Dear Sirs,

The Immune Deficiency Foundation (IDF), Towson, Maryland, USA, would like to make a submission to the Expert Committee on the Selection and Use of Essential Medicines, on the need to retain Human Immunoglobulin on the World Health Organization’s essential drug list.

1. Summary statement of the proposal for inclusion, change or deletion

There are over 100 known Primary Immunodeficiency Diseases (PIDD). They are the result of genetic defects that involve the immune system and its responses. Presently, the exact genetic defect for each of the diseases is only known for a minority of the conditions. Definition of the precise molecular genetic defect is a prime area of global research. Affected individuals have abnormalities of cells or proteins of the immune system. The affected cells include B-cells that produce antibodies; T-Cells that coordinate the immune system’s responses; and leukocytes (white blood cells) that fight infections. In PIDD, some of the critical defective or missing proteins are immunoglobulins also known as gamma globulins, complement proteins, and blocking agents such as C1 Esterase Inhibitor.

Many individuals with genetic disorders of the immune system have a quantitative or qualitative defect in antibody production that leads to recurrent, poorly responsive, severe, or unusual infections. Affected individuals may also have autoimmune diseases and cancer as a result of their immune system abnormalities.

Immune deficiency should be suspected if a person of any age has more than one episode of pneumonia per decade (10 years) of life, chronic sinusitis requiring antibiotic therapy, chronic bronchitis without a history of smoking, increasing numbers of ear
infections after age two years, chronic diarrhea lasting weeks to months or recurrent bacteremia (blood stream infection). Infections may occur as frequently as every two to three months. These infections and frequencies give an indication of the seriousness of the clinical diseases and its impacts on patients.

Treatment with polyvalent immunoglobulin is essential because individuals with PIDD have lifelong conditions and are affected by serious and life threatening infections. There are no alternative therapies available. As indicated above, without immunoglobulin replacement, affected individuals are at risk for substantial morbidity and mortality from infectious diseases.

2. Name of the focal point in WHO supporting the application

WHO Division: Blood Transfusion Safety Team

Dr Neelam Dhingra – Acting Coordinator, Blood Transfusion Safety (BTS/EHT)

3. Name of the Organization consulted and or supporting the application

Immune Deficiency Foundation (IDF) and the IDF Medical Advisory Committee

4. International Nonproprietary Name (INN, generic name) of the medicine

19.2 Sera and immunoglobulins

<table>
<thead>
<tr>
<th>Polyvalent human immunoglobulins</th>
<th>Infusion 0.4 – 0.8 g/kg/month for life or until successful gene therapy or bonemarrow transplantation is performed</th>
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As indicated in the following paragraphs, immunoglobulin, human normal was removed from the essential medicines list in 2003.
**Medicines WITHDRAWN from the 13th Model list**

**immunoglobulin, human normal**

*Used in a variety of conditions as replacement therapy for patients who are immune deficient.*


*No reviews or randomized controlled trials found.*

(Cochrane Library: 2002 Issue 1)

(Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use)

(Limited indications or narrow spectrum of activity)

*Note: Deleted from the Model List of Essential Medicines, April 2003*

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested as a therapeutic group including immunoglobulin for intravenous, subcutaneous, and/or intramuscular use.

6. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Estimates of the true frequency of primary immunodeficiency diseases in the general population have been reported for several countries.

The registries used to determine these frequencies may actually underestimate the true prevalence of primary immunodeficiency diseases for several reasons:

- Lack of clinical recognition
- Lack of reporting to the registries
- Overrepresentation of certain referral centers
- Lack of a standardized case definition
- Death before disease state recognition

In sum, the overall estimated incidence of diagnosed primary immunodeficiency diseases has been reported as 1/10,000 persons.


This incidence is consistent with the definition of an Orphan (Rare) Disease in the United States of fewer than 200,000 affected individuals. (1/10,000 of 294,000,000 inhabitants = 29,400 individuals with primary immunodeficiency diseases). Similar definitions are met for the EU. If rare diseases such as primary immunodeficiency diseases were excluded from public funding 1 in 10 people would be deprived of essential treatments because their disease is not "prevalent" enough. Those affected by rare diseases may encounter difficulty with diagnosis and not have access to health care provider expertise for treatment decision-making.

7. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)
In the US, approximately 67% of affected individuals systematically surveyed by the IDF in 2002 were treated with immunoglobulin as the centerpiece of their regimen. 

(Second National Survey of Patients with Primary Immune Deficiency Diseases - over 1,500 patients with primary immune deficiency diseases completed a four-page, self-administered questionnaire). 13% of prior users have stopped use of immunoglobulin generally due to financial problems, not disease improvement. Nearly seventy percent of individuals with primary immunodeficiency diseases perceive their own health as good, very good, or excellent with the use of immunoglobulin.

Self-Assessment of Overall Health Status

Immunoglobulin is used by patients with many of the primary immunodeficiency diagnoses in the US. As expected, over 90% of the “agamma” and over 80% of the SCID and Hyper IgM patients are treated with immunoglobulin.

Current Use of IGIV By Diagnosis
Patients are typically infused every three or four weeks in the US according to the IDF 2002 Survey. However, some are infused as frequently as every two weeks in an effort to maintain plasma immunoglobulin trough levels. Typical lifelong dose ranges are from 0.4 to 0.8 g/kg/month. Approximately 40% of those surveyed by the IDF are infused in the home, generally by medically trained nursing personnel.

**Scientific Literature supporting the use of immunoglobulin therapy:**
Several investigators, over the last 20 years, have determined the benefits of the use of immunoglobulin therapy in individuals with primary immune deficiency diseases:
Treatment facilities and skills required

Through the International Patient Organisation for Patients with Primary Immunodeficiencies (IPOPI) and the World Immunodeficiency Network (WIN) of the Jeffrey Modell Foundation, National Member Organizations have been created in North America, Latin America, Europe, the Middle East, Australia, and Asia. These organizations help identify regional health care providers who have adequate knowledge of the treatment of primary immunodeficiency diseases including the use of immunoglobulin.

Therefore, if immunoglobulin, human, is available, the facilities for diagnosis and the skills to provide treatment are already in place in many parts of the world.

Treatment Guidelines:

Information on practice parameters followed in the United States is presented.

The Joint Council of Allergy & Immunology was established in May, 1975, as the socio-economic/political arm of the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology. JCAAI's purpose is to provide a mechanism for keeping allergists/immunologists abreast of the critical socio-economic issues which impact upon their practices. The JCAAI represents allergy/immunology in federal and state regulatory and governmental agencies, the Congress, in areas of reimbursement, and in other socio-economic areas where appropriate. JCAAI serves as a single voice in these areas representing the specialty of allergy/immunology.

The JCAAI represents approximately 4200 allergists.

The JCAAI has developed and distributed practice parameters for the use of immunoglobulin, human. The parameters follow. Section III is especially relevant to the deliberations of the WHO. The Panel Members writing the document are listed at the end of the parameters.

### Humoral Immunodeficiency

#### Practice Parameters

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>ICD-9 CODE NO.</th>
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<tbody>
<tr>
<td>Bruton X-linked agammaglobulinemia</td>
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</tr>
<tr>
<td>Dysgammaglobulinemia</td>
<td>279.06</td>
</tr>
<tr>
<td>Gamma globulin deficiency in blood</td>
<td>279.00</td>
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<td>Humoral deficiencies</td>
<td>279.00</td>
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<tr>
<td>IgA</td>
<td>279.01</td>
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</table>

IDF Essential Medicines Submission - Immunoglobulin
Diagnosis and Evaluation

I. Clinical Evaluation of Immunodeficiency

It should be recognized that:

- Congenital immunodeficiency usually (but not always) has a characteristic appearance in infants, children, and adults according to the sex of the child, age of the patient, immunization history with live vaccines, and exposure to infections.
- Recurrent, serious infection, especially with encapsulated organisms is the hallmark of humoral immunodeficiency.
- Family history, particularly of affected males, is extremely important in the diagnosis of immunodeficiency.
- Physical examination of the patient is essential with attention to failure-to-thrive, weight loss, enlargement or absence of lymph nodes, organomegaly, dermatitis, oral candidiasis, short stature, clubbing, and listlessness.

II. Specific Diagnostic Techniques

It should be recognized that:

- Evaluation of humoral immunodeficiency requires age-matched laboratory controls.
- A complete blood count with morphologic review should be performed.
- Serum immunoglobulin measurements alone may not establish a diagnosis of immunodeficiency.
- Serum isohemagglutinin titer is a useful screening test for antibody function in infants and children even as early as 4 to 6 months of age.
- A sweat chloride determination should be performed in children with recurrent sinopulmonary infections.
- Consideration should be given to performing tests for HIV infection.
- Specific antibody deficiency is the sine qua non of diagnosing humoral immune deficiency as based upon pre- and post-immunization antibody responses.
- Measurement of IgG subclasses should not be used as a screening test and may not yield any more useful information than the total serum IgG level.

III. Management of Humoral Immune Deficiencies

It should be recognized that:

- Intravenous immunoglobulin (IVIG) replacement therapy should only be given to patients with specific antibody deficiency involving IgG.
- IVIG therapy for patients with normal humoral immunity but recurrent infections, particularly upper respiratory infections, has no scientific rationale.
• IVIG replacement therapy should be initiated with a dose of 200 to 400 mg/kg/3 to 4 wk in most circumstances; adjustment to higher doses and shorter intervals may benefit some patients.
• IVIG replacement therapy in humoral immunodeficient patients is usually life-long.
• Concomitant therapy with systemic antibiotics is necessary in patients receiving IVIG who develop infections, such as chronic lung and sinus disease.
• Avoidance of live viral vaccines is mandatory in patients with complete absence of serum immunoglobulins.
• Patient/parent education and genetic counseling are essential for adjustment of the patient to a chronic disease.

IV. Special Considerations

It should be recognized that:

• It is important to determine what type of agammaglobulinemia is present in a patient.
• The carrier state of females with some X-linked forms of humoral immunodeficiency can now be determined.
• Prenatal diagnosis of some forms of humoral immune deficiency can now be accomplished, giving parents information on reproductive choices.
• The advent of gene therapy for newly discovered molecular lesions in humoral immunodeficiencies may revolutionize patient management in the future.

V. The Immunologist as Consultant

It should be realized that:

• Patients with recurrent infections should be considered for referral to an allergist/immunologist for evaluation of humoral immunodeficiency.
• The allergist/immunologist has special expertise in evaluating, diagnosing, and managing patients with humoral immune defects.
• Because humoral immune defects are a form of chronic disease, communication and follow-up consultation on a continuing basis between the referring physician and the allergist/immunologist is essential.
• In certain circumstances the allergist/immunologist and the primary care physician will need to consult specialists in otorhinolaryngology, infectious diseases, metabolism, hematology/oncology, pulmonology, rheumatology, gastroenterology, surgery, and other fields.
In addition, in 1990, the US National Institutes of Health (NIH) conducted a Consensus Development Conference on Intravenous Immunoglobulin: Prevention and Treatment of Disease. Panelists were asked:

**What Are the Data To Support the Efficacy of IVIG in These Circumstances?**

**Response for the Primary Immunodeficiencies:**

The beneficial effects of intramuscular (IM) injection of immune globulin (IG) in the prophylactic treatment of patients with primary immunodeficiency syndromes have been well established. Early studies based on small sample sizes have indicated that almost any desired blood level of IgG can be obtained by use of intravenous immunoglobulin and that infection rates are reduced by use of IVIG as compared with IM IG. IVIG has been shown to ameliorate chronic sinopulmonary disease that developed in patients on long-term IM IG. There is a suggestion that chronic enterovirus meningoencephalitis in patients with X-linked agammaglobulinemia may be less frequent in those receiving prophylactic IVIG as compared with historical data in which IM IG was used. Hence, IVIG has become the current standard in clinical practice for replacement therapy of patients with primary immunodeficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency and immunoglobulin subclass deficiency in which deficiencies of antibody production to common pathogens can be demonstrated). Studies have shown that maintenance of a trough level of 500 mg/dL is beneficial. Dose ranges of 200-800 mg/kg/month have been shown to be effective, but dose or frequency of infusions must be tailored to the individual patient, because half-life of infused IVIG varies widely.

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SPEAKERS IN ATTENDANCE COMMENTING ON PRIMARY IMMUNODEFICIENCY AND IGIV:

Charlotte Cunningham-Rundles, M.D., Ph.D.
"Intravenous Immunoglobulin: Development as a Therapy and Unresolved Issues"
Associate Professor
Department of Pediatrics and Medicine
Mt. Sinai Medical Center
New York, New York

Erwin W. Gelfand, M.D.
"Dosing Regimens for Replacement Therapy in Primary/Secondary Antibody Deficiency"
Chairman
Department of Pediatrics
Professor
Pediatrics, Microbiology and Immunology
National Jewish Center for Immunology and Respiratory Medicine
Denver, Colorado

Hans D. Ochs, M.D.
"Intravenous Immunoglobulin (IVIG) in Primary Immunodeficiencies"
Professor
Department of Pediatrics
University of Washington School of Medicine
Seattle, Washington

Fred S. Rosen, M.D.
"Overview of Issues"
Director
Center for Blood Research
Boston, Massachusetts

William T. Shearer, M.D., Ph.D.
"Review of Clinical Trials in the Literature"
Professor of Pediatrics
Baylor College of Medicine
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8. Summary of comparative effectiveness in a variety of clinical settings:
US licensure trials have recently been completed for three immunoglobulin products. These trials included important safety and efficacy information that confirm the overall and specific utility of human immunoglobulins.

- Roifman CM, Schroeder H, Berger M, et al. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency. Intl Immunopharm 3;2003:1325-1333.

172 subjects were evaluated over nine months. The annual validated infection rate in the IGIV-C group was 0.18 compared to 0.43 in the IGIV-SD (solvent detergent) group. Adverse reactions were similar in frequency and severity in both groups. No evidence of viral transmission was observed.


46 subjects were studied for 12 months. The estimated serious infection rate was 0.1 per subject per year. Adverse events potentially related to Octagam® occurred in 5% of infusions. There was no evidence of viral transmission during the trial.


51 subjects were treated at seven clinical sites. The serious infection rate for the intent-to-treat population was 0.061 per subject per year. The incidence of adverse events potentially related to Flebogamma® 5% was approximately 8%. Several secondary variables were assessed. Study subjects missed an average of 6.24 days/subject year compared to 8.5 days/subject year for the general US population. Study subjects experienced 1.1 mean days of hospitalization/subject year compared to 4.9 for the general US population. Emergency room or unscheduled physician visits were similar for the research subjects, 3.9, and the general US population, 3.1.
9. Summary of comparative evidence on safety:

- Estimate of total patient exposure to date
- Description of adverse effects/reactions
- Identification of variation in safety due to health systems and patient factors
- Summary of comparative safety against comparators

Immunoglobulins have been used for antibody replacement therapy in primary immune deficiency diseases for over fifty years. Tens of thousands of patients have been treated. In the US, patients with primary immune deficiency diseases use approximately 6000 kilograms of IGIV. At an average dose of 0.4 g/kg/month this equates to nearly 20,000 patients being infused with IGIV.

Adverse events are well characterized and consist of chills, headache, fever, nausea, back pain and muscle pains all of which may be related to the speed of infusion. Some individuals receive antihistamines, antipyretics, or anti-inflammatory agents prior to infusions to reduce the incidence or severity of reactions. In addition to these generally milder adverse events, there are well described more serious reports. These include an aseptic meningitis syndrome, renal failure, and possibly TRALI (Transfusion Related Acute Lung Injury Syndrome).

Viral transmissions were described for hepatitis C in certain IGIV products in the early 1990’s.


Since that time, all IGIV products have included dedicated viral inactivation steps such as solvent/detergent treatment or pasteurization in the manufacturing process. There has never been a report of HIV-1 transmission by IGIV. All products are currently regarded as safe regarding Hepatitis C and Hepatitis B.


There is no comparator for immunoglobulin in the management of those with primary immune deficiency diseases. Plasma could be administered, but would contain only the antibodies derived from a very small number of people, probably insufficient to offer the immunodeficient patient the protection they require against a broad menu of pathogens. In addition, plasma does not undergo dedicated, validated, effective viral inactivation steps creating an unnecessary risk for the recipients.
The safety of plasma-derived immunoglobulin has dramatically improved, so that no transmission of HBV, HCV or HIV has been documented since the adoption of virucidal measures.

**Need to retain immunoglobulin products on the essential drug list:**

Fewer available products in the developing world will lead to an increased number of deaths and disabilities because of:

1) The unavailability of products to prevent life threatening infectious disease episodes; and
2) The replacement of safe products with unsafe local plasma or by IGIV products manufactured using lower quality plasma obtained from less reliable sources

10. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

- range of costs of the proposed medicine
- comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

**General Information on Immunoglobulin:**

It has been estimated that the cost per quality adjusted life year is $50,000. This is roughly equivalent to $4/mL of product. In the US, IGIV products are sold for prices that range from the $30 to $50+ /gram.

11. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Immunoglobulin is licensed in countries on all continents except Antarctica.


The United States Pharmacopoeia recognizes immune globulin, intramuscular and has monographs on the specific, intramuscular immune globulins.

These products are registered and listed in the pharmacopoeia’s of most countries in the world and are approved by the United States Food and Drug Administration
13. Proposed (new/adapted) text for the WHO Model Formulary

Polyvalent human immunoglobulin is used as prophylactic protection against infection in patients with primary immunodeficiencies. Immunoglobulin therapy is lifelong and prevents mortality and morbidity from serious infections in those with proven antibody deficiency.

We submit that polyvalent human immunoglobulins should remain on the WHO Essential Drug List for the following reasons:

1. The primary immune deficiency diseases are rare diseases.
2. A combination of locally available experts and laboratory tests are found in many countries and are adequate to make a proper diagnosis in many circumstances.
3. Knowledgeable practitioners are located in countries throughout the world.
4. Immunoglobulins have a documented record of efficacy and are life saving and life improving in many clinical situations
5. Viral inactivated and purified immunoglobulins have documented safety records.
6. Reliance on less pure preparations such as plasma or intramuscular immunoglobulins could respectively increase the risk of viral transmissions to persons with primary immune deficiency diseases or not achieve adequate blood levels of immunoglobulin to prevent infections.
7. Individuals affected by a primary immune deficiency disease may benefit through the use of immunoglobulins, obtained at an ‘affordable’ cost (perhaps through a well organized and competitive national tender). Use of these immunoglobulins may increase survival rates, decrease numbers and types of infections and, increase functional independence and eliminate the risk of death or injury from transfusion transmitted viruses.
8. Governments rely on WHO recommendations. Therefore if immunoglobulins are reinstated to the essential medicines list it will help National Member Organizations of IPOPI and WIN ensure that National Health Departments make some provision in their budgets for primary immune deficiency disease.
9. Funding of immunoglobulins for the treatment of primary immune deficiency disease may help governments put in place national primary immune deficiency programs. The expertise of the medical team brought together and augmented by such a program can be used within the country to improve treatment for the less common primary immunodeficiency diseases and provide a model for the effective treatment of a series of genetic diseases.