled human immunoglobulin has been recently launched but no details are available.[142]

Evidence is lacking on the effectiveness of IG in the treatment of Alzheimer Disease

Chronic fatigue syndrome

The Chronic fatigue syndrome (CFS) is a condition characterised by severe, disabling fatigue in the absence of exertion, and is marked by a dramatic decline in activity level. Currently, the aetiology of CFS remains unknown.

The beneficial effect of IG for CFS patients is controversial. Three RCTs obtained mixed results: a RCT conducted in 1990 found improvements in symptom scores and functional capacity at three months;[143] a second found improvement in immune indicators but not in symptom and functional measures,[144] the third trial was more recent and larger (involving 99 adult patients).[145] It found no effect of treatment, but reported adverse reactions in 70-80% patients, with no relationship to IG treatment. It concluded that IG cannot be recommended as a therapy for CFS.

There is conflicting evidence on the effect of IG in CFS, but the larger and more recent trial showed no effect, with a high rate of adverse events.

3.3 CONSUMPTION OF IMMUNOGLOBULINS

3.3.1 Consumption in other countries

Few studies investigating IG use and its trends are available. No study has been found on IG consumption in European countries. However, eight studies with quantitative data on recent IG use per indication were found from Australia, Canada, New Zealand and the US.[146,147,148,149,150,151,152,153].

3.3.1.1 Consumption by medical speciality and indication

The results of the four studies analyzing prescription data after 2000 are described below.[146,147-149]. The distribution of the total quantities of IG used, by indication and major specialty, is shown in Table 22, based on the four studies analyzing IG use per indication. Though variations are observed across studies, the majority of IG was prescribed by two clinical specialities: neurology, which consume in average one third of total IG amount; and immuno-haematology, which consume around half of the total amount. An exception to this pattern was the Massachusset general hospital (US) where a very high consumption in neurology (71%) is biasing other relative estimates.

Table 22: Distribution of the total amount of immunoglobulin used per disease in four studies in three countries, 2000-2004 (New Zealand, Canada, US). Weighted average of the four studies.

Studies	New Zealand	Toronto	Massach US	Canada Atlantic	Weighted average
Diseases/year	**2004**	**2000**	**2004**	**2003-04**	
Guillain-Barré syndrome	6%	5%	3%	4%	*5%*
Chronic inflammatory demyelinating polyneuropathy	13%	9%		12%	*19%*
Multifocal motor neuropathy	3%	3%	62%	8%	*4%*
Relapsing-remitting multiple sclerosis				3%	*3%*
Myasthenia gravis	2%	1%	4%	5%	*3%*
Dermatomyositis		2%	2%	2%	*2%*
Total neurology - muscular	*25%*	*20%*	*71%*	*35%*	*32%*
Idiopathic thrombocytopenic purpura	9%	16%	8%	17%	*13%*
Primary immune deficiencies	32%	15%	9%	15%	*19%*
Secondary immune deficiency in general	*15%*	*19%*	*9%*	*10%*	*14%*
- Chronic lymphocytic leukaemia	5%			1%	*4%*
- Multiple myeloma				1%	*1%*
- Bone marrow / stem cell transplant	8%	19%		4%	*11%*
- Children with HIV			1%		*1%*
- solid organ transplants	2%		1%	4%	*2%*
Acute leukaemia in childhood	4%				*4%*
Autoimmune haemolytic anaemia		2%	1%		*2%*
Total immuno-hemato	*60%*	*51%*	*27%*	*42%*	*48%*
Kawasaki disease in children			0%	1%	*0%*
Toxic shock syndrome		3%	2%	1%	*2%*
Others	*15%*	*27%*	*1%*	*22%*	*17%*
Total amount IG	101.496 g	100.208 g	48.230 g	65.240 g	315.174 g

The analysis of IG distribution per indication shows that a few diseases treated with long term maintenance IG consume a high proportion of the total IG amount. Among the neurological indications, chronic inflammatory demyelinating polyneuropathy (CIDP) accounts for the highest consumption per disease (19% of total use in average), and combined with multifocal motor neuropathy (MMN) consumed as much as 62% of the IG amount in Massachusset, while it represents 11-20% in other studies. Among the immuno-haematological indications, the main consumers are primary and secondary immune deficiencies (PID and SID), representing together 34% of total use (ranging 18-47%). Idiopathic thrombocytopenic purpura (ITP) and stem cell transplants (included in secondary immune deficiencies) represents 13 and 11% of total IG use respectively but this proportion widely varies across countries, reflecting diverging views on the IG use for these indications.

Similar geographical variations were observed across Canadian regions (Tonronto vs. Atlantic regions), as well as across Australian regions.[146, 148, 151]

Some other specialties or indications were responsible for a high IG use, which contrasted with the recommendations in use. For instance, the Toronto study showed an unexpectedly high amount of IG used for infectious diseases (18%) and dermatology (7%).[148] Unexpected patterns of IG use were also observed in specific regions: in the New Zealand study, one region was an extraordinarily high user of IG for obstetric purposes, using 11-fold more IG per capita in this category than the other regions, and also used large amounts for respiratory and rheumatic diseases. Another region used more IG for cardiological diagnoses than all other regions combined.[149] The Toronto study also noticed that individual physicians with specific clinical interest were responsible for large proportions of the total IG prescribed.[148] A high number of patients received IG as a single dose, for other indications that those commonly accepted; each patient consumed relatively little IG but made up of nearly one-third of all patients treated. Most of these single-use patients probably represents empirical use of IG in which a clinician attempts to rescue a seriously ill patient for whom there are few other treatments available, or when physicians are confronted with an undefined medical problem, such as a peripheral neuropathy. This pattern was also suggested by the Canadian Atlantic study.[146]

The distribution of the total number of patients treated with IG per disease (Table 23) suggests a similar distribution. However, the proportion of patients treated for neurological disorders tends to be lower than the respective proportion of IG use, especially in Massachusset where 39% cases with neurological disorder consume 71% of total IG use. This is due to the high amount of IG used for the long term immuno-modulatory treatment of neurological indications such as CIDP and MMN: the dosage ranges 1-2g/kg body weight (vs. 0.3-0.6g for PID and 0.8-1g for ITP) and these patients are mostly adults.

The average IG amount used to treat a case with a defined disease is presented in Table 24. It indeed confirms the (non significantly) higher average dose per patient used to treat the neurological diseases (ranging 173-486g per patient) as compared to immuno-haematological indications (ranging 90-302g per patient). Diseases ranking the highest in IG use per patient (weighted average) were dermatomyositis, multiple sclerosis, CIDP, MMN, stem cell transplant, acute leukaemia and solid organ transplants. Primary and other secondary immune deficiencies are consuming lower amounts per case (ranging 150-229g per patient), due to the lower dosage per kg used for IG supplementation.

Table 23: Distribution of the number of cases treated with immunoglobulins, per disease, in four studies in three countries, 2000-2004 (New Zealand, Canada, US).

Studies	New Zealand	Toronto	Massach US	Canada Atlantic	Total cases
Diseases/year	**2004**	**2000**	**2004**	**2003-04**	
Guillain-Barré syndrome	7%	11%	4%	5%	**106**
Chronic inflammatory demyelinating polyneuropathy	10%	11%		7%	**149**
Multifocal motor neuropathy	3%	1%	29%	3%	**27**
Relapsing-remitting multiple sclerosis				2%	**6**
Myasthenia gravis	2%	2%	5%	5%	**44**
Dermatomyositis		1%	1%	1%	**12**
Total neurology - muscular	23%	26%	39%	22%	24%
Idiopathic thrombocytopenic purpura	12%	15%	10%	15%	**190**
Primary immune deficiencies	30%	6%	13%	19%	**253**
Secondary immune deficiency in general			*18%*	*8%*	**61**
- Chronic lymphocytic leukaemia	5%				**24**
- Multiple myeloma				1%	**5**
- Bone marrow / stem cell transplant	5%	15%		7%	**113**
- Children with HIV			1%		**2**
- solid organ transplants	1%		1%		**7**
Acute leukaemia in childhood	3%				**12**
Autoimmune haemolytic anaemia		3%	1%		**14**
Total immuno-hemato	56%	39%	45%	50%	48%
Kawasaki disease in children			0%	3%	**11**
Toxic shock syndrome		4%	2%	1%	**24**
Others					
Total amount IG	457	429	194	339	**1419**

Table 24: Immunoglobulin amount used per patient, per year and per disease, in four studies in three countries, 2000-2004 (New Zealand, Canada, US). Weighted average of the four studies.

Studies	New Zealand	Toronto	Massach US	Canada Atlantic	Weighted average
Diseases/year	**2004**	***2000***	**2004**	**2003-04**	
Guillain-Barré syndrome	188 g	160 g	190 g	174 g	**173 g**
Chronic inflammatory demyelinating polyneuropathy	297 g	182 g			**348 g**
Multifocal motor neuropathy	248 g	708 g	530 g		**486 g**
Relapsing-remitting multiple sclerosis				354 g	**354 g**
Myasthenia gravis	219 g	169 g	190 g	200 g	**198 g**
Dermatomyositis		439 g	490 g		**453 g**
Idiopathic thrombocytopenic purpura	170 g	*243 g*	190 g	217 g	**210 g**
Primary immune deficiencies	239 g	233 g	170 g		**229 g**
Secondary immune deficiencies:					
- Chronic lymphocytic leukaemia	219 g				**219 g**
- Multiple myeloma					
- Bone marrow / stem cell transplant	342 g	287 g			**302 g**
- Children with HIV			150 g		**150 g**
- solid organ transplants	426 g		*80 g*		**286 g**
Acute leukaemia in childhood	299 g				**299 g**
Autoimmune haemolytic anaemia		166 g	10 g		**146 g**
Kawasaki disease in children			20 g	52 g	**51 g**
Toxic shock syndrome		160 g	120 g	87 g	**140 g**

3.3.1.2 *Trends over time*

An increase in overall IG consumption has been described worldwide. For instance, annual utilisation in Australia rose by an average of 14.8% from 1994-95 to 2004-05.[16] In Canada, the IG use has steadily risen since 1990, at a mean annual rate of 12.5%.[146]

However, only a few studies have analyzed the distribution of IG use per indication (or specialty) over time. An unpublished US study shows that the weight of each medical specialty has undergone noticeable changes within a 5-year period of time (2002-2007, Table 25). The Toronto study reported that dermatological conditions increased from 0% of annual consumption in 1995 to 16% by 2000, and this was linked to the establishment of specialized dermatological clinics.[148]

This suggests that diversification in IG use or IG demand, resulting from either newly approved indications or changes in prescription practices, may appear in any country in a relatively short period of time.

Table 25: Distribution of the total amount of immunoglobulin used per medical specialty in the US, 2002-2007

Medical Specialty	2002	2007
Allergy Immunology	19,0%	21,6%
Rheumatology Nephrology	2,1%	7,8%
Dermatology	6,3%	7,6%
Neurology	20,2%	22,0%
Hematology	30,8%	11,3%
Cardiology	0,0%	3,4%
Obstetrics Gynecology	0,0%	6,7%
Infectious Diseases	14,1%	10,0%
Ophtalmology	2,0%	9,1%
Others	5,5%	0,0%

Source: presentation of Marketing Research Bureau/ IPPC-PPTA Congress 3-4 March 2009

3.3.1.3 *Unlabelled use of immunoglobulin*

Several studies compared the proportion of IG used or the proportion of patients treated with IG for an unlabelled indication, as defined in each country (Table 26).[146] It is noteworthy that these unlabelled indications represented more than half of the total number of patients receiving IG (52-64%) in all studies. However, most of these IG administrations were scientifically accepted and often included in the national recommendations, in accordance with the last guidelines. This concept of labelled and unlabelled indication for IG is thus no longer related to the concept of scientifically proven benefit. In Canada (Atlantic Provinces), the introduction of detailed recommendations did not impact on the proportion of IG administered for unlabelled indications, at least in the first year.[146]

Table 26: Use of immunoglobulins for unlabeled indications in the US and Canada, 2000-2005.

Country	% total (year)	Comments
US, 12 academic centres	52% patients (Chen, 2000)	Drug authority allows all uses
US, Massachusset hospital	54% patients (Darabi, 2004)	Drug authority allows all uses
Canada, Atlantic provinces	64% of IVIG amount (Constantine 2005)	Study pre and post recommendations

Key points

- **In other industrialized countries, around half of the total amount of immunoglobulins is used to treat immuno-haematological diseases, and around one third is used to treat neurological and neuro-muscular diseases.**
- **Some specialities or indications that are usually not included in recommendations consume an unexpectedly high amount of IG, with large variations across hospitals and geographical areas. Individual physicians or clinics may impact on large proportions of the total IG prescribed**
- **A few diseases consume a high proportion of the total IG. For instance, four diseases (chronic inflammatory demyelinating polyneuropathy, primary and secondary immune deficiencies and idiopathic thrombocytopenic purpura) consumed in average two third of the total IG amount. Three of these diseases require long term treatment with IG.**

3.3.2 Consumption in Belgium

3.3.2.1 Methods

Data on IG use in Belgium were collected from two sources:

1. Data on the period January 2004 - June 2007 from the National Institute for Health and Disability Insurance (INAMI/RIZIV) on the IG amounts reimbursed, per quarter;
2. Data on the year 2008 on IG used by hospitals (reimbursed or not) and collected by an ad-hoc survey.

The KCE carried out a survey in March-June 2009 addressed to all pharmacists responsible for hospital pharmacies in Belgium, with the collaboration of the two regional associations of hospital pharmacists. We requested data on the amount of each IG brand product (per label and dosage) used in 2008, by medical specialty of the prescriber, based on the last three numbers of the INAMI/RIZIV codes. All non-responding hospitals that had consumed >1 500 gr or spent >60 000€ for IG in 2006 were then contacted personally.

Data were then analyzed by summing all brand products expressed in grams. Distribution per hospital, medical specialties and type of producer (CAF and non-CAF) are presented. Though data come from two non-fully comparable sources, we have compared data over the 2004-2008 period to identify trends.

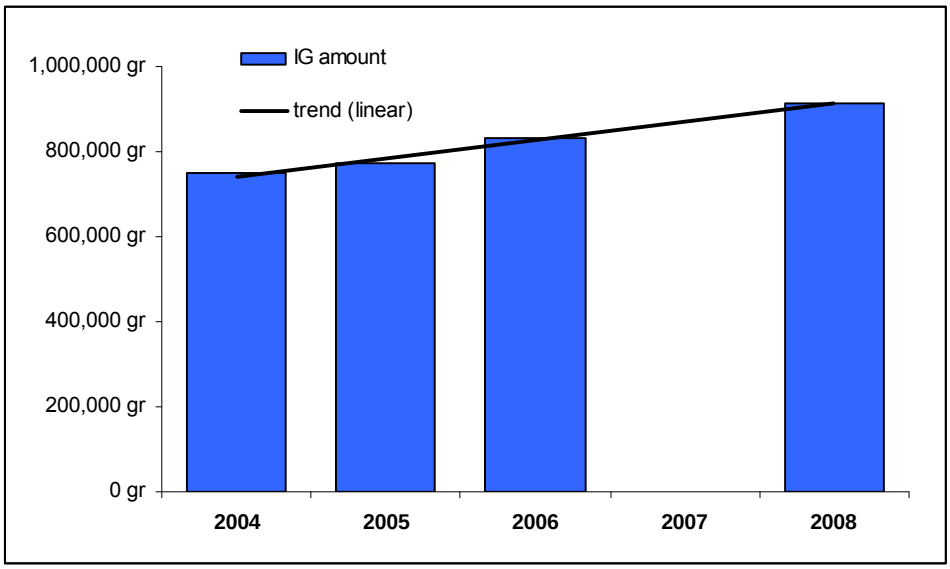
Information on the indications for which IG has been prescribed is not available. This survey does not aim at assessing the relevance of IG prescription in hospitals.

3.3.2.2 Overall IG amounts used in 2004-2008

INAMI/RIZIV data for the 2004-2006 period have been presented under "Use of plasma derivatives in Belgium" and are compared below to the 2008 data (Figure 7).

The KCE received data on 2008 IG amounts used from 102 hospitals reporting a total use of 919.6 kg of IG, all products combined. These 102 hospitals represent a response rate of 82% on the 125 hospitals that reported IG use in 2006 and accounted for as much as 99% of national IG use in 2006.

Figure 7: Yearly quantities of IG consumed during the period 2004-2008



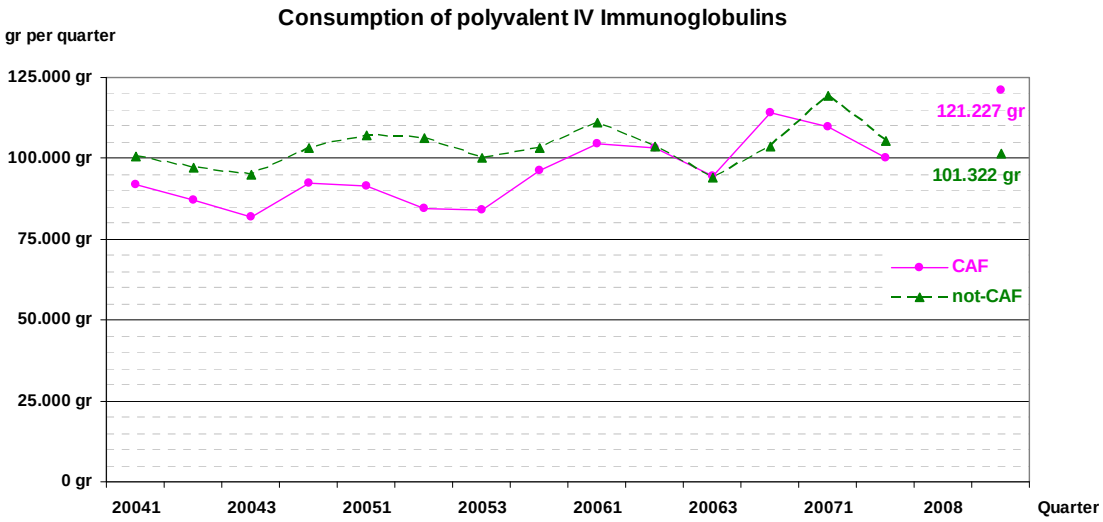
Sources: INAMI (2004-2006) and KCE survey (2008)

Figure 7 shows the yearly increase of IG consumed over the period 2004-2008 and its linear trend. Data on 2007 are only available for the first two quarter of 2007. It must be noted that the two data sources are not fully comparable: 2004-2006 data cover reimbursed IG data provided by INAMI/RIZIV in all Belgian hospitals; 2008 data collected by the survey cover reimbursed and non-reimbursed IG reported by Belgian hospitals representing 99% of IG use in 2006. However, we observed that the 2008 estimate fits with the linear trend on the 2004-2006 data.

Figure 8 presents the evolution (per quarter) of intravenous IG (IVIG) used, per producer (CAF-DCF and other producers). The systematically lower consumption in the third quarter may be explained by the discontinuation of IG supplementation in mild immune deficiencies during summer (see Patterns of use). The proportion of CAF-DCF IVIG used increased over the period (except in 2007) to reach 54.4% of all IVIG in the second quarter of 2008.

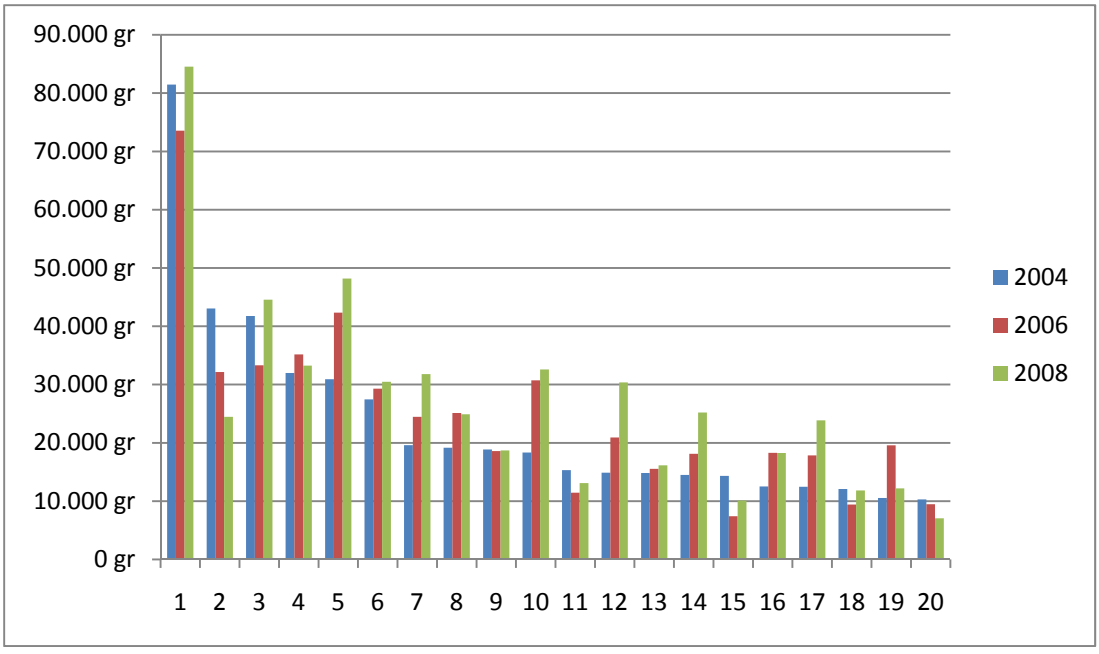
In Figure 9, the IG consumption over the years 2004, 2006 and 2008 is compared for the 20 hospitals showing the highest IG consumption. The absolute amounts of IG used are not compared across hospitals by level of activity, by lack of suitable criteria or indicator. But the comparison of trends across hospitals show divergences in IG consumption trends over this 5 year period: some hospitals have nearly doubled their IG use (hospitals 10, 12 and 17), others showed a milder increase or a relative stabilization of IG use, and a minority of them have decreased IG use from 2004 to 2008.

Figure 8: Quantities of IG consumed in 2004-2008, per quarter and producer



Sources: INAMI (2004–2007 first half-year) and KCE survey (2008)

Figure 9: Evolution of the consumption of IG (2004 – 2006 – 2008) in the 20 Belgian hospitals with highest consumption

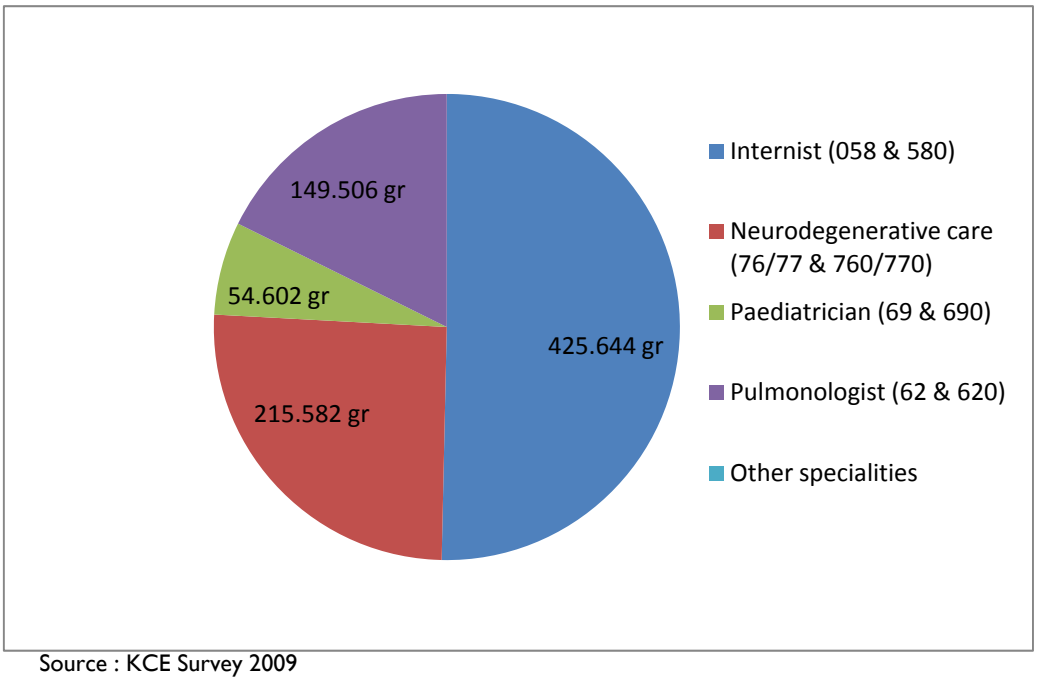


3.3.2.3 *Amounts prescribed per medical speciality in 2008*

Based on the last three numbers of the INAMI/RIZIV code for prescribers, we have analyzed 2008 IG prescription by medical specialty.

Table 27 indicates that four major specialities prescribed 92% of the IG 2008 amount: internists (all sub-specialties confounded) prescribed around half of IG, neurologists around one quarter, pneumologists one sixth and paediatricians 6%.

Figure 10: Quantities of immunoglobulins prescribed by medical specialty in 2008, Belgium



Source : KCE Survey 2009

The prescription by medical specialty shows variations between the university / academic hospitals (UZGent, UZA, KULeuven, AZ-VUB, UCL St Luc and Mont-Godinne, Erasme and Children Hospital Reine Fabiola, CHU-Liège) and the other hospitals (als but 23% in other hospitals.

Table 27). The widest discrepancy is observed in the distribution of IG prescribed by lung specialists: it represents 2% of all IG prescribed in academic hospitals but 23% in other hospitals.

Table 27: Amounts of immunoglobulins prescribed by medical specialty in 2008, academic vs. non-academic hospitals

Specialty	Use in all hospitals	% of total amount	Use in academic hospitals	% of total amount in academic	Use in other hospitals	% of total amount in other hospitals
N hospitals	*102*		*8*		*94*	
Internists	425.644 gr	46%	148.067 gr	50%	277.578 gr	44%
Neurology and related	215.582 gr	23%	89.818 gr	31%	125.764 gr	20%
Paediatricians	54.602 gr	6%	26.898 gr	9%	27.704 gr	4%
Pneumologists	149.506 gr	16%	6.030 gr	2%	143.476 gr	23%
Other specialities	74.338 gr	8%	22.948 gr	8%	51.390 gr	8%
Total reported	**919.672 gr**	100%	**293.761 gr**	100%	**625.912 gr**	100%

In order to further investigate these differences, we have also compared the total amount prescribed by hospital and medical specialty, as well as the proportion it represents on the total IG amount prescribed in each hospital. The tables below per specialty present in the first line the consumption in all academic hospital together, per linguistic regime (for the Flemish part: UZGent, UZA, KULeuven and AZ-VUB and for the French-speaking part: UCL St Luc and Mont-Godinne, Erasme and Children Hospital Reine Fabiola, CHU-Liège); the following lines present, by hospital and linguistic regime, the consumption in the hospitals with highest IG amount, in decreasing order.

Table 28: Amounts of immunoglobulins prescribed by internists in 2008 and proportion of the total amount prescribed per hospital

	Flemish		French-speaking	
	Amount	%	Amount	%
All academic general internists	108.25 kg	57.1%	39.82 kg	38.3%
	23.74 kg	77.9%	11.73 kg	91,0%
	23.61 kg	88.4%	9.37 kg	92,7%
	19.60 kg	78.7%	7.90 kg	45,8%
	7.44 kg	40.7%	7.12 kg	54,4%
	7.13 kg	60.3%	5.78 kg	64,5%
	6.72 kg	78.2%	5.46 kg	76,4%
	5.82 kg	52.9%	5.33 kg	40,7%
	5.19 kg	15.6%	5.27 kg	72,3%
	5.16 kg	37.7%	4.89 kg	61,8%
	3.83 kg	52.0%	4.80 kg	58,9%
	3.73 kg	36.6%	4.44 kg	61,2%
	3.63 kg	19.4%	4.39 kg	68,4%
	3.26 kg	72.7%	3.77 kg	63,5%
	3.09 kg	25.3%	3.18 kg	70,5%
	2.62 kg	62.9%	2.40 kg	34,0%
	2.39 kg	7.3%	2.11 kg	42,6%
	2.37 kg	46.6%	2.10 kg	36,0%
	2.02 kg	24.9%	1.92 kg	70,1%
	2.02 kg	75.7%	1.65 kg	51,4%
All Belgian general internists	425.594 kg		46.3%	

Table 29: Amounts of immunoglobulins prescribed by neurologists & neuro-psychiatrists in 2008 and proportion of the total amount prescribed per hospital

	Flemish		French-speaking	
	Amount	%	Amount	%
All academic neurologists & neuro-psychiatrists	43.41 kg	22.9%	46.41 kg	44.6%
	18.65 kg	57.2%	3.84 kg	22.2%
	9.43 kg	58.4%	2.95 kg	22.5%
	6.99 kg	65.7%	2.64 kg	29.5%
	4.60 kg	13.8%	2.52 kg	51.0%
	4.01 kg	32.9%	2.07 kg	35.4%
	3.63 kg	33.0%	1.97 kg	15.0%
	3.56 kg	11.7%	1.87 kg	52.2%
	3.46 kg	18.9%	1.47 kg	60.2%
	3.00 kg	29.4%	1.40 kg	19.2%
	2.96 kg	75.8%	1.33 kg	16.4%
	2.39 kg	9.6%	1.22 kg	17.1%
	2.26 kg	53.7%	1.22 kg	20.5%
	2.20 kg	47.8%		
All Belgian neurologists & neuropsychiatrists	215.58 kg		23.4%	

Table 28 and Table 29 show variations in amounts prescribed and proportion these represent in each hospital for the specialities internal medicine and neurology. However, no conclusion can be drawn as we did not compare these values with the number of cases requiring IG and treated in these hospitals.

Table 30: Amounts of immunoglobulins prescribed by lung specialists in 2008 and proportion of the total amount prescribed per hospital

	Flemish		French-speaking	
	Amount	%	Amount	%
All academic pulmonologists	4.57 kg	2.4%	1.46 kg	1.4%
	21.09 kg	63.4%	4.29 kg	60.7%
	12.32 kg	65.9%	2.83 kg	21.6%
	10.94 kg	33.6%	2.13 kg	29.4%
	10.23 kg	93,7%	1.95 kg	23.9%
	7.62 kg	55.7%	1.37 kg	7.9%
	6.40 kg	70.8%		
	6.03 kg	66.1%		
	5.42 kg	33.6%		
	5.35 kg	29.3%		
	4.23 kg	52.1%		
	3.31 kg	32.5%		
	2.35 kg	59.1%		
	2.26 kg	59.5%		
	2.25 kg	54.8%		
	2.24 kg	7.4%		
	2.06 kg	17.4%		
	2.04 kg	7.6%		
All Belgian lung specialists	149.51 kg		16.3%	

In Table 30, we observe a severe discrepancy between the prescription of IG by lung specialists in academic and the prescription in non-academic hospitals: the Flemish hospital where lung specialists prescribed the highest IG amount accounted for 21.1 kg or 4.6 times the amount consumed in all university hospitals combined. The French-speaking hospital having prescribed most IG in pneumology, consumed three times the amount prescribed in all French-speaking university hospitals. In both hospitals, IG prescribed by pneumologists represented more than 60% of the IG prescribed for the whole hospital, while this proportion represents 1.4% and 2.4% in academic hospitals.

This high prescription for lung disease is especially noticeable in Flanders: in at least 11 non-academic hospitals, over 50% of the total IG is prescribed by pneumologists. This prescription pattern and high IG use in pneumology cannot be unexplained by current reimbursed indications, as no respiratory pathology is included in the current indications for IG, except for agammaglobulinemia and hypogammaglobulinemia with repeated bacterial infections that may affect the respiratory tract. Experts reported that IG is frequently prescribed in some peripheral hospitals for other immune deficiencies, such as isolated Ig G subclasses deficiencies without recurrent infections and without abnormal antibody response after pneumococcal vaccination. However, these patients are neither an indication for IG nor is IG reimbursed for these situations. It should also be noted that the criteria for IG reimbursement clearly state that "IG are not reimbursed if the IgG/IgG2/IgG3 deficiency is due to a long term treatment with steroids, for instance as in the chronic obstructive pulmonary disease".

In a few other specialties, similar patterns are also observed, to a lower extent: a high level of heterogeneity in prescription is seen across hospitals and some hospitals are prescribing significant IG amount in some specialties for which no indication is reimbursed or usually recommended based on evidence; for instance, in surgery, obstetrics, gynaecology and gastro-enterology.

Table 31: Amounts of immunoglobulins prescribed by paediatricians in 2008 and proportion of the total amount prescribed per hospital

	Flemish	Flemish	French	French
All academic paediatricians	14.61 kg	7.7%	12.28 kg	11.8%
	2.44 kg	9.8%	3.05 kg	17.7%
	0.96 kg	5.9%	1.82 kg	23.0%
	0.96 kg	5.2%	1.54 kg	11.8%
	0.89 kg	7.5%	1.00 kg	7.6%
	0.84 kg	11.4%	0.66 kg	20.5%
	0.61 kg	1.9%	0.56 kg	7.7%
	0.58 kg	7.1%	0.51 kg	5.7%
	0.53 kg	2.8%	0.50 kg	6.8%
All Belgian paediatricians	54.62 kg		5.9%	

Table 32: Amounts of immunoglobulins prescribed by rheumatologists in 2008 and proportion of the total amount prescribed per hospital

	Flemish	Flemish	French	French
All academic rheumatologistss	2.52 kg	1.3%	0.20 kg	0.2%
	4.45 kg	36.5%	2.19 kg	61.5%
	1.51 kg	4.5%		
	1.42 kg	12.9%		
	1.21 kg	35.7%		
	1.06 kg	36.0%		
All Belgian rheumatologists	18.89 kg		2.1%	

Table 33: Amounts of immunoglobulins prescribed in intensive care units for adults in 2008 and proportion of the total amount prescribed per hospital

	Flemish	Flemish	French	French
All academic IC units for adults	4.04 kg	2.5%	2.92 kg	3.8%
	1.47 kg	4.6%	0.83 kg	17.1%
	0.63 kg	10.7%	0.65 kg	6.7%
All Belgian IC units for adults	20.55 kg		2.5%	

Table 34: Amounts of immunoglobulins prescribed by gastro-enterologists in 2008 and proportion of the total amount prescribed per hospital

	Flemish	Flemish	French	French
All academic gastroenterologists	2.09 kg	1.1%	0.54 kg	0.5%
	1.11 kg	12.1%		
	0.63 kg	7.8%		
All Belgian gastroenterologists	7.71 kg		0.8%	

Table 35: Amounts of immunoglobulins prescribed by surgeons in 2008 and proportion of the total amount prescribed per hospital

	Flemish	Flemish	French	French
All academic general surgeons	1.47 kg	0.8%	1.37 kg	1.3%
			2.37 kg	18,0%
All Belgian general surgeons	6.50 kg		0.7%	

Table 36: Amounts of immunoglobulins prescribed by hospital general practitionners (GPs) in 2008 and proportion of the total amount prescribed per hospital

	Flemish	Flemish	French	French
All GPs in academic hospitals	1.98 kg	1.0%	0.16 kg	0.2%
			1.03 kg	92.3%
			1.02 kg	15.8%
All Belgian general practitioners in hospitals	5.56 kg		0.6%	

Table 37: Amounts of immunoglobulins prescribed by cardiologists in 2008 and proportion of the total amount prescribed per hospital

	Flemish	Flemish	French	French
All academic cardiologists	3.11 kg	1.6%	0.50 kg	0.5%
	0.64 kg	16.1%		
All Belgian cardiologists	6.46 kg		0.7%	

Table 38: Amounts of immunoglobulins prescribed by gynecologists in 2008 and proportion of the total amount prescribed per hospital

	Flemish	Flemish	French	French
All academic gynecologists	0.96 kg	0.3%	0.00 kg	0.0%
	0.24 kg	12.2%	0.77 kg	4.4%
	0.19 kg	1.0%	0.23 kg	3.9%
All Belgian gynecologists	3.04 kg		0.3%	

3.3.2.4 Discussion on IG consumption

Data on IG consumption in Belgium indicate similar patterns than those found in other countries: IG consumption is increasing over time, four main specialties consume the majority of IG, the use of IG is heterogeneous across hospitals and some hospitals consume a high IG amount in specialties that are not related to the authorized or reimbursed indications.

Two additional findings in Belgium have been revealed by the KCE survey:

1. A high amount of IG is prescribed by lung specialists, though this cannot be justified by current reimbursed indications or available evidence, as no respiratory pathology is included in the current indications for IG (except for specific immune deficiencies with repeated respiratory tract infections). This was not observed in any of the academic hospitals but was predominant in 11 Flemish and one Walloon hospitals. At international level, this was only reported in one region in the New Zealand study. As we did not have access to data on IG consumption per indication, we could not explain this prescription with available data. This finding deserves further investigation.
2. The survey showed wide variations in prescription patterns between academic and non-academic hospitals. A major finding is that a number of non-academic hospitals prescribe significant IG amounts for four other specialties (surgery, obstetrics, gynaecology and gastro-enterology) that are not related to reimbursed indications - or to other indications for which a benefit of IG has been proven. This unexpectedly high IG use is not observed in academic hospitals. Unexpected patterns of IG use in some hospitals or geographical areas were also observed in New Zealand where one region used 11-fold more IG per capita for obstetric purposes than the other regions. The Toronto study also noticed that individual physicians with specific clinical interest were responsible for large proportions of the total IG prescribed.

The reasons for the overall increase in IG consumption over the recent years could not be investigated based on these Belgian data. We had no access to data allowing us to determine for which indications IG has been prescribed over time.

For instance, a growth in IG used in neurology was expected with the gradual introduction of CIDP and MMN in the list of reimbursed indications over 2002-2008 (Table 19), but this could not be verified. It is remarkable to observe that a few hospitals have decreased their IG consumption while others have doubled it over a 5 year period.

3.3.2.5 Patterns of use

In order to understand IG use in Belgium and help determine the IG amount that would be required to treat the most IG consuming indications, two expert meetings and a survey were organized. The aim was to assess current practices in Belgium regarding the characteristics of patients treated, the dosage used, the frequency of IG treatment in maintenance therapy and the expected trends in IG use.

In immuno-haematological diseases

A survey was undertaken among 10 main centres administering IG for immuno-deficiencies. Questionnaires were addressed to paediatricians and haematologists to obtain information on how IG are used in Belgium. We requested 2008 data on the number of patients treated per reimbursed indication, number of IG administrations and usual dosage for the reimbursed indications. Responses were received from 7 hospitals, and 6 hospitals provided the data requested. Survey results were presented to an expert committee and discussed. The questionnaires are provided in appendix.

Collected questionnaires covered 846 cases, including 562 cases with an immunological or haematological disease or a Kawasaki disease: 186 cases with primary immune deficiency (PID) under maintenance treatment, 148 transplant cases, 75 ITP cases, 58 cases with MM or CLL, 31 Kawasaki disease cases, 37 neonates treated with IG for infection or severe ABO incompatibility and 27 cases with other immune deficiencies. Among these cases, 338 were children (154 PID, 36 transplants, 53 ITP, 31 Kawasaki disease, 37 neonates and 27 other immune deficiencies).

No cases treated with IG for septic shock syndrome were reported, though this is a reimbursed indication for IG. Based on several assumptions, we estimated that all these cases - with the exclusion of neurological indications - accounted for a total IG use of 108 kg in 2008, representing around 12% of total national use in 2008.

DOSAGE PER INDICATION

Results showed that similar dosage of IG supplementation per kg body weight are administered in all centres to PID cases (around 0.4g), in accordance with guidelines published by the Primary Immune deficiency Belgian group,[34] and for transplant cases. But dosage for other indications showed wide variations. In ITP, doses ranged 0.8-2g/kg; two hospitals use a dose of 0.8g/kg in children as it has shown similar efficacy than higher doses in a recent study. In Kawasaki disease, dose ranged 1 to 2g/kg but 2g was the most frequent. For the other indications, only one or two centres reported cases and no conclusion can be drawn.

FREQUENCY OF TREATMENT

The annual frequency and duration of intravenous IG (IVIG) administrations per patient requiring long term treatment also showed differences across centres:

- For PID, the frequency of IVIG administration varied from an average of 6.4 to 14.3 per year in 2008. However, centres reporting a lower frequency had many patients switching from IV to SC administration in 2008 and a more documented monitoring. In addition, the frequency in IG administration depends on the type of immune deficiency: patient with severe antibody deficiencies must receive treatment all year long, mostly every 3-4 weeks, requiring 12-14 administrations per year; while in transient or mild hypogammaglobulinemia with recurrent severe infections, IG treatment can be stopped during summer.

- For bone marrow or stem cell transplant, the frequency of administration averaged 10.8 per year, ranging 2.6-12.9. In general in children, treatment is administered before transplant and during at least 3 months, mostly 6 months and up to 1-2 years in cases of persistent B-cell abnormalities. However, the recent decrease in myeloablative transplants, due to an increase in non-myeloablative techniques, has decreased the level and duration of secondary immune deficiency - and the consequent IG needs. This is mostly described in adult patients.
- For ITP, the frequency of administration was not available in most hospitals but was 1.4 per case in average in 3 hospitals.
- In Kawasaki disease, the frequency of administration could not be established based on available data, but experts advised the administration of a single dose, followed by a 2nd dose in a few patients in which inflammatory signs and symptoms are still present.

WHICH CASES SHOULD BE TREATED WITH IG

The proportion of patients receiving IG for each of these indications in Belgium was difficult to assess in this survey, as clinicians could not always collect data on the total number of cases that visited their centre.

For bone marrow or stem cell transplant, paediatricians considered that nearly all paediatric cases require IG supplementation; in adults, only a selected subgroup of patients having a symptomatic secondary immunodeficiency following the transplant can benefit from IG treatment, and this should be decided on an individual basis.

Secondary immune deficiencies due to the use of therapies depleting B-cells or impairing B-cell response (eg. some anticancer drugs) and inducing symptomatic hypogammaglobulinemia are also medical conditions for which IG may be necessary.

Experts proposed that cases with secondary hypogammaglobulinemia be treated with IG during for the period of the hypogammaglobulinemia, irrespective of its cause. This is line with the approach of PID cases, though the treatment would be mostly limited to a period of 6-12 months.

ESTIMATION OF AMOUNTS

The amount of IG used for each immuno-haematological indication in these centres has been estimated, based on the assumption of an average 75kg body weight per adult, 25 kg per child and 4 kg per neonate. Under these assumptions, treatment of PID patients would represent 61% of the total IG use for immuno-haematological indications, CLL and MM 14% and transplants 10%. However, these estimates are biased by a better response rate among paediatricians as compared to haematologists treating adult cases.

USE OF SUB-CUTANEOUS IG

Subcutaneous administration of IG was used for PID in 5 out of the 6 hospitals and used to treat 44% of the PID paediatric cases in average. This practice was predominant in two hospitals where 48-71% of PID children received SC administration, and is a growing practice in the other paediatric wards of these centres. Expert paediatricians consider that SC administration is a first choice for long-term treatment as it improves quality of life of the patient and is more effective to control immunodeficiencies, as IG levels are better maintained with weekly infusions. In adult cases however, only two out of four hospitals were using SC administration, and this concerned 14 and 44% of the PID adult cases.

In neurological diseases

In order to know the current use of IG in Belgium for the neurological and neuro-muscular indications consuming large amounts of IG, an expert meeting was organized. The criteria for IG treatment, proportion of cases treated, dosage and frequency of IG treatment were discussed, based on information found in the scientific literature and the Belgian situation. The survey also collected data on 284 IG administrations for neurological cases (Guillain Barré disease, CIDP and MMN).

However, results should be taken with caution as data were only provided by 3 hospitals and were not exhaustive for each hospital (focus on paediatrics). The main findings are summarized below:

- For Guillain Barré syndrome, dosage and frequency described in the literature is also applied in Belgium. In the above mentioned survey, only 34 cases were reported by 3 hospitals, and data on adult cases were only reported by one hospital. IG dosage ranged 1 to 2g/kg in the 3 hospitals.
- For CIDP, the Moniteur Belge / Belgisch Staatblad (MB/BS) stipulates that the first line treatment is steroids, and only patients with contra-indications or treatment failure to steroids should receive IG. Experts estimate that about two-third of CIDP patients receive IG treatment. This proportion also depends on the clinician expertise; unnecessary IG treatment has been observed in patients referred by peripheral centres to the university centres. Dosage also ranges 1 to 2g/kg. The current practice is to rapidly decrease the initial dose according to the clinical response, then to reach a minimal maintenance dose. This dose being patient-dependant, no strict guideline can be established. The upper limit in IG quantities accepted for reimbursement in the MB/BS (9g/kg per semester) is considered by experts as too low to treat some specific cases. Treatment requires good knowledge of the disease and its clinical manifestations.
- For MMN, a higher proportion of cases are treated because mild disease is less frequent and there is no alternative treatment. The dose also needs to be adapted to the clinical response, and the treatment is more difficult to adjust than for CIDP. It may require increasing doses and decreasing treatment intervals, especially in the long term, due to a known decline of treatment effectiveness after prolonged treatment. However a few patients may have sustained remission and even stop treatment. The average dose usually varies from 0.4 to 1g/kg.
- IgM paraprotein demyelinating neuropathies are treated with IG if they fit with the criteria established for CIDP. These cases represent 5-10% of CIDP cases.
- In multiple sclerosis (MS), IG is mainly used in the pre and post-partum period to reduce relapses. IG may also be used in the few MS cases with relapsing-remitting cases that do not respond to steroids; one single treatment is given in case of relapse. Some private insurance companies are covering the costs. This concerns a very small number of cases. All together, the proportion of all MS cases that are treated with IG is estimated to range 0-3%, as observed in other countries.
- In myasthenia gravis (MG), IG is only used in cases that do not respond to other treatments (plasma exchange and immunosuppressive therapy). Though IG has replaced plasma exchange as a first line treatment in many countries, IG is not reimbursed for this disease in Belgium - or only by the solidarity fund when criteria are met. However, due to a lack of expertise in this rare disease, experts fear that IG would be overused if reimbursement for MG would be introduced.
- In dermatomyositis and inclusion body myositis, IG use for this disease is limited and relatively similar to myasthenia gravis.
- Stiff person syndrome is a rare disease, but experts estimated that there may be around 20 patients in Belgium. Plasma exchange is the first treatment option.

3.3.2.6 Limitations

A major limitation of this analysis of IG prescription is that we have no data in 2004-2006 on non reimbursed IG. Likewise, it is unclear whether the IG quantities reported by hospitals include IG prescribed for compassionate use. According to some experts, compassionate use may represent a significant proportion of IG consumption. This is likely resulting in an underestimation of overall IG consumption.

Another limitation of this survey and expert meeting is the lack of representativeness of the Belgium situation: it only involved clinicians working in large university centres and a small numbers of experts (only paediatricians for the immuno-haematological indications) could attend. Problems of higher dose, higher frequency and non-indicated IG therapy have been reported in peripheral hospitals or practices, but available data did not allow investigating this hypothesis.

However, prescription patterns per specialty tend to confirm this hypothesis. Experts reported that this may be due to the lack of experience among peripheral clinicians, as the low frequency of these diseases result that non-specialized clinicians rarely encounter these diseases, added to the fact that strict diagnosis criteria are mostly not required for the reimbursement of IG. Experts also reported a strong lobby from the plasma industry to use IG for most hypogammaglobulinemia. This implies that the estimation of IG quantities based on this survey is likely to underestimate the real IG use.

Key points

- **IG consumption is increasing over time in Belgium as in other countries. However, individual hospitals show diverging trends: a few hospitals have decrease their IG consumption while other have doubled it over a 5 year period.**
- **Four main specialties prescribe 92% of the total IG amount prescribed in Belgium: internal medicine (46%), neurology and related diseases (23%), lung disease (16%) and paediatrics (6%). The high prescription of IG by lung specialists was neither expected nor reported by studies in other countries; this was only found in non-academic hospitals but accounted for a significant amount of IG use.**
- **We observed huge variations in IG prescriptions across Belgian hospitals, as also reported in other countries. Some non-academic hospitals consume a high IG amount in specialties that are not related to the indications reimbursed. Experts also reported an over-use of IG for specific immune deficiencies and peripheral neuropathies in peripheral hospitals, where clinicians may be less familiar to these diseases due to their low prevalence.**
- **For most immune deficiencies and neurological disorders, academic centres reported similar practices regarding who should be treated and the dosage. For two indications, stem cell transplants and idiopathic thrombocytopenic purpura, practices differed regarding which patients are treated, length of treatment and dosage.**
- **The long term treatment of these rare immune deficiencies and peripheral neuropathies requires a good knowledge of the disease to adapt IG dosage and frequency of treatment to the clinical response.**
- **The use of sub-cutaneous IG is emerging for PID cases and was used for 44% of PID patients in academic centres in 2008, mainly for paediatric cases.**

3.3.3 Estimation of IG quantities to treat the main indications

The objective of this exercise was to estimate the needs in plasma derivatives that would be required in Belgium to treat the main indications.

3.3.3.1 Methodology

This estimation represents the theoretical quantities that are required yearly, based on two assumptions: indications are clearly defined, all cases are correctly diagnosed, and patients under long term IG treatment are receiving IG all year long, without interruption.

Selection of diseases

Based on the literature review and the recommendations for IG use in Belgium and other countries, we have selected a first list of 22 diseases in which evidence shows a benefit of IG, or in which sufficient evidence on IG benefit is not available but for which IG therapy is recommended in most industrialized countries (Table 37).

Table 39: Diseases for which IG treatment has a proven benefit and/or is recommended in EU countries: selection for the estimation of IG quantities

Indications	Selected for IG estimation
Idiopathic thrombocytopenic purpura	Yes
Primary immune deficiency conditions	Yes
Multiple myeloma	Yes
Chronic lymphocytic leukaemia	Yes
Allogenic stem cell transplant	Yes
Paediatric HIV/AIDS	No (few cases)
Prophylaxis in solid organ transplant	No
Prevention of treatment of infections in neonates	No (small amounts - low weight)
In preterm and/or low birth weight	No (small amounts - low weight)
Isoimmune haemolytic jaundice in neonates	No (small amounts - low weight)
Guillain-Barré syndrome (and variants)	Yes
CIDP	Yes
Multifocal motor neuropathy	Yes
Multiple sclerosis (relapsing remitting)	Yes
Paraprotein-associated peripheral neuropathies	No (infrequent disease)
Lambert-Eaton myasthenic syndrome	No (infrequent disease)
Myasthenia gravis	Yes
Dermatomyositis and polymyositis	Yes
Inclusion body myositis	No (no available data and low use)
Stiff person syndrome	No (infrequent disease)
Kawasaki disease	Yes
Treating sepsis and septic shock	No (few cases treated in Belgium)

Based on the analysis of the IG amounts used to treat these diseases in other countries (see above), we have selected the 12 diseases that are consuming the highest amount of IG and accounted for respectively 88%, 80% and 68% of total IG use in the US (Massachusset), New Zealand and Canada (Toronto). Further estimations of IG quantities have been limited to these 12 diseases.

Data on disease frequency and IG use per disease

As data on the number of cases treated for each of these diseases were mostly not available in Belgian databases, we have extracted the following indicators from studies conducted in other countries:

- The yearly incidence and/or prevalence rate, depending whether the treatment is applied once or as long term maintenance therapy: incidence rate was searched when treatment is administered once or twice per patient; prevalence rate was used for maintenance treatment. For disease presenting an acute and a chronic form, both incidence and prevalence were used.

- The proportion of patients treated with IG, per disease.
- The dosage used per treatment (g/kg) and the frequency of treatment (per patient or per year for maintenance treatment).

The source studies were selected according to the following criteria: studies including data from 1995 onwards, having a large study population size (>1 million inhabitants mostly), and carried out in Western EU countries - or in other industrialized countries when other EU studies were not available. When disease rates vary significantly per geographical area (e.g. prevalence of multiple sclerosis varying with latitude), we have only consider studies conducted in similar geographical areas.

The values found for the proportion of patient treated with IG, the dosage used per treatment and the frequency of treatment were discussed and validated in two expert meetings. For a few indications, the annual numbers of cases were found in Belgian databases (e.g. transplants). Similarly, the dosage and frequency of administration obtained through the survey in Belgian hospitals were used when considered as methodologically reliable and representative, based on expert opinion and information on current practice.

Estimation of the annual IG amounts per disease

The annual IG quantities estimated to treat these 12 diseases in Belgium were calculated based on the following:

- Data from other countries were aggregated to produce averages for incidence or prevalence rate, proportion of patients treated and frequency of treatment, after being weighted by survey size ("weighted average").
- The expected annual number of cases under treatment in Belgium was calculated by multiplying the weighted average of the incidence or prevalence rate by the Belgian population size (per age group when relevant) and by the proportion of patients treated with IG.
- The IG amount used per patient and per year was obtained by multiplying the average dosage per treatment (in g/kg) by the average body weight (per age group when relevant) and the frequency of treatment (when multiple doses are given), named as "method A". An alternative estimation (method B) was based on the average IG amounts per case and per year found in studies from other countries (weighted average), see Table 24.
- The annual quantities needed to treat each disease were obtained by multiplying the annual number of patients under treatment by the IG amount used per patient (by method A and B).

Estimates found for the above indicators are described below. The annual IG quantities estimated to treat these 12 diseases in Belgium are described in Table 40 and below.

3.3.3.2 Estimates per disease

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) can present as acute or chronic disease; chronic disease is defined by a duration of ITP for more than 6 months. Studies on the incidence of acute and chronic ITP show variations in case definition (especially in terms of threshold for platelet count) and age studied. These directly influences incidence estimates as a very sensitive threshold for platelet counts overestimates the frequency of clinical ITP, and the frequency of chronic ITP increases with age.

IN CHILDREN

Three studies in Norway, Germany and Nordic countries, estimated the incidence rate of acute ITP in children using similar criteria (bleeding +/- platelet count <30 x 10(9)/L). Incidence rate ranged 2.5-5.3 per 100,000 in 1996-1999 in children aged <15-17 years, and the average incidence was computed at 3.3 per 100,000.[154-156]

The proportion of acute ITP that had evolved into chronic ITP was estimated in four studies in Norway, France, Denmark and Nordic countries in 1996-99 and ranged 18-33% (average 26%).[155, 156,157,158] We then extrapolated the incidence rate of chronic ITP at 0.8 per 100,000 in children <15 years.

The proportion of acute paediatric ITP treated with IG widely depends on national and local guidelines, and particularly on the criteria for treatment: in France, IG is the first therapeutic option and is administered to children with low platelet count, regardless of symptoms; in Italy and Canada, IG is one of the treatment options for acute ITP with very low platelet count (<20x10(9)/L). In Belgium, criteria for ITP cases that warrant reimbursement of IG are not defined and vary by hospital.

Three studies in France, Germany and Norway estimated the proportion of all acute paediatric ITP that are treated with IG at 62-88%, with a weighted average at 74%.[158,154, 156] The proportion of chronic ITP cases treated a second time in France and Sweden was 46% in average.[158,159]

However, the estimated number of cases treated with IG in Belgium based on these parameters is not in line with the results of the Belgian survey: using the above parameters, we can calculate that 44 acute ITP paediatric cases would need IG in Belgium. But the 6 Belgian hospitals already reported a total of 52 cases under IG treatment, though these hospitals only represent 14% of all paediatric beds in 2006.

This discrepancy may be due to the diversity in methodology and prevalence values from published studies, and the fact that studies date from more than 10 years (1996-1999).

Dosage ranged 0.8-2g/kg for children (average 1.4g/kg) in the Belgian survey. A second dose is usually administered if there is no clinical answer after 48 h or for chronic cases. The Belgian survey reported an average of 1.4 treatments per ITP case, which is consistent with data from the above mentioned studies.

IN ADULTS

Epidemiological data on ITP in adults are scarce, studies are old and different case definitions are used. But a recent comprehensive study conducted in the UK using data from general practice database estimated the ITP incidence among adults at 3.9 per 100,000 from 1992 to 2005.[160]

In Belgium, IG is reserved for adults with high risk of bleeding or before surgery, in line with other national and international guidelines. Based on the use of a score for bleeding high risk, a French study showed that IG was required in 50% of the patients, alone or in combination with steroids.[161]

Dosage for adult ITP was 2g/kg in the Belgian survey (2 hospitals) and is the standard dose in many countries, though a study suggested it could be reduced to 1g/kg.[162]

In chronic ITP cases, the use of IG is poorly described and many other therapies are discussed; the proportion of cases that would receive maintenance therapy has not been documented but is assumed to be very low. Our estimation is therefore excluding the long term treatment of chronic ITP adult cases. In addition, the introduction of new drugs such as romiplostine is likely to decrease the need in IG in adult ITP.

Primary immune deficiencies

The prevalence of primary immune deficiency (PID) in Belgium or European countries is largely undocumented and European data are scarce. Data from the Belgian PID registry suggested a prevalence of 2.4 per 100 000 inhabitants in 2004 but the registry is not complete and up to date; an Irish study found a prevalence of 2.9 in the period 1996-2003 which is reportedly under-estimated. Two European studies showed that in average 47% of PID patients receive IG supplementation.[24,163]

In Belgium, a survey covering 6 centres for paediatric PID and 3 centres for adult PID reported a total of 437 PID cases under follow up, but this figure is also incomplete. Among these, 263 have received IG treatment in 2008. In order to estimate the total number of PID cases treated in Belgium, we have used as proxy the proportion of all Belgian bone marrow transplants that were conducted in these centres, as reported to the INAMI/RIZIV. Though the proportion of transplants is not directly linked to the proportion of PID treated, this was considered as a proxy of specialized immunological activity of these centres. The 6 centres providing data on paediatric cases and the 3 centres providing data on adult cases represent respectively 34% and 29% of all marrow transplants in 2007. The number of PID cases under treatment is thus estimated at 806 cases. In Belgian centres surveyed, the dosage ranged 0.3-0.5g/kg and most centres used 0.4g/kg. The annual number of IVIG treatment per year ranged 6.4-14.4 per year for children (average 11.3) and 12.0-13.3 per year for adults (average 11.8). The amount of IG required for SC administration has been estimated as equivalent to those required for IV administration.

Multiple myeloma (MM)

In Belgium, a range of 617-690 new cases of MM were reported per year to the cancer registry in 2004-2008 and the incidence is increasing with age. Prevalence data are not available from Belgium or other EU countries. We used the 2006 age-specific prevalence rates reported among the white population in the US and extrapolated to the Belgian population by age-group.[8] A number of 2390 prevalent cases of MM are estimated. This figure may be an underestimation of the Belgian situation because the MM incidence rates in the US are slightly lower than the Belgian incidence rates.

The proportion of MM patients treated was not documented in the literature, but expert advice provided a range of 10-15%, based on experience.

The survey among immuno-haematologists collected data on MM from one Belgian university hospital only. The dosage of 0.4g/kg was similar to the recommendations of other countries and in average 10 treatments were provided per case and year.

Chronic lymphocytic leukaemia (CLL)

National data are not available on the incidence or prevalence of CLL but 636 new cases of lymphoid leukaemia (acute and chronic) were reported in 2008. No prevalence data were found from other countries. The proportion of patients treated was also not available.

As for MM, the survey among immuno-haematologists collected data on MM from one Belgian university hospital only. The dosage was 0.4g/kg and an average of 10 treatments was provided per case and year.

Due to the lack of data, IG amounts required to treat CLL cases could not be calculated.

Allogenous bone marrow or stem cell transplant (SCT)

The number of bone marrow transplants is collected by the INAMI/RIZIV in the framework of the convention with transplant centres. In 2007, 284 allogenous transplants were recorded, and the 2005-07 data show a gradual increase in the number of allogenous SCT (+31% in 2 years). The number of transplant was then estimated at 320 for 2008, assuming a linear trend from 2005 to 2007. However, this number may be underestimated as hospitals that are not included in the Convention may also perform allogenous SCT (INAMI, personal communication).

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8 Estimated US cancer prevalence counts at on Jan 1, 2006 by Race/Ethnicity, Sex and Years Since Diagnosis. National Cancer Institute: Surveillance Epidemiology and End Results Cancer Statistics Review 1975 – 2006. http://seer.cancer.gov/csr/1975_2006/browse_csr.php?section=18&page=sect_18_table.18.html

The proportion of SCT cases receiving IG supplementation has not been found in the scientific publications. In Belgium, it varies across centres, type of transplant and age group. The increase in non-myeloablative SCT, mainly in adults, has likely decrease the IG needs in this group. The principle is that IG treatment should be administered in cases of severe antibody deficiency and thus tailored to the patient. Among children, the consensus among paediatricians during the expert consultation was that most paediatric cases require IG supplementation, as post-SCT humoral immunodeficiency is common. Among adults, experts consider that the prophylactic and pre-emptive use of antibiotics, antifungal and antiviral drugs has replaced the routine use of IVIG, and that only patients having a (transient) symptomatic secondary immunodeficiency should receive IVIG, on an individual basis.

Based on comparison between survey results and INAMI data sources on allogenous BMT, we estimated that 33% of all allogenous SCT (children and adult confounded) receive IG supplementation.

The dosage used in Belgium ranges 0.2-0.5g/kg, with the majority of centres using 0.4g/kg. In the Netherlands, treatment scheme was 0.5g/kg per week (before transplant) then followed by 0.5g/kg per month as maintenance dose; in France, 0.4-0.6g/kg as loading dose followed by 0.3g/kg. In most studies, IG prophylaxis was given for 3 months and the maximum period of administration was 1 year. Most guidelines recommend continuing IG after transplant until reconstitution of B cell and antibody production has been achieved. We estimated that IG treatments were administered in average 12 times per year, based on the survey results (10.8 in children and 12 in adults).

Guillain-Barré Syndrome (GBS)

Five epidemiological studies, conducted in the period 1992-2000 in the UK, Italy (2 studies), Spain and Sweden were selected for the estimation of incidence rate.[164,165,166,167,168] A German study based on hospital records has been excluded as the methods did not include validation of diagnosis;[169] indeed, such studies were shown to over-estimate disease incidence.[167] Most studies reported similar values, suggesting that GBS occur evenly, at least throughout the Western hemisphere: the incidence rate ranged 1.26-1.63 per 100,000 in the five studies, and the weighted average is 1.42 per 100,000.

In four studies conducted in Italy, Spain and Sweden (two studies) in the period 1996-1999 and involving a total of 343 cases, the proportion of GBS cases treated with IG ranged 65-82% with a weighted average at 75%.[165, 166, 170, 171]

The dosage was 2 g/kg per treatment in all studies and reviews. Only one Dutch publication described the proportion of cases requiring a second treatment from two studies, which amounted at 7% of the GBS cases initially treated.[172]

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Two EU studies (Italy and England) and an Australian study calculated the CIDP prevalence, which ranged 1.9-3.6.[173,174,175] These differences are explained by a lack of diagnostic gold standard or clear diagnostic criteria. The weighted averaged incidence rate was calculated at 2.7 per 100,000.

The proportion of all CIDP cases that were treated with long term IG were estimated in 3 studies from France (2 studies) and the UK, published in 2007-2008, and ranged 51-63%.[175],[176],[177] The weighted average was 56%.

The dosage ranged 0.4-2g/kg in studies and national recommendations. In Belgium, the maximum reimbursed dose ranges 0.25-2g/kg with a maximum of 9g/kg/6 months. The practice for CIDP (and MMN) is to start at 2g/kg dose and rapidly decrease the dose according to the clinical response, to reach a minimal maintenance dose; it has been estimated at 1.5g/kg in average. The median interval for IVIG administration in studies was 3 weeks (frequency of 17.3 per year).

Multifocal motor neuropathy (MMN)

Epidemiological data on MMN prevalence are scarce: only two EU prevalence studies from England and the Netherlands were found in conference abstracts, with very similar values.[178] The average could not be weighted for study size as the number of cases was missing in the English study. The 2008 prevalence was respectively 0.53 and 0.58 per 100,000 in England and the Netherlands, and the average incidence rate calculated at 0.56 per 100,000.

Data on the proportion of all MMN cases that were treated with IG were found in 3 recent EU studies, conducted in the UK, the Netherlands and France and published in 2007-2008.[179,178,180] This proportion ranged 51-76% and the weighted average was 66%.

The dosage was 2 g/kg per treatment in all studies, though the maximum reimbursed in Belgium ranges 0.25-2g/kg with a maximum of 9g/kg/6 months. The median interval for IVIG administration in studies was 3 weeks (frequency of 17.3 per year). However, the annual IG amount used to treat one case widely varied across studies, ranging 248g in New Zealand to 1728g in the UK.[149,179]

Multiple sclerosis (MS)

Several epidemiological studies on MS prevalence in Europe were found but showed very diverging values. Due to an observed North-South gradient in prevalence, our analysis was limited to countries or regions having a latitude similar to Belgium and a population of >2 millions inhabitants to decrease the inaccuracies due to small numbers of cases. Only studies using the Poser criteria for MS diagnosis and validation of diagnosis were selected. Studies based on community surveys and self reported cases were excluded.

A survey was conducted in Flanders in 1991 but was excluded as it did not fit in inclusion period.[181] Indeed prevalence is increasing over time, likely due to improved diagnosis and unknown factors. The two selected studies were conducted in France and Austria and the prevalence for definite and probable cases was 120 and 99 per 100,000 respectively, with a weighted average at 103 per 100,000.[182,183]

Immunoglobulins may be used for very specific MS cases, i.e. in cases of relapses that are resistant to other treatment, when other therapies are not tolerated, as well as in the post-partum for the prevention of relapses. No studies were found on the proportion of MS patients that are treated with IG. Experts estimate that 0-3% of MS patients are treated with IG for treatment (or prevention) of relapses. Considering that IG are mostly used for the prevention of post-partum relapses, that women in post-partum represent 1.1% of the Belgian population and that a large European prospective study estimated that 28% of pregnant women experience a relapse in the 3 months post-partum, we can assume that a maximum 0.31% of MS cases could benefit from IG.[184] IG is not reimbursed in Belgium for this disease but some private insurance might reimburse it.

The doses used ranged 0.15-2g/kg/month, with no superiority of a given dose shown. An observational Austrian study among pregnant women calculated that an average dose of 0.24 g/kg/month was given.[85] The mean treatment duration was 3.4 +/- 1.8 years and the mean time to first relapse with IG therapy was 247 days (median 199 days) in the first 2 years.

Myasthenia gravis

Studies on myasthenia gravis (MG) prevalence showed very different values, depending on the diagnostic criteria. Three studies conducted in Sweden, the Netherlands and England in 1997-1999 estimated a prevalence ranging 11.9-14.1 per 100,000.[105],[185],[186] A study in Greece was excluded because MG cases were limited to those having antibodies against the acetylcholine receptor, which represented only 79% of total cases in both the Dutch and the English studies. The weighted average of the three selected studies was 12.7 per 100,000. However, this estimate probably underestimates the current figure as prevalence increases over the years, due to the ageing of population combined to a higher prevalence found among the elderly.

The proportion of MG cases treated with long term IG was not found. The 1997 English study described 3% patients being under plasma exchange therapy (the golden standard for myasthenic crisis at that time).[185] Since this therapy has often been replaced by IG in recent years, we estimated that 3% MG patient would be treated with IG, and experts considered this estimate to be valid for the Belgian situation.

The dosage was 2g/kg in most studies and national recommendations, but a study comparing a dose of 1g vs. 2g/kg body weight suggested that 1g/kg may be sufficient. There is no evidence to support IG use as a long-term treatment, thus a single treatment in case of crisis or exacerbations was assumed.

Dermatomyositis and polymyositis

Dermatomyositis and polymyositis cases were not distinguished as both diseases are idiopathic inflammatory myopathies, usually studied together. Only one recent study estimating the prevalence of dermatomyositis and polymyositis was identified, conducted in Canada in a population of 7.5 million inhabitants, and found a 2003 prevalence at 21.5/100,000.[187] Older estimates from the USA and Japan ranged 5.0-6.3 per 100,000 in 1960-1987 but are considered to underestimate the true disease prevalence.[188]

Data on the proportion of dermatomyositis patients treated was only found in an older cohort study on juvenile dermatomyositis in Canada, representing 9% of cases, and cannot be used to extrapolate to other age groups.[189]) It is only known that IG is only needed in special cases and seems the treatment of choice in severe myositis with dysphagia.[190]

The dosage was 2g/kg every 3-6 weeks in most studies. Data on practice in Belgium have not been found. In the 15 patients included in the only RCT conducted so far, the frequency of treatment varied from every 3 to 6 weeks (average 4 weeks) and two patients could stop IG treatment.[110]

As no data are available on the proportion of cases treated, this disease has not been included in the calculation. However, as we know that the treatment of dermatomyositis cases represented 2% of total amount of IG used in the three studies in other countries (Table 22), the same proportion of the total IG amount has been assumed in Belgium.

Kawasaki disease

The incidence of Kawasaki disease (KD) was estimated in Denmark, Sweden and New Zealand, while other recent studies were based on rates of hospitalization for KD.[191,192,193] Incidence among children <5 years ranged 4.6 in New Zealand to 6.2 in Sweden per 100,000 in children under 5 years in 1999-2004, with an average at 5.2 per 100,000. In Denmark, it showed a gradual increase from 1981 to 1990.[191]

Most KD cases are usually treated with IG and this proportion was 92% in a New Zealand study.[193] The percentage of cases requiring re-treatment could not be calculated in Belgium but was 16% of initially treated cases in a Danish study[191].

In Belgium, the dosage was 2 g/kg body weight except for one hospital (1g/kg), as it is recommended in France, Netherlands and the UK.

3.3.3.3 Annual IG quantities estimated per indication and discussion

Results are presented in Table 40 for 11 diseases or medical conditions, with the exclusion of CLL due to the lack of data found in the literature search. The "Method A" calculated amounts per patient and per year based on an average dose in g/kg multiplied by an average body weight and by an average frequency of treatment; this correspond a theoretical IG amount and tends to represents an over-estimation of IG amounts used. The "method B" is based on IG amounts calculated in real life settings in other countries (Canada, New Zealand and the US), representing the average amount of IG used per patient with this disease and per year, see Table 24. It is likely that the method B reaches a better approximation of the real life data, but the estimates are based on different settings (non-EU countries).

Based on these methods and the assumptions described under table 40, we have estimated that 576 kg (method A) and 483 kg (method B) of IG would be annually needed to treat these 11 diseases, thus not including CLL. This would represent respectively 70% (A) and 59% (B) of the IG amount reimbursed in 2006 based on INAMI/RIZIV data (Table 41).

Though we have not used statistical tests given the high intrinsic uncertainty around some estimates and assumptions, the proportion of total IG use that would be required to treat these 11 diseases is lower than calculated in the 4 studies, for both methods A and B: these 11 diseases consumed 75%, 68%, 88% and 72% of the total IG amount in New Zealand, Toronto (Canada), Massachusset (US) and the Canadian Atlantic provinces, with a weighted average of 74%. If we compare our estimates to the annual IG amount reported by Belgian hospitals in 2008 (919.6 kg, KCE survey), this proportion would be even lower, representing 63% (A) and 53% (B) of total amount.

Our estimation suggests that a higher proportion of IG is used for other indications than those included here, compared to other countries. In other studies, 12% to 32% of total IG amounts was consumed by the remaining indications, while this would represent as much as 37% (A) and 41% (B) in Belgium. This is not surprising when we observed that, in Belgium, already 16% of IG has been prescribed by lung specialists in 2008.

However conclusions on the yearly amount of IG required in Belgium cannot be based on this exercise, as this estimation has many methodological limitations.

3.3.3.4 Limitations

The main limitations to this estimation that we have identified are:

- This method has probably underestimated the number of cases under IG treatment for several diseases: First, our calculations were based on data from scientific studies, where all cases were verified for adherence with defined case definition and criteria; in a real life setting, many more cases are likely to be treated. For instance, we estimated that 150 cases of Guilllain Barré occur every year in Belgium, based on incidence from neighbouring countries, while RCM/MKG data for code ICD9CM 357-0 in 2000-2007 show annual numbers ranging 609-717 cases. Second, many studies were based on old data from the nineties and probably underestimated disease rate as the prevalence of several diseases is known to increase with time, due to population ageing and improved diagnostic.
- This estimation could not include cases of CLL.
- We have found several other inconsistencies when comparing our estimates to other Belgian data, which may be due to the assumptions used or the lack of representativeness of practices in the centres surveyed. This was mainly observed for bone marrow transplant (BMT) where we likely underestimated the number of cases under treatment: the proportion of transplant cases treated with IG is based on data from two university hospitals and may be higher in other hospitals. Indeed, 56 transplant cases under treatment were reported in the survey from 4 paediatric wards and an adult ward, while our overall estimate of BMT treated with IG in the whole Belgium is 105. This was also suggested by the lower proportion of total IG amount used in BMT in Belgium compared to other studies (3-4% vs. 11%). The number of ITP cases under IG treatment extrapolated from incidence rates from other studies did not correspond to the number reported by Belgian centres (52 cases under treatment are reported from 5 university hospitals vs. 49 for all Belgium based on other studies).
- Data on IG use are compared to four studies from three non-European countries (US, Canada, New Zealand), where IG use was reported to be high.

- Many estimates were based on the Belgian survey and expert meetings, which may not be representative of the overall Belgian situation.

In spite of the limitations due to this method, we reach the same overall conclusions than the studies based on real IG consumption: the highest IG use is observed for immuno-haematological disorders (41-43% of IG amount) but covers as much as 1545 cases, compared to neuro-muscular diseases which may consume 25-28% of total IG amount but only covers 367 cases. The diseases likely to consume the highest amount of IG are: primary immune deficiencies, CIDP, MM, ITP and MMN.

Key points

- **Based on theoretical needs and assumptions, we estimated that from 483 to 576 kg of IG would be annually needed to treat the 11 indications consuming the highest amount of IG in Belgium, excluding CLL. This would represent 53-63% of the total IG amount prescribed in Belgium in 2008. Compared to studies from other countries (Canada, New Zealand and the US), this represents a lower proportion of the total IG amount to treat these diseases.**
- **This comparison suggests that in Belgium, a higher proportion of IG is used to treat the remaining indications (37-41% in Belgium vs. 12-32% in the other countries). Part of this difference may be explained by the 16% of total IG that has been prescribed by lung specialists in 2008.**
- **However conclusions on the yearly amount of IG required in Belgium cannot be based on this exercise, as this estimation has many methodological limitations and probably underestimates the amount that would be required in a "real life" setting.**

Table 40: Theoretical estimation of annual amounts of immunoglobulins needed to cover the treatment of 11 diseases in Belgium

			A	B	C	D	E	F	G	H		
Disease / medical condition	**Incidence rate (per 100,000/year)**	**Prevalence rate (case per 100,000)**	**N patients considered**	**% patients treated w/ IVIG/SCIG**	**N patients treated per year**	**N treatments per patient year***	**Dose per treatment (g/kg)**	**Amount per patient per treatment (g)**	**Amount per patient per year (g) A**	**Amount per patient per year (g) B**	**IG amount in g per year (A)**	**IG amount in g per year (B)**
Idiopathic thrombocytopenic purpura (all)	see detail			see detail	323		see detail	see detail	see detail	210	**32.850**	**67.769**
- ITP in children (<15 years)	NA (outdated)		NA	74,0%	152	1,40	1,4	34	47,6		7.253	
- ITP in adults	3,90		341	50,0%	171	1,00	2,0	150	150,0		25.597	
Primary immune deficiency total		survey	survey	47,0%	806					229	**188.502**	**184.362**
- Primary immune deficiency in children		survey	survey	survey	402	11,32	0,4	10	113,2		45.538	
- Primary immune deficiency in adults		survey	survey	survey	404	11,79	0,4	30	353,6		142.964	
Multiple myeloma		NA	2390	13,0%	311	10,00	0,4	30,0	300,0	219	**93.210**	**68.121**
Chronic lymphocytic lymphoma (CLL)		NA	NA	NA (rare)	NA	10,00	0,4	30,0	300,0	219	NA	NA
Bone marrow / stem cell transplant		NA	320	32,7%	105	12,00	0,4	4,8	240,0	302	**25.121**	**31.593**
Total immuno-hemato											**339.683**	**351.845**
Guillain-Barré syndrome	1,42		150	74,6%	112	1,07	2,0	150	160,5	173	**16.768**	**19.383**
Chronic inflammatory demyelinating polyneuropathy		2,7	282	55,6%	156	13,00	0,8	60	780,0	348	**122.033**	**54.374**
Multifocal motor neuropathy		0,6	59	66,3%	39	14,86	1,5	113	1671,4	486	**64.942**	**18.896**
Relapsing-remitting multiple sclerosis		59,9	6313	0,3%	*19*	12,00	0,2	18	216,0	354	**4.200**	**6.883**
Myasthenia gravis		12,7	1343	3,0%	40	1,00	2,0	150	190,0	198	**7.657**	**7.966**
Dermatomyositis and polymyositis		21,5	2268	NA (rare)	NA	13,00	2,0	100	1300,0	453	**16.400**	**16.400**
Total neurology - muscular											**232.001**	**123.902**
Kawasaki disease in children	5,2		94	92,0%	87	1,16	2,0	50	58,0	87	**4.326**	**7.527**
Total estimated											**576.009**	**483.274**
*: taking into account the proportion of second treatment per case	*from literature*	*from literature*	*from I and P*	*from lit. / survey*	*=A*B*	*from lit. / survey*	*from lit. / survey*	*= C * avg weight*	*= D*F*	*from literature*	*= C*G*	*=C*H*

Based on the following assumptions:

Population figures:

Population Belgium (2007):	10.547.958
Population children < 15 years (2007):	1.796.916
Population adults (> 15 years) 2007:	8.751.042

Average body weight:

Adults:	75,0 kg
Children:	25,0 kg
Whole population:	50,0 kg

Table 41: Estimation of the proportion of immunoglobulins needed (or used) to treat 11 diseases in Belgium and in 4 studies

Disease / medical condition	IG amount in g per year (A)	IG amount in g per year (B)	% total (A) in 2006	% total (B) in 2006	% total in four studies (avg)
Idiopathic thrombocytopenic purpura (all)	**32.850**	**67.769**	4,0%	8,3%	13%
- ITP in children (<15 years)	7.253				
- ITP in adults	25.597				
Primary immune deficiency total	**188.502**	**184.362**	23,0%	22,5%	19%
- Primary immune deficiency in children	45.538		5,6%	0,0	
- Primary immune deficiency in adults	142.964		17,4%	0,0	
Multiple myeloma	**93.210**	**68.121**	11,4%	8,3%	1%
Chronic lymphocytic lymphoma (CLL)	NA	NA	NA	NA	4%
Bone marrow / stem cell transplant	**25.121**	**31.593**	3,1%	3,9%	11%
Total immuno-hemato	**339.683**	**351.845**	**41,4%**	**42,9%**	**48,0%**
Guillain-Barré syndrome	**16.768**	**19.383**	2,0%	2,4%	5%
Chronic inflammatory demyelinating polyneuropathy	**122.033**	**54.374**	14,9%	6,6%	19%
Multifocal motor neuropathy	**64.942**	**18.896**	7,9%	2,3%	4%
Relapsing-remitting multiple sclerosis	**4.200**	**6.883**	0,5%	0,8%	3%
Myasthenia gravis	**7.657**	**7.966**	0,9%	1,0%	3%
Dermatomyositis and polymyositis	**16.400**	**16.400**	2,0%	2,0%	2%
Total neurology - muscular	**232.001**	**123.902**	**28,3%**	**15,1%**	**32,0%**
Kawasaki disease in children	**4.326**	**7.527**	0,5%	0,9%	0,2%
Total estimated	**576.009**	**483.274**	70,2%	58,9%	100%

3.3.4 Expected trends in consumption

We have identified a few trends and scientific progresses that may influence future trends in IG use and consumption, to help predict future trends.

1. The number of allogenic bone marrow transplants performed in Belgium is increasing from year to year, from 216 in 2005 to 284 in 2007 (+31% in 2 years). In Europe, a study estimated a more conservative 13% rise in bone marrow transplants to be expected from 2005 to 2010.[194] This would imply an increased IG use over time. However, the increase in non-myeloablative transplants in adults, with a consequent lower level and shorter duration of hypogammaglobulinemia, would tend to decrease IG needs.
2. The prognosis of patients with MM has improved significantly during the last three decades, resulting in increased survival.[195] This will likely increase the disease prevalence and related needs in IG. But alternative therapies for MM and CLL are also increasingly used and this may result in decreased needs in IG supplementation.
3. The prevalence of multiple sclerosis and myasthenia gravis is increasing with time, due to ageing of the population and better diagnostic tools, and could result in increasing IG needs.
4. Alternative treatments for ITP and for the prevention of infections in transplant are under development. Some therapies are arriving on the market (e.g. Rituximab and Romiplostine) could potentially decrease IG use for these indications.
5. Many studies are conducted to test alternative treatment that would allow decreasing or even stopping IG maintenance treatment in CIDP cases. If successful and available, these therapies would decrease IG use for this disease.
6. Alzheimer disease, any auto-immune disease, asthma and some other frequent diseases related to immunity and for which no alternative treatment has shown efficacy, may be considered by some physicians as new indications for IG. This may represent a problem before any RCT could demonstrate the efficacy - or lack of efficacy - of IG for these diseases.

4 SELF SUFFICIENCY OF BELGIUM

4.1 WHAT ARE THE RISKS AT WORLDWIDE LEVEL ?

4.1.1 Plasma collection: Key role of the North American Region

Over the last years, total volume of plasma available worldwide for fractionation has slightly increased (22.3 million litres in 2000, 21.4 million litres in 2005) and reached 26.5 million litres in 2007, broken down as below:

- 17.9 million of apherese plasma (9.2 million in 2000 ; 13.7 in 2005)
- 8.6 million of recovered plasma (13.2 million in 2000 ; 7.7 in 2005)

Of the 26.5 million of plasma mentioned above:

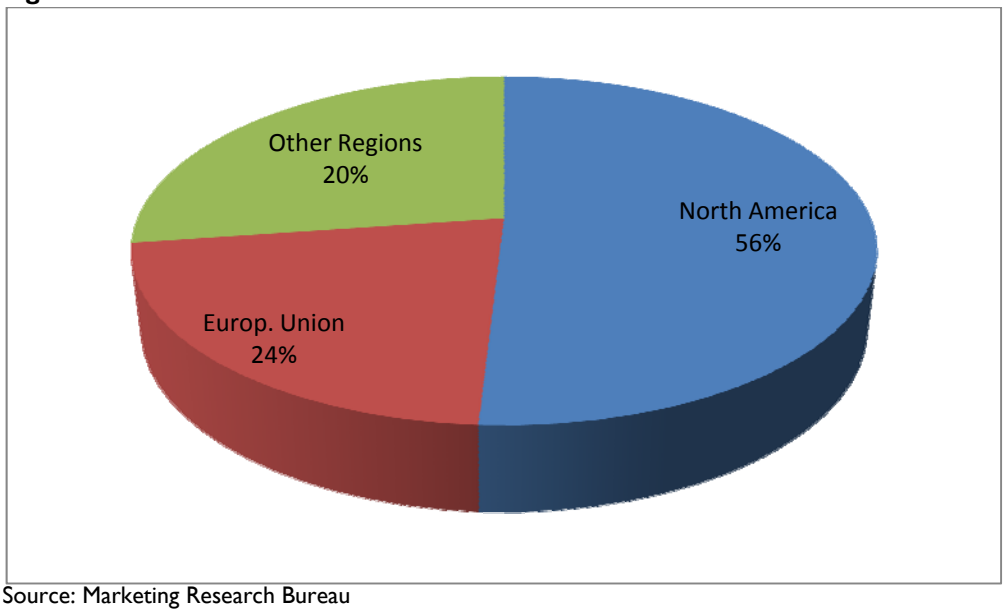
- 15 million are collected in the North American region (56%)
- 6.4 million are collected in the European Region (24%)

These ratios have remained stable since 2000.

Of the 17.9 million litres of apherese plasma mentioned above,

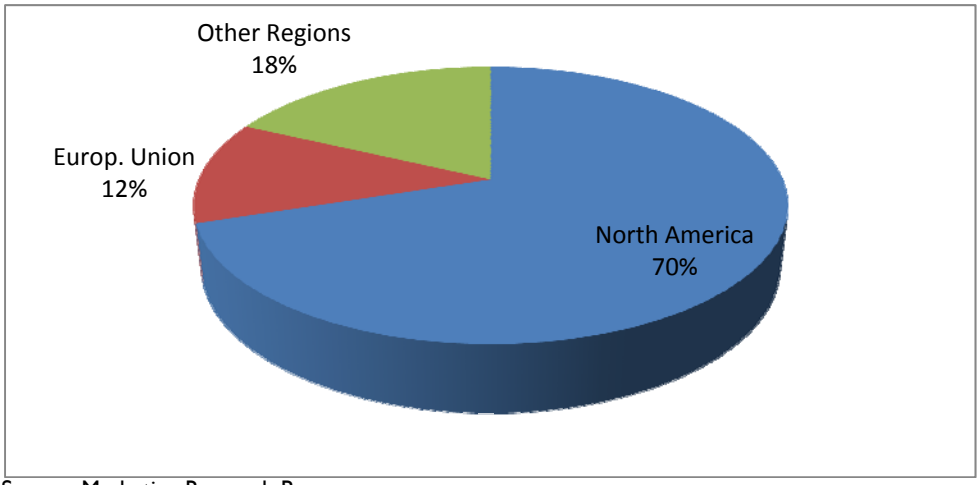
- 12.5 million are collected in the North American region (70%).
- 2.1 million are collected in the European Region (12%)

Figure 11: Shares in Global Collection of Plasma



Source: Marketing Research Bureau

Figure 12: Focus: Shares in Global Collection of Plasmapherese



Source: Marketing Research Bureau

From a geographical point of view, North America clearly remains the key stakeholder in plasma collection. Conversely, one must bear in mind that Europe remains the key stakeholder in the fractionation industry.

As explained above, more than 50% of plasma collected worldwide is collected in North America (mainly in the USA). This ration reaches 70% for apherese plasma.

Plasma donation and collection in the USA (as well as blood donation and collection in general) is based on purely private and commercial principles. Donor selection is organized on a risk-management basis, and blood donation is paid. This ethical and organisational framework is largely different from the European one.

In practice, a large part of the plasma collected in the United States needs to be exported to Europe in order to be processed, and re-imported into the United States for clinical use. Therefore, it is also of paramount importance to underline that Europe-based fractionation facilities are often devoted to the supply of the world market, especially the American one. In other words, European fractionation capacity is largely devoted to the needs of non European (especially US) patients.

In order to fulfil the American patients' needs, it is vital for American stakeholders to secure the supply of plasma products, the latter being largely produced by Europe-based companies. This may lead American stakeholders to implement specific corporate strategies (especially long term supply contracts) or even purchase strategies in Europe. For obvious reasons, these strategies are implemented, with a view to improving the American patients (whatever the needs of the European patients may be).

Should a shortage of plasma products appear (eg sharp and quick raise in global needs due to new indications), potential competition between American patients' needs and European patients' needs could be clearly identified.

Moreover, as mentioned below, any change in the use of plasma products, especially indications in the USA (or even changes in prescription habits) is likely to have an impact on the US demand and then indirectly on the European fractionation industry. Basically, considering today's situation of American and European plasma fractionation industry, the main concern of American stakeholders is to secure the stream of plasma products across the Atlantic. As a practical matter, if US health authorities decided to restrict export of their own raw plasma, European countries would not be in the position to fulfil immediately the needs of European patients.

4.1.2 Worldwide demand for plasma products / Focus on IVIG (2000-2008)

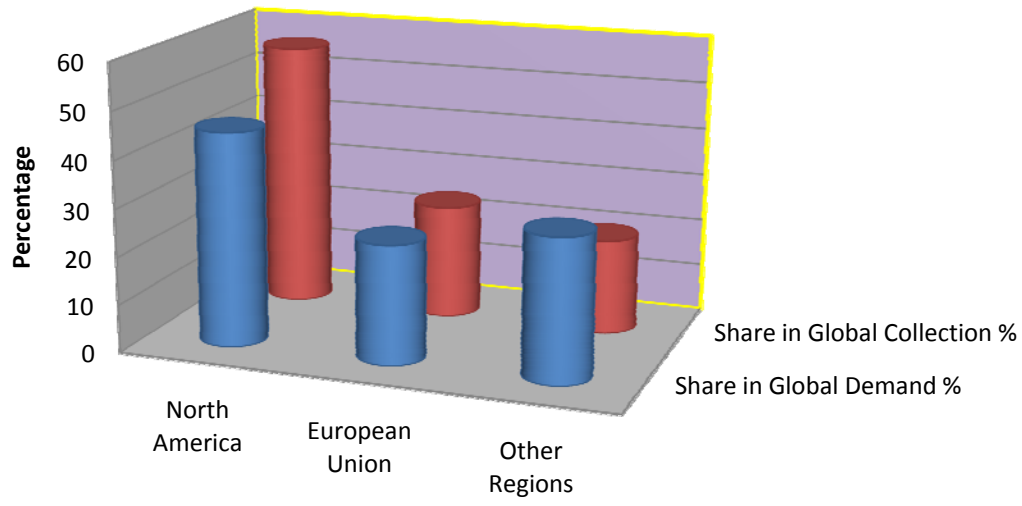
Over the last years, global demand for polyvalent Intravenous immune-globulin has raised firmly and steadily.

Whereas global demand for polyvalent IVIG amounted to ca 47 000 tons in 2000, it reached more than 82 000 tons in 2008.(ie an increase by 75% in an eight-year period of time).

In 2007, the share of the European Region in the global demand amounted to 25%, whereas the one of the North American Region reached 45%.

In financial terms, the demand of the European Region reached 762 million US dollars (20% of the global demand), whereas the one of the North American Region amounted to 2199 million US dollars (57% of the global demand).

Figure 13: Global collection and Demand of IVIG



	North America	European Union	Other Regions
Share in Global Demand %	45	25	30
Share in Global Collection %	56	24	20

Source: Marketing Research Bureau

4.1.3 Potential changes in demand structure

Indications have evolved over the last years. Therefore, it is important to stress that these evolutions have had an impact (or even a major) on the demand of plasma products. It remains difficult to forecast evolution of consumption precisely, as different factors must be taken into account: research progress and new evidence-based indications, but also dissemination of premature and non evidence-based practices or expert opinions.

Further information in Appendix "Emerging Countries" on the Brazilian and the Chinese market

Key points

- **The North American region (especially the United States) remains the "World's plasma collector" whereas Europe remains the "World's plasma fractionator".**
- **The main concern of the American stakeholders is to secure the supply for plasma products, by different means (long term supply contracts, control of fractionation capacities), whereas the fulfilling of European patients simultaneously requires large imports of American plasma.**
- **Should US health authorities decide to restrict export of their own raw plasma, European patients would be put in a predicament. Any change of American practices (new indications or change in prescription habits) must be kept under close scrutiny as it could lead to a similar deadlock. Conversely, American patients need to rely on the EU fractionation industry to fulfil their own needs.**
- **Emerging countries are likely to play an ever greater role on the world market, which means greater competition between purchasers.**

4.2 CONCEPT OF SELF SUFFICIENCY

4.2.1 In Belgium

Belgian regulations do not define the proportion of plasma derivatives that must be produced in Belgium to minimise the risk of shortages of plasma derivatives. A Royal Decree of 18 June 1998 simply states that in order to ensure self-sufficiency and the quality of the supplies of stable blood products of human origin, the price of a litre of plasma, manufactured by plasmapheresis and sold by the Red Cross to the CAF-DCF, will be subsidised and that a firm of auditors will communicate each year to the SPF the number of litres sold in order to calculate correctly the subsidy.

Since the quantity guaranteeing self-sufficiency is not explicitly stated in the decree, it transpires from verbal explanations gathered that the auditor[i] deems that self-sufficiency is achieved if the CAF-DCF provides

- "a level of production covering 60% of the average national consumption of the main plasma-derived products – i.e. Factor VIII, Albumin, and IVIG - in normal sanitary and epidemiological conditions, and considering approved indications"
- "a quarantine stock covering 90 days of average national consumption for the three main products mentioned above". In practice, this stock comprises 8000 bottles of Albumin, 1 million doses of Factor VIII, and 50kg of IVIG.

This quantity is shown on the first line of the table below. PWC then deducts from this quantity the number of litres of non-subsidised plasma (RP) (line 2) and adds to it the number of litres taken from stocks (line 4) to calculate the number of litres to be subsidised (line 5).

[i] This role is assumed by the firm PricewaterhouseCoopers. See 'Plasma from plasmapheresis required for self-sufficiency in Belgium in 2008' PWC

Table 42: Volumes of plasma bought by CAF-DCF and subsidized in Belgium between 2000 and 2008

	Type of plasma	2000	2001	2002	2003	2004	2005	2006	2007	2008
1	Quantities of plasma necessary for self sufficiency	196,479	197,527	210,564	212,827	243,795	202,24	182,149	170,497	157,472
2	**Recovered** plasma bought by CAF – DCF from all collectors	140,451	138,141	136,348	135,141	123,78	115,896	113,731	114,375	106,923
3	**Source** plasma bought by CAF – DCF from all collectors	56,028	59,386	74,216	68,087	96,024	80,25	59,751	50,488	42,592
4	Intake from **stock**							8,667	5,634	7,957
5	**Source** plasma subsidized	56,028	59,386	74,216	77,686	120,015	86,344	68,418	56,122	50,549

Source: PWC

Note that the quantities of source plasma purchased by the CAF-DCF from the SFS and VDB according to PWC are not the same as those received by the Federal Agency for Medicines :

Table 43: Comparison of quantities purchased by the CAF and collected by SFS-VDB

	2000	2001	2002	2003	2004	2005	2006	2007	2008
SP purchased by CAF from SFS + VDB (source: PWC)	n.a.	n.a.	n.a.	68.087	96.024	80.250	59.751	50.488	42.592
Sp purchased by CAF from SFS + VDB (source: Federal Agency for Drug)	76.561	77.736	74.865	67.908	93.860	78.052	59.462	50.125	45.324
SP collected by SFS + VDB (source: SFS & VDB)	77.052	77.808	74.865	67.915	94.176	78.068	57.225	50.125	45.324

But these quantities are approximately the same than the collected quantities except for 2006. We didn't receive any explanation for this difference of 2.237 litres (i.e. 3.9% of the total volume of SP collected in 2006).

It clearly emerges that the term self-sufficiency is no longer adequate to describe the data from these calculations. PWC starts with a total quantity of plasma, which is the quantity that the CAF-DCF would have to buy to supply a quantity of derivatives over and above those supplied by commercial firms in Belgium. It is important to understand that the total market for plasma derivatives is not divided between the existing vendors in a fixed distribution pattern. It is the interplay of competition that determines the quantities that the CAF-DCF and the other foreign commercial vendors will sell during a given year to the various hospitals. This clearly establishes that self-sufficiency only relates to a part of Belgian consumption, which results from competition between the firms operating in the market.

It appears that the authority has no clear intention of achieving total independence. But does the coverage of 60%, extended to 180 days, which seems somewhat arbitrary, truly reflect a reasonable risk? Nobody knows. We also find no scientific justification for the quarantine period (during which the plasma must be kept before fractionation).

This was extended from 50 to 180 days between 1998 and 2006 with no justification for this extension from the standpoint of medical safety. It therefore appears that the concepts of self-sufficiency and quarantine have never been properly considered and defined in Belgium.

Key points

- **Free competition has led to a market distribution of 60-40 between the CAF-DCF and the other firms producing blood derivatives**
- **There does not appear to have been any discussion of whether or not this distribution is optimal from the standpoint of securing coverage of our needs**

4.2.2 In other countries

4.2.2.1 In Australia

Australian official definition of Self-sufficiency

The promotion of national self-sufficiency in respect of blood and blood products is a policy aim of Australia's Commonwealth, state and territory governments. The Australian Health Ministers' Conference Policy Statement on National Self Sufficiency in the Supply of Blood and Blood Products, issued in April 2006[196], defines self-sufficiency as: "Australia striving to source blood components and plasma from within Australia to meet appropriate clinical demand".

Self-Sufficiency objective and National Blood Agreement

All Australian, State and Territory Governments are signatories to the National Blood Agreement 2003, which sets out, the policy objectives and aims for Australia's national blood sector, which are:

- provide an adequate, safe, secure and affordable supply of blood products,blood related products and blood related services;
- promote safe, high quality management and use of blood products, blood related products and blood related services in Australia.

Therefore all stakeholders are clearly committed in the field implementation of self-sufficiency policy.

However, national self-sufficiency objective does not preclude Australia from importing blood or plasma products in a narrow range of circumstances, ie where there is an inability to meet clinical needs through the domestic supply, and where supply chain risks must be addressed. The Australian Health Ministers' Conference statement acknowledged that Australia is (and has never been) not totally self-sufficient in plasma products and derivatives.

Therefore the agreement signed between health authorities and CSL-Limited also gave room for some flexibility on the matter of import of plasma products and derivatives, within a strict framework that:

- ensures adequacy of supply to Australian patients in need;
- minimizes the supply security and product safety risks to patients;
- ensures affordability of products to the Australian health sector; and
- recognizes the practicalities of production and distribution.

Self sufficiency and Australian national blood policy

The Australian example has been selected, since Australia is the only western country that has succeeded in setting up a comprehensive blood and plasma policy, from a

- practical point of view : organization of donation, collection, fractionation of blood and plasma
- legal point of view : strong interface between suppliers and health authorities
- clinical point of view : interface between clinical practices and supply policy.

It must be outlined that such a policy requires an unfailing and long-lasting political commitment of the national health authorities. In Australia this policy this policy has been initiated in the fifties: the Commonwealth Serum Laboratories (hereafter "CSL") originally founded in 1916 commenced production of fractionated products in 1953, thanks to the Australian Government's support. CSL was later privatized and merged with Behring.

The Australian policy was elaborated step by step, and in 1995 the Commonwealth Review of the Australian Blood and Blood Product System identified the need for a single, integrated, blood supply agency in Australia with a view to enhancing the safety, efficacy,and adequacy of supply of blood and blood products. As a result of that, the separate state and territory blood services combined to form the Australian Red Cross Blood Service in 1996.

The Review of the Australian Blood Banking and Plasma sector, which was completed in 2001, recommended the establishment of an authority to provide national management and oversight of Australia's blood system. Following this review, the National Blood Authority (hereafter "NBA") was set up in 2003.

Background: Australian administrative structure

ROLE OF THE NATIONAL BLOOD AUTHORITY

Australian blood and blood products policy (especially in the field of plasma products) has been centralized and rationalized every angle: one single public body is entrusted to manage the whole Australian policy. The National Blood Authority is a statutory and overarching agency established under the National Blood Authority Act 2003 . The NBA is central to Australia's national blood and plasma policy. The most important and interesting characteristic of the NBA is that it covers the whole scope of this policy:

- Coordination of demand and supply planning of blood and blood products and purchase those products on behalf of Health authorities
- Negotiation and follow-up of the contracts with suppliers of blood, blood products and blood services, including development of a national pricing schedule.
- Implementation of an efficient blood use based on evidence-based principles and good clinical practice. (incl. information and advice to governments).
- Coordination of the development of the National Health and Medical Research Council's Clinical Practice Guidelines for the Use of Blood Components.
- Follow-up of legal issues

Further information is provided on institutional aspects (NBA and other institutions in the appendix).

Access to plasma derivatives: key points

APPROVAL PROCESS AS DESIGNED UNTIL MARCH 2008

Access to plasma-derived products has been rationalized and must abide by a specific clinical and administrative process. Processes may vary across the Australian States (some of them being more demanding or than others); however, the key point of the Australian policy is to rationalize the use of plasma derived products (especially IVIG which represents two-thirds of Australia's demand in this field) both for ethical reasons (optimal use of donated blood) but also for practical reasons (avoiding shortage).

From a purely clinical point of view indications have been grouped into three groups depending on the level of clinical accuracy:

- Category 1: indications for which strong evidence of IVIg benefit has been identified.
- Category 2: indications for which evidence of this benefit is inconclusive for the following reasons:

- Conflicting evidence
- Low level of evidence
- Little research, especially for rare conditions

Category 3: indications for which there is convincing evidence that IVIg brings no benefit. A strong financial connection has been established between accuracy of indications – as described above – and funding policy. In short, prescription of Category 1 IVIg is funded on the basis of a specific cost-sharing arrangement, called Australia's National Blood Agreement ie 63% by the Australian Government (national level) and 37% by the State / Territory level. Prescription of imported IVIg products outside of Category 1 are not co-funded, and IVIg products must be purchased at full price by prescribers (hospitals) directly from the relevant manufacturer which are responsible for production of IVIg. Hence, there is a financial incentive for an evidence-based and rational use of IVIg products.

The ARCBS approved requests that meet category 1. If insufficient information was provided by the clinician to the ARCBS, the request was forwarded to the local IVIG Working Group. This IVIG Working Group consisted of 8 clinicians, representing specialities who had an interest in IVIG issues, and made the final decision (approval or not).

In March 2008 (ongoing reform), the new "Criteria for the clinical use of intravenous immunoglobulin in Australia" (hereafter "Criteria") have been officially issued by the Australian. In short, the conditions are categorised in the Criteria under those for which IVIG has:

- An established therapeutic role
- An emerging therapeutic role
- A use in exceptional circumstances
- Conditions for which IVIG is not indicated

Supply contracts with CSL-Ltd: Plasma Products Agreement and other contractual arrangements[197]

BACKGROUND

In 1994 CSL became a public company limited by shares and taken to be registered under the *Companies Act 1981* (Cwlth). At this time, certain legislative obligations were imposed upon CSL Limited, in line with the *Commonwealth Serum Laboratories Act 1961* (CSL Act), as described below:

- Provide that CSL Limited is to remain Australian-controlled.
- CSL is also required to maintain a register of foreign-held voting shares and must provide this register, or a copy thereof, to the Minister if requested to do so by the Minister, in writing.
- Require CSL, when manufacturing plasma products from Australian-donated plasma, to produce those products in Australia.
- Prohibit CSL from disposing of its manufacturing facility at Broadmeadows, which may not be sold or encumbered without Ministerial permission.
- Provide for court orders where the Commonwealth can show that CSL is breaching, or threatening to breach, a contractual obligation.

An ind-depth analysis of fractionation arrangements had been carried out and completed in 2006[196]. In today's form – Plasma Products Agreement mentioned above - relationship between CSL-Ltd and Australian health authorities can be summarized as a close partnership based on a monopoly for fractionation in exchange for strict and demanding performance and safety standards[164] (see table below):

Table 44: The Plasma Products Agreement between CSL-Ltd and the Australian National Blood Authority

Heading	Content
Section A: Interpretation and Term	*Definitions, rules of interpretation*
Section B: Relationship Management	*Relationship between the parties, Contacts and notices, Management meetings and reviews, Public Affairs Management, Variations to the Deed, CSL contracts with other Nat. Blood Suppliers*
Section C: Products / Services Obligations	*Provision of products (quantity; notice obligations, etc..)* *Exclusive right to fractionate plasma, Reporting obligations, Obligations under Therapeutic Goods Act, CSL general obligations (as a manufacturer and where CSL is not a manufacturer)* *Product compliance and return,* *Performance requirements for goods and services*
Section D: Payment Obligations	*Payments by the NBA, Invoicing obligations, Recovery of money by the NBA,*
Section E: Ownership Issues	*Possession of products, Intellectual property, Moral rights*
Section F: Protection of Information	*Confidentiality, Data security, Privacy, Conf. of Interest*
Section G: Treatment of Risks	*Risk Manag. Warranties, Indemnities, Undertakings, Insurance, Supply continuity plans & options*
Section H: Other Requirements of CSL	*Records, Access to information & Premises, Audit.*
Section I: Termination and Disputes	*Termin. for default, for change of policy, Handover obligations, Dispute Resolution,*
Section J: Miscellaneous	*Assignment (by CSL, by NBA), Execution of separate documents.*

CSL Limited is also in charge of maintaining the National Reserve of plasma products for the NBA, under a contractual arrangement separate to the PPA.

4.2.2.2 In France

French Approach of self-sufficiency

In France, there is no official and legal definition of "self-sufficiency" as such. However, a general approach of this concept could be defined as the turnover of LFB (national fractionator enjoying the monopoly of EFS plasma fractionation) compared to the total turnover of fractionators operating in France. One must bear in mind that the plasma product market is subject to competition. LFB must therefore compete with other firms (Baxter, Octapharma, etc…).

Considering this approach, it must be outlined that LFB meets 75% of the needs of the French market. However, it must be underlined that LFB corporate objective is to be in the position to fulfil 100% of these needs in 2011 (specific investments have been planned accordingly).

Another important point is the very last update of the French regulation framework. In Summer 2009, the new French Law on Health Care organization (Loi Hôpital Patients Santé et Territoire – Loi HPST) officially stated that fulfilling the French patients' needs must be LFB's priority (in return of its monopoly of EFS plasma fractionation).

Supply of blood and plasma-derived products: the French monitoring system

Following the shortage of Factor VIII in France in 2000-2001 (and consequential problems for haemophilia patients), the French Department of Health decided to set up a long-term monitoring system -National Steering Committee- to address this specific kind of problems. The latter has been organized since 2001 (by means of a Department of Health's Circular dated 28 June 2001) under the leadership of the AFSSAPS Agence Française de Sécurité Sanitaire des Produits de Santé– French Agency for the Safety of Health Products.

Following the meetings of these groups, and depending on the likelihood of shortage of plasma derivatives, national official recommendations – including priority orders - can be officially set out and published by the AFSSAPS and to rationalize the use of these products accordingly (eg: Fibrinogene-derived products in December 2008 and the following months).

As far as IVIG products are concerned, a specific steering group has been set up to organize routine monitoring of IVIG products supply. All relevant private and public stakeholders are involved: representatives of the Department of Health, several representatives of pharmacists (incl. the French Pharmaceutical Association), Networks of heath care establishments, clinical experts, but also the leading fractionation firms on the French market.

Supply and storage issues are discussed every angle: data collection on consumption and supply, clinical dimension, industrial problems etc…The minutes of these meetings are not public domain and they remain confidential. However, this routine monitoring system plays a key-role in shortage prevention and also covers the interface between public decision-makers and private fractionation industry on that matters.

4.2.2.3 In Germany

German approach of self-sufficiency

As stated by Art 4.7 of the German Transfusion Act "Compensation is also an aspect of self-sufficiency. Should it not be allowed to pay a compensation, this would cause a highly visible loss of donors. This would be counter-productive to the aim of self-sufficiency". "Blood and Plasma donors may receive a compensation for the donation time and effort. However, this compensation must not become a payment".

However, from a purely legal and conceptual point there is no one single definition of "self-sufficiency" as such, but several ratios followed up on the national level by the Paul Ehrlich Institut thanks to a centralized data collection system.

The key objective of the German Health Authorities is to have a clear overview of plasma quantities actually available for fractionation and also to analyze the German industry's actual capacity to fractionate the German plasma.

As often underlined by the Paul Ehrlich Institut's experts, increasing plasma collection is not an end in itself. A sensible approach requires a specific follow-op of plasma collection but also a specific monitoring of the German actual fractionation capacity for the whole range of plasma products meeting the German patients' demand.

Practical follow-up of self-sufficiency issues

This data collection system is a regulatory obligation, based on Article 21 and 22 of the German National Transfusion Act ("Transfusionsgesetz" in German).

- Blood and plasma collectors (Red Cross, Private Centres, Municipal Centres, German Army) are subject to this specific reporting obligation, but also:
- Fractionation industry : all firms acting on the German market
- On the demand side: panel doctors and hospitals and specialized health care establishments.

This reporting system refers to a specific data set, set out by the German regulation mentioned above. Therefore, the German health authorities are in the position to organize a follow-up of a specific range of routine indicators and to have a clear overview of Germany's situation in terms of self-sufficiency.

SUPPLY SIDE

In practice all the concerned data are validated, sorted and entered onto the Paul Ehrlich Institut's data bases. Considering our subject, one of the most accurate monitoring tool is the "Balance Sheet" that records the following flows (2006 Data):

Quantity Collected (Liters)	Loss	Expiry (Manufacturer)	Total Export	Total Import	Quantity Available on the German Market	Fractionation in Germany
2 143 205	154 881	5 990	1 001 911	609 584	1 750 878	1 201 613

Thanks to this follow-up of imports, the Institute can have a clear view of Germany's situation for the whole range of plasma products, including those that are not manufactured in Germany.

DEMAND SIDE

A specific follow-up is also routinely carried out by the Paul Ehrlich Institut.

- *One of the self sufficiency key indicators is the following: "Quantities manufactured in Germany relating to consumption in Germany". Based on this approach, the self-sufficiency ratios are:*
    - Factor VIII from plasma : above 100%
    - Factor IX from plasma: 66%
    - IG (normal): 99%
    - IG (specific / Anti D): 94%
    - IG (other specific IGs): Above 100%

Among all plasma products, some are not manufactured in Germany, but imports are subject to a precise follow-up. Consumption of each plasma product is also subject to a precise follow-up. However, in spite of this follow-up mechanism, the Paul Ehrlich Institute had to admit that there is some uncertainty about reliability of data on the latter subject.

Recent strengthening of supply capacity in Germany (2000-2008)

A DYNAMIC COLLECTION POLICY

As a whole, the situation of Germany has evolved quite positively over the last ten years. Plasma actually collected in Germany has raised from 1.5 million litters in 2000 to 2.5 million litters in 2008.

A SURGE IN PLASMA FRACTIONATION CAPACITY

The amount of plasma actually fractionated in Germany has raised accordingly: 750 000 litters in 2004, 1.2 Million litres in 2006 (see above), and 2 Million litres in 2008.

4.2.2.4 In Canada

Canadian historical background

Historically, gratuity of donation of blood and plasma has been considered as the underpinning principle of the whole Canadian donation system. In the nineties, a major public health scandal called the "tainted blood scandal" seriously undermined the public and the donors' trust in the donation institutions, especially the Canadian Red Cross.

In compliance with the conclusions of the Krever Commission of Inquiry of 1997 (see below), the Canadian Red Cross eventually transferred its blood and plasma services to the newly founded "Canadian Blood Services- CBS" (and Héma-Québec for this latter province).

Canadian Reflection on the ethical framework

As mentioned above, the Krever Commission of Inquiry conducted an in-depth analysis of the whole donation system and issued key statements (1997) on the principles that must underpin the future Canadian donation system (the following points are official statements):

- "Donors of blood and plasma should not be paid, except in rare circumstances"
- "Significant efforts must be made to ensure that blood products used in Canada are made from unpaid donors"
- "Plasma must be collected in sufficient quantities in Canada to meet domestic needs for blood products"
- "Safety should be paramount"

Following these principles, gratuity of donation remained untouched but security and quantitative aspects of plasma supply were also underlined. However, further principles also had to be taken into account as set out by the Founding Memorandum of Understanding (1997):

- Ensuring access to a safe, secure and affordable supply of blood, blood products and alternatives, and supports their appropriate use.
- Addressing inventory imbalances (shortages / surpluses) to minimize waste and ensure adequate supply
- Considering decision making in a health risk management framework which places on an equal footing the three critical elements of cost, benefit and risk.

Therefore the newly founded donation system – ie the Canadian Blood Services to which the Red Cross donation activities were transferred – had to pursue several goals in the same time:

- Ensuring blood safety, which is of paramount importance considering the Canadian historical background. More generally it is an objective as such for any country.
- Improving level of self-sufficiency is also an objective as such, from a public health and from a political point of view.
- Increasing volume of domestic donation for blood and plasma, which is strongly connected with the previous point.
- Maintaining gratuity of donation, as a key ethical option.
- Reducing risk of supply disruption (especially in the field of IVIG) to avoid any danger for patients' safety.

Today's situation of Canada in terms of IVIG self-sufficiency:

In 2008-2009, Canada will be about:

- 28% sufficient in IVIG (made from Canadian Plasma)
- 72% of the IVIG distributed to Canadian hospitals comes from plasma collected commercially in the US

Therefore, Canada has to face two thorny problems simultaneously: security (as described above) but also a poor level of self-sufficiency, and thus possible disruption in plasma (especially IVIG) supply. Once again this situation is quite close to the Belgian one.

This situation raised several questions: the adequate of national self-sufficiency , the ways and means to reach this level of self-sufficiency.

Canadian strategy

At the end of the reflection process, the official target of 100% Self-sufficiency through domestic collection and supply was eventually abandoned for Canadian Blood Services for the following reasons:

- It would require huge investments (18 new plasma centres within the next 7 years)
- It would not be cost efficient as Canadian production costs remain much higher than the US ones.
- It is not scientifically justified in terms of blood safety

For all the reasons mentioned above, the official self-sufficiency target has been revised downwards to 40%. A wide range of options had been originally considered to close this gap (28% to 40%): raising the level of domestic collection, improving processes, etc… Today's Canadian strategy can thus be described as a "sufficiency aimed at optimally reducing risk of IVIG supply disruption". In practice it can be described as a "policy-mix". In practice, several measures were implemented in the same time:

- Improvement of collection methodology

- Reintroduction of source plasma collection at some sites, when required
- Increased volume per collection
- Usage of platelet additive solutions
- Improvement of fractionation capacities: seeking to have two fractionators licensed for Canadian plasma

Key points

- **There is no universal definition of "self-sufficiency" but all selected countries have conducted an in-depth reflection on this concept, in connection with other subjects.**
- **All selected countries have set up a monitoring system of self-sufficiency ratios, or at least a centralized data collection on the subject.**
- **Clear connection between self-sufficiency and remuneration issues must be born in mind.**
- **Australian policy is probably the most comprehensive policy as it has established a close connection between this dimension and all related issues within the framework of the National Blood Authority, which covers all aspects of blood and plasma supply.**
- **A short synthetic table of foreign policies in displayed in the table below.**

Table 45: Summary

	Germany	France	Canada	Australia
Ethical framework	Financial Compensation allowed (Max:25€) to collector's discretion	Non-Remunerated	Non-Remunerated	Non-Remunerated
Collection	Free Competition: Red Cr.,Private	EFS monopoly Delivery targets to LFB	Canada Blood Service monopoly	Red Cross monopoly
Fractionation	Several institutions	LFB Monopoly on fraction. of EFS plasma (but no monopoly on sales)	Two fractionators expected around 2014	CSL Ltd Monopoly on fractionation and sales (import if unavailable)
Self-Sufficiency Approach	Self-Sufficiency national ratios	LFB Turnover ratio	Official definition	Official definition
Self-Sufficiency follow-up	Regulatory data collection Public annual reports	Routine and compulsory data collection	Routine and compulsory data collection	N.B.A.: All self-sufficiency aspects
Self-Sufficiency strategy	Policy mix Increas.collection (demo. approach) and fractionation capacity ; control of consumption	Policy mix Increasing collection Increasing LFB-fractionation capacity ; control of consumption	Policy mix Increasing collection, fractionation capacity ; control of consumption	NBA policy: All aspects: collection , fractionation, contract with CSL Ltd and consumption

4.3 HOW TO STAY OR BECOME SELF SUFFICIENT

There is no answer to the question of self sufficiency in terms of figures in this report. This is a political choice to be made in the light of the risk-aversion of Belgian decision-makers. The fundamental question is to determine the desired level of independence. Supply security considerations must govern this choice. For this we need to determine whether the trend in demand in countries deemed to have a high level of consumption could lead to a shortage of derivative products. Such a risk could also result if the collection in these countries no longer covered their own requirements for derivatives. Price levels and volatility are another risk factor to be considered. Being more dependent on foreign supplies could mean suffering substantial price variations, which are the first adjustment variable affecting variations in supply and demand. Beyond a certain level of shortage, there are fears that simple purchasing power may no longer be enough.

To minimise the cost of production for Belgian plasma derivatives for a given level of coverage, we could strive for:

- A reduction in the demand for these products
- An increasing of the capacities of collecting plasma
- Transparency and better control of the supply of derivatives

4.3.1 Strategies to decrease IG use: lessons learned

4.3.1.1 Experience from other countries

Several countries, confronted to increased IG consumption, shortage or risk of shortage, and growing cost, have published the measures that they planned or have undertaken to improve the supply and demand balance.(Hume, Anderson, TMR 2007; Constantine 2007, UK DOH National Immunoglobulin Database Update[j], Australia[k]). However, very few studies have evaluated the impact of these measures.

Table 45 summarized the overall strategies used in different countries. We focus here on the reduction of IG use. The main measures taken or proposed include:

Classifying indications in priority groups for IG treatment

A list of indications for which IG can be used has been defined in most countries. In addition, a few countries such as France, the UK and Australia, that experienced shortage (or its risk), have decided on prioritization of IG use and classified indications (labeled or not) into groups or higher and lower priority. However, this classification has been applied in many different ways:

- In Australia, very clear categories for priority setting have been established: 1. Conditions for which IG has an established therapeutic role; 2. conditions for which IVIg has an emerging therapeutic role; 3. conditions for which IVIg are used in exceptional circumstances; 4. conditions for which IVIg use is not indicated.
- In the UK, three well defined categories have been established, coded by colour (red, blue and grey), to facilitate the clinician understanding of the level of priority.
- In France, the drug agency (AFSSAPS) defined 7 groups, using different levels of priority, distinguishing labeled and non labeled indications, with no clear rationale; the priority of each group of indications above the others is not always clear.[l]

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j Source: National Immunoglobulin Database Update. DOH. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_097670

k Source: Criteria for the clinical use of intravenous immunoglobulin in Australia. Australian Health Ministers' Conference. December 2007.

l Source: AFSSAPS: http://www.afssaps.fr/Infos-de-securite/Autres-mesures-de-securite/Proposition-de-hierarchisation-des-indications-des-immunoglobulines-humaines-intraveineuses-IgIV-en-situation-de-tension-forte-sur-les-approvisionnements-pour-le-marche-francais2

A difficulty with this system is that the rationale behind the choice of classification is not always stated or made clear, the categories need to be regulary updated, and the application of this priorization is not always described: in the absence of shortage, should a patient from a last priority group receive IG or not?

Establishing guidelines and criteria for use

The Canada, Australia and the UK have invested important resources and time to produce guidelines, based on evidence and consensus sessions among experts:

- The Canadian Blood Services and the National Advisory Committee on Blood and Blood Products began in 2004 to develop detailed and evidence based guidelines for the use of IVIG in hematological and neurological conditions. The results of this work are published in a supplement of the journal Transfusion Medicine Reviews in 2007.[18-21]
- In Australia, the "Criteria for the Clinical Use of Intravenous Immunoglobulin" was developed in 2004-2007, based on evidence identified through systematic reviews of the literature and the opinions of clinical experts. The clinical criteria are contained within condition pro-forma and have been set out to cover four major issues: list of indications for IG use; qualifying criteria, exclusion criteria and review criteria.[22]
- In the UK, as part of the "Demand Management Programme", National Clinical Guidelines for the appropriate use of IVIG have been produced based on available evidence and expert opinion in the period 2006-2008. After literature review and expert review, interested bodies registered as "Stakeholders" provided comments on the document. Regular updates are ensured, at least yearly.
- In France, the CEDIT has issued recommendations that are widely used. National guidelines are also expected at national level, based on the CEDIT work.[1]
- In Australia, the concept of 'criteria for use' constitutes a more directive framework for decisions about the use of a particular treatment, as opposed to the concept of "guidelines" that usually refer to the management of conditions rather than to the use of specific therapeutic products such as IVIG.[22] The latter term has been selected to describe the circumstances, based on evidence and clinical experience, under which the clinical use of IVIG is considered appropriate in Australia.

It should be noted that in each country, the production of guidelines has cost a considerable amount of time (around 3 years), in literature review and negotiations with experts and stakeholders. Guidelines also need to be regularly updated.

Only one study assessed the impact of guidelines on IG use. In the Atlantic region of Canada, a study compared IVIG use between a baseline phase (2003-2004) before guideline use, and after implementation of "optimization tools" (2005). In the second period, they found a 7% decrease in IG use, contrasting with the previous annual rises (7% in 2002-03 to 2003-04 and 10% from 2003-04 to 2004-05).[146]

Limiting prescription of IG to specific groups

In the UK under the "Commissioning Policy", all immunoglobulin must be prescribed by a consultant with specialist knowledge of its use; no GP may prescribe. Prescribers must monitor future communications on any risks to supply and understand the mechanism for handling any shortages.

Improving awareness of clinicians and patients

Two countries mention the information to clinicians in their plan: France planned to implement information to pharmacists and prescribe.[m] In the UK, the demand management programme states that patients should be fully informed of arrangements for their treatment and the implications of any supply shortages.

Improving evaluation of use and monitoring

Several countries have initiated a registry for patients under IG treatment or a national database. However, no further information is available on the application of these systems and its impact.

- In the UK, the "Commissioning Policy" stated that all patients should be logged with the national immunoglobulin database and their data provided. All patients receiving long-term immunoglobulin should be reviewed annually to assess disease activity and determine the best therapeutic option.
- In Australia, The national Blood Agency has also included in its plans the development of a system to collect data that will provide information about the effectiveness of IVIG therapy.[22] This information was planned to be assessed by experts and used to inform future reviews of this "criteria for use". However, we have no information on whether this strategy has been effectively implemented.
- In some Canadian regions, such as the Atlantic Provinces, a working group was created to monitor IVIG use and a registry of IVIG was created. Assessment of indication appropriateness is determined based on guidelines, and feedback reports are distributed to stakeholders.
- France launched a data collection on IVIG consumption per indication, to evaluate the appropriateness of IVIG use in clinical practice.

Other lessons learned

In the US, a shortage in IVIG occurred in 1997.[198] The authorities informed the medical community but did not respond to the shortage in a timely of effective manner. Instead, it took a passive role, leaving IVIG manufacturers and distributors, health care institutions, and clinicians to fend for themselves. Regulatory steps and recommendations were made but after prolonged debate. No updated national recommendation on appropriate use of IVIG has been issued. Institutions have developed their own guidelines to restrict the use of IVIG for off-label conditions. Guidelines varied substantially across institutions. Consequently IVIG was distributed at often extremely elevated prices and not according to the criteria of need and urgency. The shortage likely had an uneven impact on patients, based on the relative market strength of the health care institutions in which they received care and the individual patient's ability to absorb the increasing out-of-pocket costs of scarce IVIG.

Overall impact of strategies to reduce IG use

Several countries are conducting audits in hospitals (eg. the UK and the US) but few countries have evaluated the overall impact of their set of strategies on IG consumption.

In France, the last available consumption data from the "Hôpitaux de Paris", following the CEDIT guidelines and prioritization, date from 2005 and show an increase in IVIG use (+18%). This increase is however lower than the increase observed at national level (+24%).[n]

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m http://cedit.aphp.fr/servlet/siteCedit?Destination=reco&numArticle=02.02/Re4/07

n Recommandation 2007 relative à l'utilisation des immunoglobulines humaines normales (intraveineuses polyvalentes (IgIV) et sous-cutanées) avec bilan des consommations en 2005 à l'AP-HP, accessed on http://cedit.aphp.fr/servlet/siteCedit?Destination=reco&numArticle=02.02/Re4/07

In the UK, preliminary analysis of the national immunoglobulin database (first 9 months) has been published but there is no comparison pre and post-intervention.[o]

Table 46: Summary of measures proposed to prevent or control IG shortage in 6 countries

Country, period	Reduce use	Improve supply	Improve evaluation / monitoring of use/supply
France (AFFSAPS and CEDIT, 1991-2008)	Guidelines on IVIG use Priority lists for indications (7 categories) Information for prescribers	Not covered	Data collection on IG use per indication group
Canada, 2004-07	Detailed guidelines on IVIG use	Not covered	Evaluation of IG use per indication (per region)
The UK, Commissioning policy	Detailed guidelines Priority list (red, blue, grey) Funding for IG linked to data provision Prescription limited to specialist (no GP)	Not covered	National IG database to register each patient Audit of trusts
Australia	Limit indications and rationalize use: criteria for use Priority lists (4 groups)	Increasing the manufacture in Australia Importing IVIg from overseas suppliers	
US, 1997[198]	None. Improve appropriate use at local level.	Encouraged producers to increase supplies	Monthly data from producers, but not effective

4.3.1.2 Experiences from Belgium

In Belgium, the Health Council (CSS/HGR) has developed guidelines for the use of red blood cells in January 2007,[p] and for the use of frozen plasma in 2007.[q] After the guidelines were issued, the consumption of both products decreased. Guidelines on the use of immunoglobulins are currently being developed at the Health Council and should be available in the near future.

In the late nineties, the BIOMED project used the technique of "benchmarking" (restitution of data documenting individual performance and comparison of these data with the group average or with external references) to impact on the red cell transfusion. After the thorough restitution of data and without the introduction of new regulations or guidelines, time was given to the participants to improve their practices, by using the strategies they deemed most appropriate for their local situation. Data collected 2.5 years later showed that the use of blood and blood products decreased markedly: a reduction of the order of 20%-25% was achieved over a 2 to 3 year period. The reduction of red cell transfusion has been obtained without any change in hematocrits at any time during hospital stay for any surgical procedure.[199]

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[o] National Immunoglobulin Database Update. April 2009. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_097668.pdf

[p] CSS/HGR. AVIS DU CONSEIL SUPERIEUR D'HYGIENE. Guide d'indications transfusionnelles pour les globules rouges. 10 janvier 2007 CSH n° 8085. https://portal.health.fgov.be/pls/portal/docs/PAGE/INTERNET_PG/HOMEPAGE_MENU/ABOUTUS1_MENU/INSTITUTIONSAPPARENTEES1_MENU/HOGEGEZONDHEIDSRAAD1_MENU/ADVIEZENENAANBEVELINGEN1_MENU/ADVIEZENENAANBEVELINGEN1_DOCS/CSH8085_INDICATIONS_TRANSFUSIONNELLES_GLOBULES_ROUGES_FR.PDF

[q] AVIS DU CONSEIL SUPERIEUR D'HYGIENE. Guide d'indications transfusionnelles pour le plasma frais congelé. 7 février 2007. CSH n° 8157

4.3.2 Strategies to decrease IG use: what could be applied in Belgium

Overall, the following measures could be considered for implementation in Belgium:

- Defining a list of indications for IG use, based on available evidence and expert panels. A list of reimbursed indications is already defined and regularly updated in Belgium, but several indications which have shown a benefit based on evidence are not included (see Chapter II). It is unclear how these diseases are currently treated in Belgium, and it is possible that significant amounts of IG are given under compassionate use.
- Classifying these indications in priority groups for IG treatment (high priority, low priority). However, establishing these priorities must be based on evidence and requires consensus and regular update. The application of these classifications in practice (how to treat these patients) is not always clear. In some countries, patients from the low priority group may be treated with IG unless there is a IG shortage.
- Establishing guidelines and criteria for use. In countries where guidelines have been developed as a response to IG shortage, this has requested important resources in terms of persons, time required (2-3 years) and expert panels and consensus. In Belgium, the Health Council is in the process of developing guidelines that should be issued at end of 2009. The Belgian experience with similar guidelines (for the use of red cell transfusion and fresh frozen plasma) has shown positive results in terms of practice and reduction of consumption. It should be noted that guidelines also need to be regularly updated.
- Limiting prescription of IG to specific groups of prescribers. In Belgium, a high IG amount is prescribed by assistants in specialization (in academic hospitals) and a IG amounts are sometimes prescribed by peripheral hospitals for specialties that should in principle not use significant amounts. An option would be to limit the initiation and supervision of IG treatment to a number of "IG reference centres", following the same model than the centres for haemophilia centres or for bone marrow transplants, through convention with the INAMI/RIZIV.
- Improving awareness of clinicians and patients. In Belgium, clinicians have access to evidence based literature, but receive no direct information on the cost of IG and the risk of shortage; good information on these aspects could help decrease the prescription of IG for the indications in which no benefit has been proven.
- Improving evaluation of use and monitoring. A registry for patients under long term IG treatment or a national data basis could be a tool to allow a better monitoring of IG use and assess indication appropriateness based on guidelines. This data collection could also be used for a "benchmarking" method, which has been successfully used for red cell transfusion in Belgium in the late nineties (see above).

4.3.3 Increasing the capacities of collecting plasma

A major part of the cost of collecting plasma doubtless stems from the difficulty in finding donors and the efforts made to seek out and persuade them. It seems self-evident that a greater number of donors would allow economies of scale in the collection of plasma and might result in collecting more than is required to cover the needs of Belgium as defined by the concept of self-sufficiency in the Royal Decree of 18 June 1998. The Red Cross could then export at a market price higher than the price it sells to the CAF-DCF. The subsidies could then be reduced accordingly.

To attract a larger number of donors it would not be allowed to resort to paying for the blood or plasma collected. The principle of voluntary donation free of charge constitutes the essential ethical framework for all European countries. But the likes of advertising campaigns, benefits in kind and tax breaks could be considered and set up at a cost probably lower than that of the subsidies given to the Red Cross to arrive at the same result.

In most European countries (see part I of this report), in particular France and Germany, it clearly emerges that a major effort has been made in recent years aimed at the priority age groups, namely 18-25 years, usually involving a close partnership with the schools and universities concerned. More generally, communication campaigns using a wide variety of media have been implemented, paying special attention to managing the donors over time in order to improve their loyalty.

Germany has given special thought to the geographical location of plasma collection centres in relation to the profile of potential donors, in particular in terms of age.

It is nevertheless necessary to reflect on the different treatment currently given to private sector and public sector employees. The quest for equal treatment of all donors could lead the authority to reduce the benefits, in terms of days of leave, granted to members of the public services and make donating blood and plasma totally charitable. This would open up the possibility of reconverting the resulting savings into campaigns promoting blood and plasma donation.

Finally, a wide-raging debate in terms of demographic prospects has taken place in Germany in order to emphasise the importance of this dimension for the future satisfaction of the needs of the population. This debate will make possible better forecasting of the donor population.

4.3.4 Transparency and better control of the supply of derivatives

As we have already seen, it seems that the quantities of derivatives sold in Belgium by the CAF-DCF are below what the firm should be able to produce if she were using all the quantity of plasma sold to it by the Red Cross. There are various possible explanations for this situation, but the information available does not enable us to identify the correct ones, largely because of the complexity of the market and of the fractionation circuit implemented via agreements with foreign firms, the terms of which are not known to us.

Given the indirect subsidy granted to the CAF-DCF via the below-market price at which plasma is sold to it, it would make sense to have public control over the terms and costs of its agreements with foreign partners.

Relations between the organisations responsible for collection and fractionation are a delicate and complex subject in all western countries.

France and Germany first sought to ensure standardisation of the technical collection process (in particular the volume of individual donations) in order to improve the volumes effectively delivered to the fractionation firms, with the same number of donors.

Of all the countries studied, it is without doubt in Australia where the debate on contractual relations between the fractionator and the other actors involved has gone furthest. The contract binding the National Blood Authority and the fractionator (CSL-Ltd) covers all aspects of the relationship between the two partners, including the financial, logistical, technical (health security, risk management) and legal dimensions (ownership clause, appeal jurisdictions, etc.). This contractual relationship also takes into account that the National Blood Authority is responsible for all functions touching on the question of the supply and distribution of blood and plasma products within the country.

4.4 CONCLUSIONS

The issue of the independence of supplies of plasma derivatives is fundamentally a political one, and the public authorities must define the degree of independence they wish to achieve and, as a corollary, the degree of insecurity that they are willing to accept. The substance of these choices would then determine the measures to be taken within the three fields of action identified in this report: plasma collection, the production of plasma derivatives and the consumption of these derivatives. Each of these fields concerns different actors that require specific instruments in order to move towards the collection of more plasma, more profitable transformation of plasma into derivatives, and consumption of derivatives more in step with recognised medical conditions. Maintaining or increasing our independence therefore requires the application of a combination of measures in these three fields. However, independently of any quest for a specific degree of independence, it would appear that consumption that satisfies the rules of good practice, collection at minimum cost and satisfactory yields from the fractionation process are basic requirements. The scale of each possible measure must be linked to established facts, in which respect it is important to take into account the limitations of any scientific study. In this case they concern international prices and certain data relating to the consumption of derivative products. For each of these limitations, further studies would make the results more robust, not forgetting the confidential nature of certain data, which will always be subject to some uncertainty. Nevertheless, it is not necessary to wait for certainty regarding every parameter before taking the necessary measures.

5 APPENDICES

APPENDIX 1: ETHICAL DIMENSION OF DONATION: QUICK OVERVIEW

REASONS FOR DONATING BLOOD AND PLASMA: EMPIRIC ANALYSIS

A specific "motivation model" ie a motivation ethical framework has been identified and recently set out by Godin in one of his most recent articles [Godin et al "Factors explaining the intention to give blood among the general population Vox Sanguinis (2005) 89, 140-149 et al. 2005] [200]. In this Canadian study (Québec), all these factors where analyzed both in the "never donors" group (ie individuals who never donated) and in the "ever donors" group (individuals who donated, at least one).

External variables (individual and collective alike) are apt to have an impact on 3 types of ethical factors:

- Attitudes (cognitive attitudes, but also emotional attitudes)
- Accepted norms: perceived behaviour control, moral norms as accepted in a specific country (at a specific time of history), and past experience of donation.
- Controls (self-initiated controls or society-initiated controls)

The three ethical factors mentioned above determine the "intention to donate", which turns into actual behaviour (ie actual donation) provided resources are available to perform it.

In both groups - "Ever donors" and "Never donors" – morals norms and perceived controls appeared as the most important factors.

PRINCIPLES UNDERPINNING BLOOD DONATION

Utilitarianism: doing what is good / decisions are made owing to the consequences of a specific behaviour. From a purely practical point of view, cost/effectiveness (both on the individual and social level) reasoning is the key principle underpinning decision-making processes. Therefore people should donate, regardless of their motives. Blood donation must be organized in such a way that maximizes rentability of donation (incentives, attractive and comfortable framework, etc…).

***Duty-Ethics*:** doing what must be done and motivated by fair intention. Donation is send and considered from the point of view of realization of each individual's freedom. However, each individual's behaviour "duty-ethical" behaviour is supposed to be considered and acknowledged as a general rule.

Contract-Ethics: donation can be seen as a part of the whole social contract. The latter can be seen as a cluster of common rules defined for the same common benefit (solidarity).

Virtue-Ethics: who can be considered as an "virtuous individual". The whole concept of "virtue" is applied to the whole individual and not to specific behaviour or punctual act. Donation is the expression of mutual dependence between people.

In short, and from an "ethical values" point of view, people must donate blood because:

- It is useful
- It is a duty
- It is the expression of solidarity
- It is a proof of virtue

FAVOURING AND HINDERING FACTORS

Given the background mentioned above, favouring and hindering factors have obviously been identified in the very specific field of blood and plasma donation.

Favouring factors:

- Altruism
- Role-identity
- Social rules
- Facilitating framework (logistics issues) as identified by Godin et al 2005, especially short distance between the potential donor's home and the blood donation centre
- Positive effects of the donation for the donor

Hindering factors

Perceived negative effect of donation and fears among potential donors about donation (fear of needles, fear of fainting experience, etc..)

Logistic problems: long distance between the donor's home and the donation centre, but also lack of intimacy.

"Free-rider" behaviour, applied to donation as explained by David B. Johnson in the British Journal of Psychology 1982 [201], ie individual's reluctance to donate because the individual contribution would have no effect no perceptible effect on the overall provision of blood and that the individual himself cannot be excluded from enjoying the benefits of the system (if case of need).

Main learnings: people's reluctance to donate is mainly explained by perceived psychological, physical or practical barriers and obstacles regarding donation (even the latter have little to do with reality). Therefore donation promotional strategies should be adapted accordingly and focus on elimination of these barriers. Strategies should obviously be adapted to each population group (donors and non donors).

Profile of donors' population

Considering Austrian compensation policy, the profile of whole blood donors and the one of plasma donors (as identified by the research team) remains quite different.

Plasma donors are in average:

- younger (18-35 important age group)
- more educated (students)
- less apt to live in stable couples (single)
- less involved in professional life (students, jobless), than whole blood donors.

Remuneration of donation / Empiric findings for Austria

One must bear in mind that financial compensation is an extremely ambivalent and controversial issue, as it may be either a hindering or a factor, depending on the existing cultural and institutional framework of the country where donation is performed.

As identified by the Austrian research team of the University of Vienna a change in remuneration policy would have a major impact on donors' behaviour, ie:

- should remuneration for whole blood donation be introduced, 84.3% of whole blood donors would stop donating whole blood
- conversely, should remuneration for plasma donation be stopped 56.2% of plasma donors would stop donating plasma

Likewise, it was clearly mentioned that donor's motives for donation remain very different, especially towards the concept of altruism vs remuneration: For whole blood donors, altruism as such is an important motive for 88.2% for donation, whereas only 50% of plasma donors feel concerned with this kind of motives. In the same time 52.1% of plasma donors clearly mention remuneration as one of the fix elements of their monthly incomes.

APPENDIX 2 : SEARCH TERMS

The following databases were searched, by using the following search terms:

- Cochrane review database, with the search term "immunoglobulin$"
- In the Centre for Reviews and Dissemination database (CRD) (http://www.crd.york.ac.uk/crdweb/), the database of abstracts of reviews of effects (DARE), with the search term "immunoglobulin$"
- Medline and Embase with the following search terms (or their equivalent): ("Immunoglobulins, Intravenous"[Mesh] AND "Randomized Controlled Trial "[Publication Type] AND (disease considered)"

In addition, cost-effectiveness studies were retrieved by searching Medline and Embase by using the following search terms (or equivalent): "Cost-Benefit Analysis"[Mesh] AND "Immunoglobulins, Intravenous"[Mesh]

APPENDIX 3: GRADE CRITERIA FOR ASSIGNING GRADE OF EVIDENCE

From "Grading quality of evidence and strength of recommendations", GRADE Working Group, BMJ. 2004;328(7454):1490.[23]

CRITERIA FOR ASSIGNING GRADE OF EVIDENCE

Judgments about quality of evidence should be guided by a systematic review of available evidence. Reviewers should consider four key elements: study design, study quality, consistency, and directness (see below). Study design refers to the basic study design, which we have broadly categorized as observational studies and randomized trials. Study quality refers to the detailed study methods and execution. Consistency refers to the similarity of estimates of effect across studies. Directness refers to the extent to which the people, interventions, and outcome measures are similar to those of interest. Another type of indirect evidence arises when there are no direct comparisons of interventions and investigators must make comparisons across studies.

Type of evidence

Randomised trial = high
Observational study = low
Any other evidence = very low

Decrease grade if:

- Serious (− 1) or very serious (− 2) limitation to study quality
- Important inconsistency (− 1)
- Some (− 1) or major (− 2) uncertainty about directness
- Imprecise or sparse data (− 1)
- High probability of reporting bias (− 1)

Increase grade if:

- Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

APPENDIX 4: IMMUNO-HAEMATOLOGICAL SURVEY

Use of immunoglobulins in the treatment of immune deficiencies and other diseases

This information is asked by the KCE to project the future needs in immunoglobulins (IG) in Belgium. This work has been requested by INAMI/RIZIV to prevent future IG shortages.

Your data will not be distributed to any other institution, and will not be used to assess appropriateness of IG use in Belgian centers.

If you have any question about this survey or the project, you can contact:
Dr Germaine Hanquet, KCE, 02/287.33.37, germaine.hanquet@kce.fgov.be
Or Dr Michel Huybrechts, KCE, 02/287.33.42, michel.huybrechts@kce.fgov.be

Thank you for your assistance!

Name of the physician:……

Name of the Centre / Hospital:……

In the first column (total patients followed), please include all patients that were seen in your centre in 2008, regardless of treatment.

1. For Primary Immune Deficiencies (PID) treated in your centre in 2008

If this information is not available for 2008, please provide data from other periods and specify.

Treatment with intravenous immunoglobulins

Indications	Total number patients followed in your centre	Number of IG perfusions administered in 2008	Average dose per perfusion in g/kg (or usual dose)
PID in adults			
PID in children			

Comments:……

Treatment with subcutaneous immunoglobulins

Indications	Total number patients followed in your centre	Number of IG perfusions prescribed in 2008	Average dose per perfusion in g/kg (or usual dose)
PID in adults			
PID in children			

Comments:……

For other immune deficiencies treated in your centre in 2008 with intravenous IG

Indications	Total number patients followed	Number IVIG treatments given in 2008	Average dose per treatment in g/kg (or usual dose)
Myeloma			
Chronic lymphocytic leukemia			
Prevention of infections in transplant			
Other immune deficiencies that required IG (please specify)			

Comments:……..

4. For other indications treated in your centre in 2008 with intravenous IG

Indications	Number IVIG treatments given in 2008	Average dose per treatment in g/kg (or usual dose)
Idiopathic thrombocytopenic purpura in children		
Idiopathic thrombocytopenic purpura in adults		
Guillain Barré syndrome		
Kawasaki syndrome		
Toxic shock syndrome		
Infections in neonates		
Others:……		

General comments:

Do you wish to receive the KCE report once published?
(it will also available be available on our website www.kce.fgov.be)

Thank you for your time!

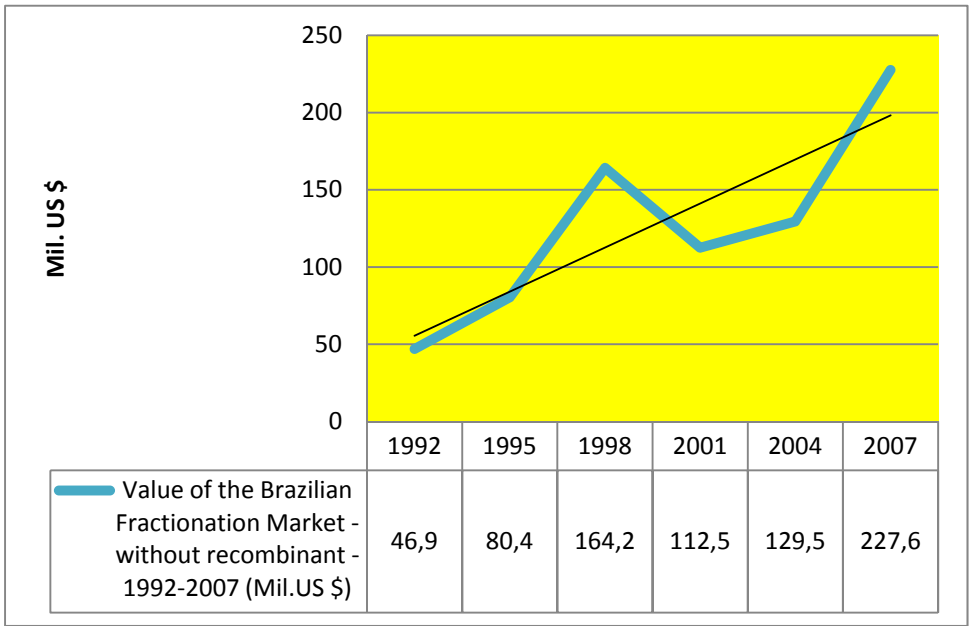
APPENDIX 5: POTENTIAL CHANGES IN DEMAND VOLUME: FOCUS ON TWO EMERGING COUNTRIES

FOCUS ON THE BRAZILIAN MARKET

Brazil's demand of plasma-derived products

In the early nineties, Brazilian plasma fractionation market was considered as a relatively minor one. However, due to the increasing demand of the population and the evolution of prescription habits, Brazil's demand for plasma products surged dramatically between 1992 and 2007, and more precisely over the last three years.

Figure 14: Value of the Brazilian Fractionation Market - without recombinant - 1992-2007 (Mil.US $)



Source: Marketing Research Bureau

On this market, and despite the surge of the population's needs and demand, no domestic company has emerged yet and Brazilian companies are virtually absent: in 2007, sixteen foreign companies (profit and non profit) fractioned and sold almost 100% of plasma products, and four of them hold key positions (Baxter, Octapharma, CSL-Behring, BPL) as described below :

Table 47: Key market Leaders in 2007

Brazilian Plasma Fractionation Market / Key Market leaders in 2007 ***(Percentage in total sales)***				
Baxter	Octapharma	CSL-Behring	BPL	Other companies
25%	23%	15%	10%	27%

As far as IVIG is concerned, Octapharma is clearly the market leader (market share of 42%).

Structure of this market is mainly centred on IVIG and Factor VIII (incl. recombinant), as described below:

Table 48: Structure of the Brazilian market in 2007

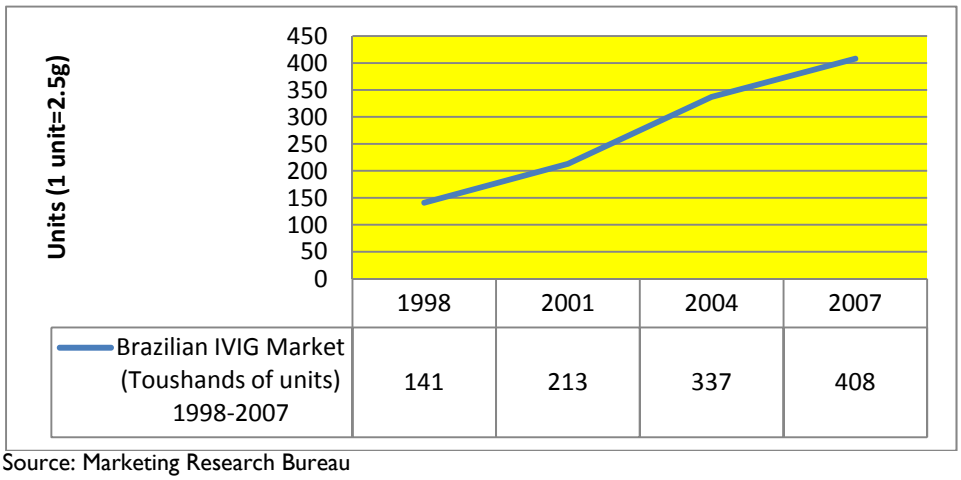
IVIG	Factor VIII	Albumin	Other
31%	20%	19%	30%

Focus : Intravenous Immune Globulin Market (IVIG) market

Within this market, IVIG demand has raised dramatically since 2001, as described below.

The slower increase of demand between 2004 and 2007 (+21%) is mainly due to a political problem (see below). This very last figure of the table should not be representative of further development of the Brazilian market.

Figure 15: Brazilian IVIG Market (Toushands of units) 1998-2007



Source: Marketing Research Bureau

Further foreseeable developments on the Brazilian market

INSTITUTIONAL CONTEXT

Given Brazil's absence of self-sufficiency, the Brazilian Federal Government, but also several federate states (eg State of Rio-de-Janeiro, State of Sao Paolo, etc..) launched international public tenders, in order to fulfil the population's needs. Between 2003 and today some problems occurred in the supply of plasma products, mainly because of the 2003 scandal also known as the "vampire scandal" that brought corruption and illegal arrangements to light, especially between the key stakeholders of the plasma market mentioned above. Following this scandal fractionation contract that expired in 2004 was renewed in 2007 only. This interruption in plasma products supply slowed down the evolution of Brazilian demand, but this was, by definition, a punctual phenomenon.

Brazilian willing to reach some self-sufficiency is quite clear as it concluded an agreement with LFB to set up a fractionation plant in Brazil: a close and official partnership has been established between LFB and Brazilian state-controlled structure "Hemobras" to implement this project and rationalize the whole collection and supply chain.

As a practical matter, the objective of this project is to set up a fractionation plant in northern Brazil, with a view to producing plasma-derived products, made from Brazilian plasma, in order to bring additional volumes of plasma products and thus improve Brazil's situation in terms of self-sufficiency.

However, this project will require some time, and self-sufficiency remains a very long term objective, and the level of import of plasma-derived products is likely to remain high over the next years.

ECONOMIC CONTEXT

The sharp increase in the demand of such products as IVIG demand illustrates the evolution of prescription habits, but also the recent ability of Brazilian citizens to purchase these products, thanks to the improvement of the Brazilian economic situation. Should this economic trend remain stable over the next years, this evolution is likely to remain comparable for the next years.

CLINICAL PRACTICES

In comparison to the situation of west European countries and North America, consumption of IVIG per capita remains low: **5.7 g** per thousand people. Should Brazilian practices conform progressively to the western standards, this consumption would obviously evolve accordingly and thus have a noticeable impact on Brazilian demand.

FOCUS ON THE CHINESE MARKET

Recent restructuring of the Chinese plasma fractionation industry has led to a reduction of domestic production of plasma products, from 4.5 to 3 million liters in 2006. This cut down in Chinese production capacity has led to imports of Albumin and recombinant factor VIII. Import of other plasma-derived products remains banned, due to the specific Chinese regulation framework.

Clinical practices and coverage of medical expenditure are the main hindering factors for further development of the plasma market:

- Such pathologies as haemophilia remain under-diagnosed (1000 patients officially diagnosed ; theoretical number of patients around 100 000)
- Access to modern treatments (especially plasma products) remains difficult for the vas majority of the population for two reasons because of the absence or the lack of health care coverage and of the ban on import of most of plasma products. Therefore, many physicians still resort to cryoprecipitate, whole blood or even traditional medicine.

Chinese ban on import of plasma products and its impact on the market remains a hindering factor for import of a wide-range of plasma products except for recombinant Factor VIII and Albumin. Given the increased awareness of innovative therapy, and simultaneously domestic suppliers' difficulty to meet the Chinese population's actual needs, it is clear that China will continue to import these two factors, at least over the very next years. However today's Chinese legal framework, ie ban on import of IVIG is unlikely to change over the very next years.

APPENDIX 6: FRANCE: PLASMA COLLECTION WITHIN THE EFS

KEY FIGURES ON DONATION: TODAY'S SITUATION

The number of donors has reached 1.5 and the number of donations about 2.5 million (ie about 8000 donations daily in average). The blood collected in France has enabled to carry out treatment for 500 000 patients yearly.

From a political point of view, the main strengths of the system are

- The tradition of donation and republican public-spiritidness.
- The indisputable visibility of the EFS.

Conversely, the main limits of the system are

- The relatively week proportion of donors (around 4% of the overall population).
- The distribution of collection centres, which is largely a heritage of the past decades, but not always cost-efficient, considering today's financial constraints.

PRACTICAL ORGANISATION AND ACTUAL POLICIES: KEY POINTS

The website of the EFS is centralized on the national level, but with regional windows. All relevant information is available on the website, and On-line booking is also available and user-friendly. Field blood and plasma collection is comparable to other countries' practices, with 175 collection sites, fixed or mobile, distributed across the French territory, both in rural and urban areas.

However, mobile collection remains important compared to fixed collection points: for this reasons, the use of human resources and facilities is not optimized in some places.

Focus on young adults

Apart from traditional campaigns (comparable to other countries' campaigns) one of the key targets of the EFS has been to focus communication on the most relevant age groups, ie young people and young adults, who are apt to become future donors, and repeat donors.

Given the crucial importance of this age group (18-26), a national competition was launched in 2008-2009. The main originality of this competition was to get this age group involved into the designing and the field organization of campaigns. After completion of these campaigns, the EFS has organized an in-depth evaluation of these campaigns, and rewarded the best campaigns. Three different awards have been defined and awarded accordingly, based on the following subjects:

- **Creativity award**: the objective is to identify the most innovative campaign to raise students' awareness of donation.
- **Interactivity award**: the objective is to identify the campaign that resorted to widest range of media simultaneously (especially multimedia tools).
- **Pedagogy Award**: the objective is to identify the most didactic campaign, and simultaneously the most faithful to the EFS values: voluntary and unpaid dimensions of donation, quality and best practices, non-profit dimension of EFS, etc..

This first step campaign is now complete. A last mailing of documents will be launched between November 2009 and April 2010, in close cooperation with the French University canteens.

As far as private firms are concerned EFS documents (thematic documents, general information on donation and blood products, and one specific poster "More than colleagues …Blood Donors"..) can be downloaded free of charge from the EFS website. However, the EFS recently laid emphasis on SMEs (ie firms employing lesser than 500 employees): a specific mailing campaign has been launched, which addressed 50 000 SMEs nationwide. The EFS obtained a positive answer from 500 SMEs (ie 1% of the target). These SMEs' data and contact details have been entered onto the databases of the different branches of the EFS in order to organize close contacts and field cooperation in line with local priorities: Newsletter, routine information, etc…

Larger firms (above 500 employees) should be the next target of the communication campaign over the next months.

However, these efforts focus on blood donation in general and not on plasma donation specifically.

Information delivered to the donor

As in other EU countries, the EFS website provides with key information on governance and values of the EFS. It also provides technical information on the organization of blood / plasma donation in practice: On-line booking; Fixed collection centres and mobile collection.

Clinical information is also available about blood groups, donation types, and the key steps of blood processing.

French population's awareness of plasma donation

However, all information delivered to the donor remain very general and addresses whole blood and plasma donors alike. Plasmapheresis technique is mentioned on the website. However no specific emphasis is laid on that subject and no further information is provided on the technical and clinical dimensions of this technique.

This situation should draw stakeholders' attention, as only 60% of French people know that plasma can be donated: as demonstrated by a recent survey of Cerphi Association (Etude Cerphi – Troisième Edition – Donner son sang en France – Cécile Bazin & Jacques Malet – Mai 2006), [202] awareness of plasma donation and plasma donation techniques remains poor in France compared to other kinds of donations (whole blood but also platelets).

APPENDIX 7: GERMANY: PLASMA COLLECTION WITHIN THE GERMAN RED CROSS AND BY OTHER STAKEHOLDERS

PLASMA COLLECTION WITHIN THE FRAMEWORK OF THE GERMAN RED CROSS (DRK)

Selection, Follow-up and retention of donors

Age-group targets

In terms of target population people below 30 (and among them students and jobless people) are clearly the most important people to focus on for plasma donation, (see : Survey of Robert Koch Institute). The DRK has the contact details of all teachers working in relevant areas (ie sciences, biology) at its disposal. Hence, it has the possibility to contact them very easily. Specific material dedicated to high school pupils are:

- High School magazine: "*We are heroes*" focusing on key scientific information and on the civic dimension of blood donation.
- Experiment material: 6 different biology experiment packages on blood, blood functions, blood groups, etc...to be performed by pupils themselves in their classroom.
- 12 scientific leaflets on: immune system, clotting process, blood groups, etc..
- Illustrated charts and posters on the main blood-related subjects.

Practical follow-up of donors by the DRK

Once a donor is identified and selected, his/her data are entered onto the DRK database, and he/she is subject to:

- a precise personal data management (online updating system available)
- a specific and very regular administrative follow-up: regular chasing of the donors is performed by E-mail, Mailings, regular phone recruiting.

Focus: key messages of the advertising and communication campaign

- No involvement of celebrities in the campaign: "No show-off models" is the first statement put forward on the website of the DRK. DRK's campaign focused on ordinary people, real life situations, and real world objects.
- Everyday life products and situations: the key messages first focus on the concept of shortage of renewable products and the trouble caused by this shortage, eg: the end of a toothpaste tube, the last match of the matchbox, the last drops of ink from a cartridge.

Contrast between consumer products and blood (and blood products): For each of the concerned products, the message clearly refers to the possibility of buying the product easily and quickly (eg: "You will find ink cartridges in shops. But not blood". Donate Blood / See below). By contrast with these products, specific nature of blood is clearly underlined, and thus the irreplaceable nature of blood donation.

Figure 16 :"Ink cartridge" Posters

Source: German Red Cross Website

- Connection between nature of blood and irreplaceable nature of blood donation

Tone of the campaign: direct commands. One must underline that "Spende Blut" means "Give Blood" with informal "you".

Targeting the donors' social life: important to stress is the ability of to stick to the specific traits of German social and cultural life. The DRK deliberately targeted students in its campaign and selected a "Stammtisch Picture" on one of its posters, to attract potential student donors. Note: The Stammtisch is an old tradition in German universities: debates on a wide range of subjects (literary, philosophical, or political).

The slogan is "You will find philosophers everywhere. Not Blood. Donate Blood!"

Figure 17: "Stammtisch" Poster

Source: German Red Cross Website

COLLECTION BY OTHER STAKEHOLDERS

Whole Blood collection in Germany

Table 49: Whole blood collection in Germany

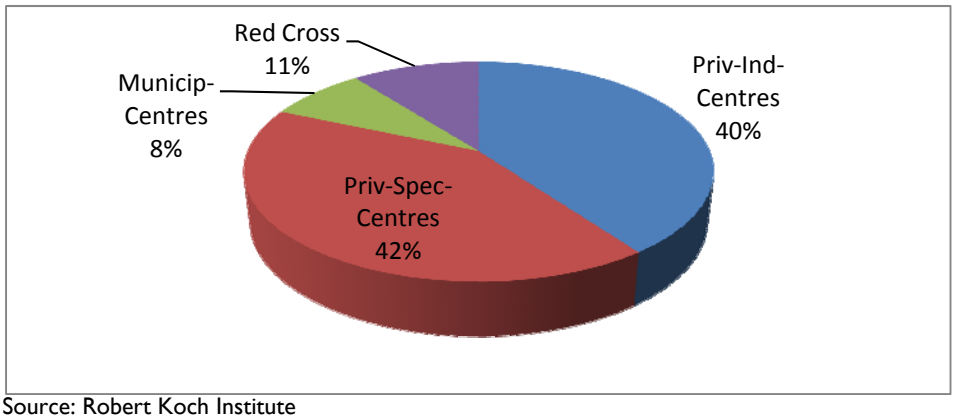
Institutions	Contribution / Total amount of whole blood donation
University Hospital – based Centres	15-20%
Red Cross	75-80%
Private Centres	***Ca 5% (increasing)***

Distribution of plasma collection in Germany: key role of the private sector

Public/Private sector: plasma repeat donors (2006 figures)

The overall number of plasma repeat donors was 128 000 in 2006 in Germany. Among them, 105 000 (ca 80%) stem from Private Industry driven and Private specialized centres.

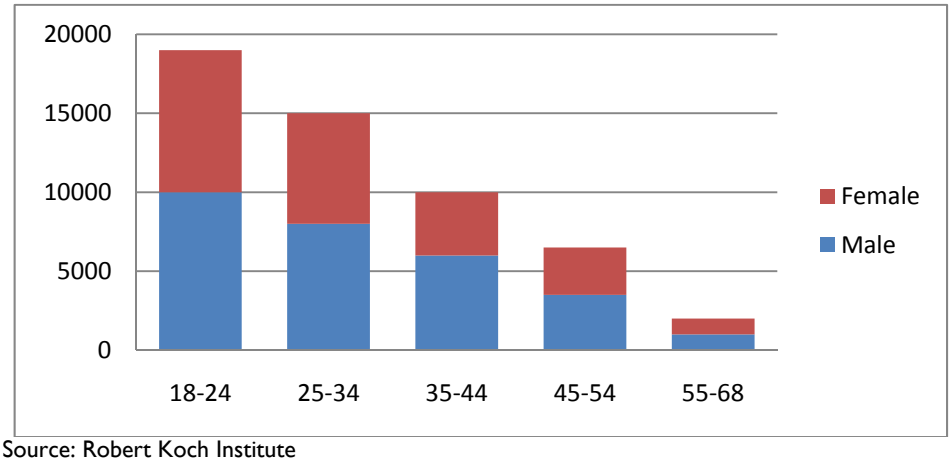
Figure 18: Plasma Collection in Germany / Repeat Donors



Source: Robert Koch Institute

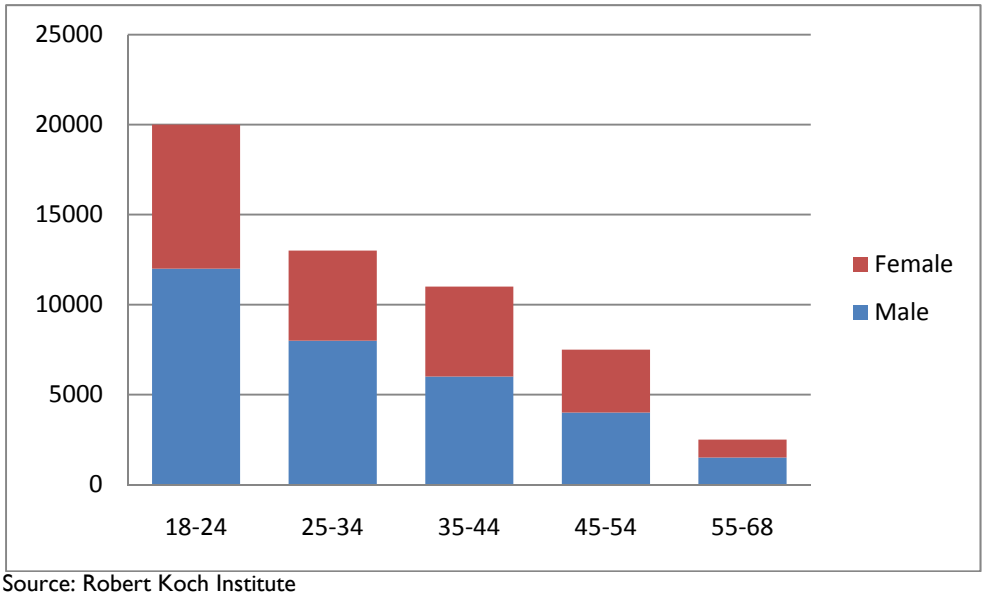
Age Profile of plasma repeat donors

Figure 19: Private Industry Centres / Repeat Donors - 2006



Source: Robert Koch Institute

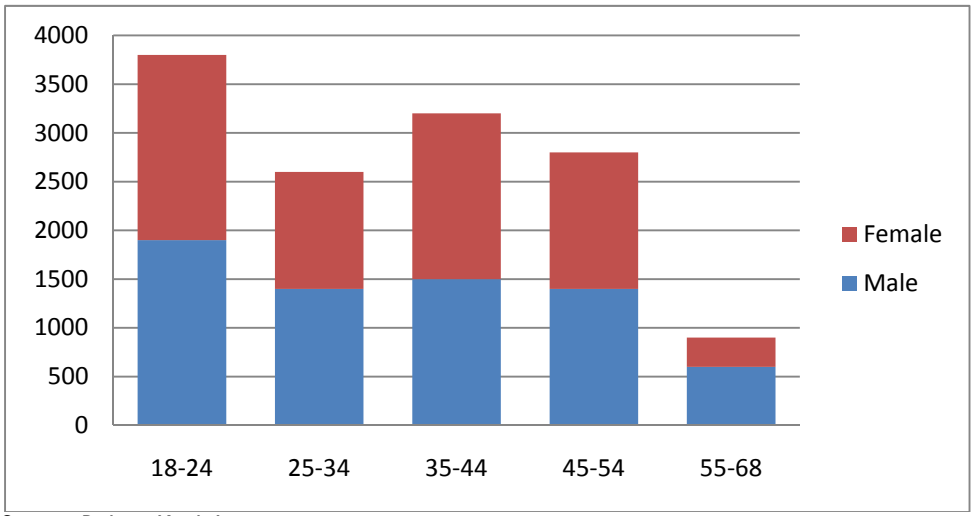
Figure 20: Private Spec. Centres / Repeat Donors 2006



Source: Robert Koch Institute

The age relationship described above has been clearly identified for private centres, but not for Municipal or Red Cross Centres. For the latter centres, age distribution is quite different and age relationship is much fuzzier, as mature people bring a noticeable contribution to donation.

Figure 21: German Red Cross Centres - Nb of Repeat Donors 2006



Source: Robert Koch Institute

Location of the private centres

Concerning plasmapheresis specifically, the German association of the plasma donation centres called Arge-Plasmapherese, founded 1997 (http://www.arge-plasmapherese.de/), delivers key information on that subject, especially on location of plasma centres:

- Location of Red Cross centres and Municipal centres is largely due to historical reasons. Red Cross and Municipal Centres are few and their distribution across Germany is relatively even.

- Conversely, location of private and industry centres has been selected on rentability-oriented criteria over the last years: rather under privileged regions: of the 60 private plasmapheresis centres registered in 32 are located in the ex- Democratic Republic of Germany, 14 in North Rhineland – Westphalia. In other words 75% of these centres are often located close to universities. It must be outlined that they are generally located in small / medium sized towns both for financial reasons (lower start-up costs for the centre itself) and for practical reasons **(**Faster penetration with marketing activities, Possibility to achieve full capacity in a shorter period of time).

Exemple of private plasma donation in Germany: Plasma Europe Service/ Biotest

Size of the town

Small towns are clearly privileged, and within each town, busy shopping streets and/or places close to university campuses and in any case easy to reach

Location of Plasma Service Centres: Which regions ?

All donation centres of this firm are located in the ex-German Democratic Republic or in North Rhineland – Westphalia (see Map below/ Source: Plasmaservice Website / www.plasmaservice.de)

Distribution of Plasma Service Europe Centres in Germany / Corporate Data

Other points on practical fitting out: Non hospital atmosphere, warm colours, Optimized distribution of beds across the donation room, Clear separation between donation rooms and manufacturing/freezing areas (restricted areas).

FINANCIAL COMPENSATION

Even within the same umbrella organization, the level of financial compensation may vary across centres. Within the organization we focused on, it ranges from 16 to 20 €.

Therefore, this compensation is not just a compensation but also part of costs management. Specific financial compensation is provided to first donors: 38€ in most centres.

TIME MANAGEMENT AND COST STRUCTURE

Tthe whole donation process (44 min) is divided into 4 steps

- *Step 1: Reception time*
- *Step 2: Medical interview*
- *Step 3: Donation in donat. room*
- *Step 4: Plasma processing and data collection*

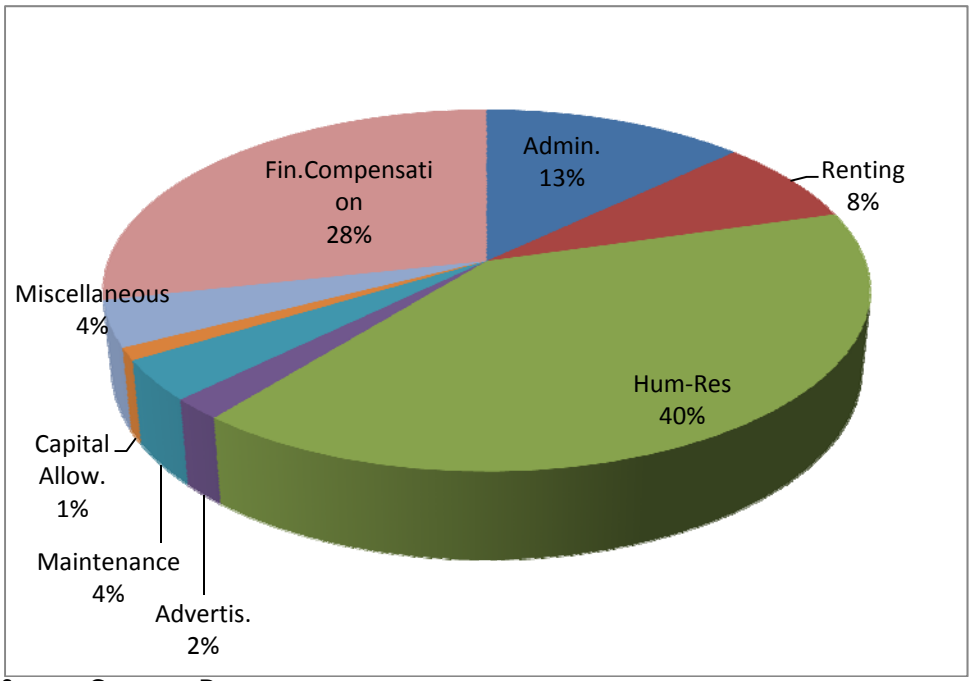
Cost Structure: see below

Table 50: Cost Structure / Plasma Service Europe

Budget Codes	Average Costs
Administrative Costs	4 €
Renting and side costs	4.10 € - 5.50 €
Personal / HR	23 – 28 €
Advertising	1.70 €
Maintenance Costs	2.30€
Capital Allowances	0.70€
Miscellaneous Expenses	2.60€
TOTAL	**40.40 € – 46.80 €**
FINANCIAL COMPENSATION	**16-20 €**
TOTAL COSTS	**56.40€ - 66.80€**

Smooth running of this industry implies a noticeable "investment" in financial compensation (28% of the costs) and Human Resources to recruit and retain donors. However, financial compensation does not prevent these centres from being financially profitable and sustainable.

Figure 22: Plasma Service Europe: Cost structure for plasma collection



Source : Corporate Data

APPENDIX 8: AUSTRALIA: INSTITUTIONAL ASPECTS

ROLE OF THE DIFFERENT STAKEHOLDERS IN AUSTRALIA

National Blood Authority

Overarching and steering institution in charge of the Australian National blood and plasma policy (see core report).

Australian Red Cross Blood Service (ARCBS)

The ARCBS is responsible for the collection of blood and plasma from donors and the distribution of fresh plasma and some imported plasma products, to the health system.

CSL Limited

This firm plays a key role in the supply chain, as it is responsible for fractionating the plasma supplied by the ARCBS and providing plasma products back to the ARCBS for further distribution. CSL Limited has to assume on many points public law obligations, as commissioned by the NBA (even if CSL is not a public law body).

Other pharmaceutical firms

More punctually, other firms can be responsible for the supply and distribution of specific range of products, whenever these products are not produced in Australia or when the Australian domestic capacity is not in the position to meet the patients' needs.

Therapeutic Goods Administration (TGA)

The TGA is an independent body that is responsible for regulating the whole sector in the field of efficacy, safety standards, and quality of blood and blood products. It is also entrusted with auditing of Good Manufacturing Practice and product recalls (see below / Contract between CSL and the NBA).

Health care professionals and suppliers

The latter stakeholders also play a role, even informally, in advising the NBA a number of formal or informal working groups and fora on technical subjects (eg: Professional Community Forum, NBA Fellows Program, and Clinical Advisory Council).

MANAGEMENT OF SUPPLY: QUICK OVERVIEW

On a routine basis, the NBA notifies the Australian Red Cross Blood Service annually of the volume of plasma to be supplied to CSL for fractionation. Under the terms of the Plasma Products Agreement (PPA), the NBA must give CSL the Annual Supply Estimate for a particular financial year by no later than the preceding 30 November. Although these forecasts are not binding on the NBA, it is required under the terms of the PPA to purchase 95% of the plasma products produced in accordance with the Confirmed Quarterly Requirements that the NBA furnishes to CSL six months in advance of each quarter. The NBA also needs to make sure that suppliers actually maintain reserve holdings of products, in order to ensure that timely and adequate supplies are available to meet clinical needs.

CRISIS AND RISK MANAGEMENT

One of the day-to-day, but also strategic objectives of the NBA is to enhance the resilience and the responsiveness of the whole sector. The latter aspect is of great importance for Australia, as a specific crisis-management framework has been defined by the NBA.

- Likelihood of a supply / demand crisis is identified by the NBA and entered onto a specific table [1: rare – 5: almost certain].
- Consequence of a crisis is also identified by the NBA and entered onto a specific table [1: Minor consequences / Buffer stock – 5: Catastrophe / Widespread national outage, Blood stocks below 24h].

Thanks to the combination of the two scales mentioned above, a **risk matrix** has been set up to assess the overall risk rate, ie the seriousness of the crisis. Following this risk assessment process, a specific framework has been set out to define preparation and mitigation of supply or demand crisis. The NBA has defined strategies to minimise the impact of such crises based on risk management plans in supply contracts, cooperation in supplier contingency planning, product reserves and contingent supply arrangements, promotion of best practice of blood and blood products and improvement in inventory management and reporting. Should these measures not be sufficient, further measures can be considered on the national level (Department of Health).

KEY SUCCESS FACTORS FOR A RELIABLE SUPPLY POLICY

- Providing the Australian governments (national and federate level) with accurate and timely information for decision-making.
- Close and day-to-day partnership with suppliers, with a view to addressing supply chain gaps.
- Close partnership with the clinical community to enhance the development of EB guidelines, standards, and programs for improving patient outcomes.

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