

Guidance for Industry

Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency

DRAFT GUIDANCE

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For questions on the content of this guidance, contact the Division of Blood Applications, at 301-827-3543 (fax: 301-827-3534).

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Paperwork Reduction Act of 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in this guidance were approved under OMB control no. 0910-0338.

Contains Nonbinding Recommendations

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Table of Contents

I.....INTRODUCTION1

II.BACKGROUND1

III.....RECOMMENDATIONS ON GENERAL PRINCIPLES CONCERNING
CLINICAL TRIAL DESIGN TO EVALUATE SAFETY, EFFICACY,
AND PHARMACOKINETICS OF INVESTIGATIONAL IGIV
PRODUCTS AS REPLACEMENT THERAPY IN PRIMARY HUMORAL
IMMUNODEFICIENCY2

A. Safety2

 1. General Principles Pertaining to Safety 2

 2. Guidance for Evaluation of Safety 2

B. Efficacy.....5

 1. General Principles Pertaining to Efficacy 5

 2. Guidance for Evaluation of Efficacy 6

C. Guidance for Pharmacokinetic Studies of IGIV7

Appendix A.9

Contains Nonbinding Recommendations

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance document provides the recommendations of the Food and Drug Administration (FDA) for testing the safety and efficacy of Immune Globulin Intravenous (Human) (IGIV) products as replacement therapy in primary humoral immunodeficiency. The document provides guidance on general principles concerning clinical trial design to evaluate safety, efficacy, and pharmacokinetics (PK) of investigational IGIV products. This is the first draft guidance document that we, the Center for Biologics Evaluation and Research, FDA, have issued on this topic. This guidance does not address evidence of clinical efficacy for other indications, or other sections of BLAs such as chemistry, manufacturing, and controls (CMC) and preclinical toxicology. We may develop additional guidance to address these areas in the future.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Polyclonal immune globulin preparations of human origin, including IGIV, have long been used as replacement therapy in patients with humoral immunodeficiencies. IGIV products are prepared from large pools of plasma collected from large numbers of individual healthy donors, and therefore contain antibodies against many bacterial, viral, and other infectious agents. We have licensed several IGIV products. To date, all licensed IGIV products carry an FDA approved indication for use in primary humoral immunodeficiency, while some of the products have additional indications, such as elevation of platelet counts to prevent and/or control bleeding in immune/idiopathic thrombocytopenic purpura (ITP).

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At the FDA Blood Products Advisory Committee (BPAC) meeting held in March, 1999, we presented a preliminary summary of a recommended clinical trial design for a pivotal trial designed to evaluate the safety and efficacy of a new IGIV product. The design involved a prospective, randomized, double-blind, parallel, positive control, non-inferiority study in 80 subjects with a documented history of primary immune deficiency, in which the safety and efficacy of the test product was to be compared head-to-head to a U.S.-licensed IGIV product. IND sponsors would evaluate efficacy by comparing the serious infection rate in each randomization group over an observation period of 12 months.

Since the March 1999 BPAC meeting, we came to recognize that alternative clinical trial design proposals involving testing in smaller numbers of subjects with primary immune deficiency might be sufficient to provide evidence of safety and efficacy. At the March, 2000 BPAC meeting, we presented an alternate approach to clinical trial design to evaluate IGIV safety and efficacy in primary immune deficiency, and we describe a similar approach below. Other approaches may also satisfy applicable requirements.

Other FDA guidance documents contain helpful information for you, the IND sponsor, to consider as you prepare license applications for biologic products. These documents are available on the FDA website: <http://www.fda.gov/cber/guidelines.htm>.

III. RECOMMENDATIONS ON GENERAL PRINCIPLES CONCERNING CLINICAL TRIAL DESIGN TO EVALUATE SAFETY, EFFICACY, AND PHARMACOKINETICS OF INVESTIGATIONAL IGIV PRODUCTS AS REPLACEMENT THERAPY IN PRIMARY HUMORAL IMMUNODEFICIENCY

A. Safety

1. General Principles Pertaining to Safety

Historically, the observed incidence of adverse experiences reported to occur in clinical trials of IGIV products has varied widely, both by product and according to the patient population/indication being studied. However, the proportion of infusions in a clinical trial population for which one or more adverse experiences has been reported to occur in association with the infusion(s) has seldom been reported to exceed approximately 0.20.

2. Guidance for Evaluation of Safety

- We evaluate product safety on the totality of pertinent safety findings and analyses.

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- For purposes of this guidance, an adverse experience (AE) is an adverse experience associated with the use of the IGIV, whether or not the adverse experience is determined to be product related.
- Under 21 CFR § 312.32(a), a serious adverse drug experience (SAE) is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- It is important for protocols to define and capture all AEs associated with the use of the product, regardless of the investigator's opinion regarding whether the AE is product related. Where appropriate, analyses of AEs should take into account the observed intra-subject correlation of the same type or any type of AE, as such within-subject events may be non-independent.
- Your protocol should define criteria for establishing an AE as an infusional AE (i.e., an AE temporally associated with an infusion). We recommend you list AEs individually by body system with subject identification numbers and report the overall incidences of all AEs that occur during or within (a) 1 hour, (b) 24 hours, and (c) 48 hours following an infusion of test product, regardless of other factors that may impact a possible causal association with product administration.
- One safety endpoint for clinical trials of IGIV should consist of the observed proportion of infusions with one or more temporally-associated AEs (including AEs that you or you investigator determine not to be product related). We believe that an appropriate target for this safety endpoint is an upper one-sided 95% confidence limit of less than 0.40. It may be appropriate to modify this target as experience with various IGIV products further increases.

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- Your protocols should provide explicit directions for starting and raising/adjusting infusion rates, including the timeframes for incremental changes and the size of infusion rate increments. A forced titration schedule may be appropriate, with explicit provision for downward adjustment of the infusion rate, or temporary or permanent cessation of the infusion, depending on the nature and/or severity of temporally associated (infusional) adverse events. Protocols should provide for the systematic evaluation of AEs as a function of infusion rate. According to the literature, the intensity (severity) of many AEs associated with infusion of IGIV is dependent on the rate of infusion.
- For adverse events that occur during infusion, it is important that the protocol and the case report form are designed to capture (1) the infusion rate in effect at the time of onset of adverse events; (2) the time AEs are first reported; and (3) the time AEs change materially in intensity and/or resolve.
- We consider the use of subject diaries kept in “real time” to be important source documents for the complete collection of AE data. Your study report should clearly distinguish data abstracted from subject diaries from data corresponding to the same data fields, but documented solely on the case report forms (CRFs). You should provide an explanation for any discrepancies between subject diary entries and CRF entries made by the clinical investigator, sub-investigators, or his/her designee(s).
- We discourage the use of premedication in clinical trials designed to evaluate the safety of biologic products, except in cases where such premedication is important to safety of the trial subjects. In such instances, it is appropriate to record the use of any premedications and their possible impact on the study data and evaluate their possible impact in the final study report.
- We recommend that your final study report include:
 - For each subject and for the study as a whole, the number of infusions administered, the total number of AEs reported at any time during the study (including AEs that you or the investigator determine were not product related), the number of AEs temporally associated with infusions, and the number and percentage of infusions temporally associated with one or more AEs. For adverse events that occur during infusion, you should report and analyze (1) the infusion rate in effect at the time of onset of adverse events; (2) the time AEs are first reported; and (3) the time

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AEs change materially in intensity and/or resolve. Listings of SAEs, AEs by severity, AEs by body system, and your determination of which AEs were product related, and which were not, are important to our review.

- The proportion of infusions administered to subjects for which “infusional” AEs have been reported.
- The proportion of subjects who experience one or more AEs at any time during the course of the trial.
- Listings of AEs as following the most recent infusion of the investigational product, described by its appropriate ordinal number (for example, following the first infusion, second infusion, third . . .). The listings should include separate reports of all AEs and of AEs judged by investigators to be associated with the infusion of the product, even if you determine the AE not to be product related. You are encouraged to include in the protocol criteria or guidelines for the causality assessment of all AEs, whether temporally associated with infusion(s) or not.

B. Efficacy

1. General Principles Pertaining to Efficacy

Historically, IGIV products have been used to reduce the frequency of serious bacterial infections in patients with primary humoral immunodeficiency. To evaluate the efficacy of an investigational IGIV, we recommend that clinical trials compare the frequency of serious bacterial infections during a period of regular administration of the test product to a historically based standard.

The available literature suggests that prior to the routine institution of immunoglobulin replacement therapy, patients with hypo/agammaglobulinemia due to primary immune deficiency experienced approximately four serious acute bacterial infections per year. That number contrasts with an observed serious infection frequency of less than 0.5 per year during periods of regular (generally every 3-4 weeks) administration of IGIV, 200-600 mg/kg per infusion. The available data do not permit identification of a target trough (pre-next-dose) total and/or specific blood immunoglobulin level, which, if achieved and maintained, would insure optimal protection from the risk of serious bacterial infection.

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2. Guidance for Evaluation of Efficacy

- We recommend that you measure the rate of serious bacterial infections during regularly repeated administration of the investigational IGIV product for 12 months (to avoid seasonal biases) and compare the observed infection rate to a relevant historical standard.
- We recommend that the protocol prospectively provide specific diagnostic criteria for each type of serious infection to be included in the primary efficacy analysis (e.g., rate of serious infections). Diagnostic criteria should not be overly restrictive, so that you capture all infections of interest. Clinical investigators at different sites should use uniform diagnostic criteria. The table found in Appendix A outlines diagnostic criteria for the types of serious infections to include in the analysis. Each of the serious infection types listed in the table in Appendix A should be included in the overall serious infection rate.
- The protocol should prospectively define the study analyses. We expect that the data analyses presented in the BLA will be consistent with the analytical plan submitted to the IND. Based on our examination of historical data, we believe that a statistical demonstration of a serious infection rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy. You may test the null hypothesis that the serious infection rate is greater than or equal to 1.0 per person-year at the 0.01 level of significance, or, equivalently, the upper one-sided 99% confidence limit would be less than 1.0.
- We recommend that you provide in the BLA descriptive statistics for the number of serious infection episodes per person-year during the period of study observation. A frequency table giving the number of subjects with 0, 1, 2... serious infections, a description of each serious infection, as well as summary statistics for the length of observation of each subject, contains information important to our review.
- You should employ a sufficient number of subjects to provide at least 80% power with one-sided hypothesis testing and an $\alpha = 0.01$. Although the responsibility for choosing the sample size rests with you, the sponsor, we anticipate that studies employing a total of approximately 40 to 50 subjects would generally prove adequate to achieve the requisite statistical power, given the design specifications listed above. When describing your statistical plan, we recommend that you pay particular attention to how you will take into account the observed intra-subject correlation of serious acute infection events because such within-subject events may not be independent.

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- We recommend that you obtain and analyze secondary endpoints, including candidate surrogate efficacy endpoints. Secondary endpoints would normally include trough total Immunoglobulin G (IgG) and specific antibody levels, all infections of any kind/seriousness, antibiotic treatment (oral, parenteral, oral plus parenteral, prophylactic, and therapeutic), hospitalizations due to infection, days lost from school and/or work due to infections and their treatment, and episodes of fever. You should prospectively define these secondary endpoints and their corresponding statistical analyses in the study protocol.

C. Guidance for Pharmacokinetic Studies of IGIV

We recommend that you submit PK data in each BLA to describe the absorption, distribution, metabolism and elimination of immune globulin products. These data will provide a basis for historical comparison between the investigational immune globulin product and licensed immune globulins, as well as help determine the optimum dosing schedule for the product.

We recommend that you obtain PK data from at least 20 patients with primary immune deficiency (either previously untreated or previously treated patients). PK parameters should be calculated for the overall PK study subject cohort, as well as for subgroups according to IGIV infusion dosing schedule (e.g., subjects dosed every 3 versus every 4 weeks). You may obtain the data as part of the Phase 3 clinical trials conducted to establish efficacy and safety. Suitable PK studies can be single arm studies based on historical data or they can be either crossover or parallel studies if you choose to include a licensed product arm as a positive control. If you use the historical control approach, your PK study should be part of a single arm 12-month phase 3 study in which the following measurements should be included:

- The steady-state trough total IgG and IgG subclass levels from the previously used IGIV.
- Sufficient plasma total IgG and selected specific (e.g., anti-pneumococcal capsular polysaccharide and anti-Haemophilus influenzae) antibody levels to derive a plasma concentration-time curve, half-life, area under the curve (AUC_{0-t} ; $AUC_{0-\infty}$), volume of distribution, C_{max} , T_{max} , and elimination rate constant(s). The serum samples for these antibody measurements should be made after a “washout” period lasting 3-5 estimated half-lives, during which time subjects receive the investigational IGIV on a regular basis. It is appropriate to justify the choice of pharmacokinetic model used to derive the PK parameters.
- You should measure the trough total IgG and IgG subclass levels monthly during the study. It may be appropriate to identify in the study protocol and provide justification for a target minimum acceptable trough level

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value. Your study report should include the proportion of subjects who failed to meet the target trough level at any time point equal to or subsequent to 5 estimated half-lives.

- You should develop a prospective plan for defining the recommended dosing schedule based on the observed/calculated PK parameters and include the plan in the PK study protocol. For patients who are previously untreated, we recommend you determine the time to reach steady state. You are encouraged to initiate exploratory studies to establish the relationship of both serious and non-serious infections to the PK parameters, the total IGIV levels, the levels of the various subclasses of IG and, if possible, the levels of selected specific antibodies such as anti-pneumococcal capsular polysaccharide and anti-Haemophilus influenzae antibodies.

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Appendix A.

<p>Infection: Bacteremia/sepsis^a</p> <ul style="list-style-type: none">▪ <i>Symptoms:</i> chills, rigors▪ <i>Physical findings-</i> fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mm Hg or a reduction of ≥ 40 mm Hg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction▪ <i>Laboratory tests:</i> positive blood culture^b, leukocytosis (white blood cell count > 12,000/mm³), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis
<p>Infection: Bacterial Meningitis</p> <ul style="list-style-type: none">▪ <i>Symptoms:</i> headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures▪ <i>Physical findings:</i> Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38 °C oral or >39°C rectal▪ <i>Laboratory tests:</i> positive cerebrospinal fluid (CSF) Gram stain and/or culture and/or positive CSF bacterial antigen assay, positive blood culture^c, CSF leukocytosis with neutrophil predominance, decrease in CSF glucose
<p>Infection: Osteomyelitis/Septic Arthritis</p> <ul style="list-style-type: none">▪ <i>Symptoms:</i> pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (Local inflammatory symptoms/signs may be lacking in adults.)▪ <i>Physical findings:</i> evidence of soft tissue infection adjacent to the involved bone/joint; drainage from sinus tract from involved bone; fever of >38°C oral or >39°C rectal▪ <i>Laboratory tests:</i> positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture▪ <i>Imaging studies:</i> positive X-ray, nuclear medicine bone scan, MRI scan, or CT scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra

Note: Items in bold are considered essential diagnostic features.

^a Two of the following should be present to make the diagnosis of sepsis in adults: temperature >38°C oral/ > 39°C rectal or <36°C oral or < 37°C rectal; heart rate >90 beats/min; respiratory rate >20 breaths/min, or PaCO₂ <32 mm Hg; white blood cell count >12,000/mm³, <4,000/mm³, or >10% immature (band) forms. For pediatric patients, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (Pediatric Crit Care Med 2005; 6:2-8).

^b Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IGIV replacement therapy. For subjects without indwelling catheters or vascular access devices, a single blood culture positive for a pathogenic organism will meet the diagnostic criteria for bacteremia. (Multiple blood cultures are typically obtained in cases of suspected bacteremia/sepsis, as per standard medical practice, and the finding of a single positive culture should prompt additional confirmatory cultures). Subjects meeting criteria for positive blood culture but without 2 or more of the sepsis criteria listed above will be classified as having bacteremia.

^c A blood culture positive for growth of *Streptococcus pneumoniae*, *Neisseria meningitides*, or *Haemophilus influenzae*, in combination with CSF leukocytosis and/or glycorrachia, can serve to confirm the diagnosis of acute bacterial meningitis.

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<p>Infection: Bacterial Pneumonia^d</p> <ul style="list-style-type: none">▪ <i>Symptoms:</i> productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias▪ <i>Physical findings:</i> rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever >38°C oral or > 39°C rectal, or <36°C, hypothermia (temperature < 36°C oral or < 37°C rectal)▪ <i>Laboratory tests:</i> leukocytosis; differential WBC count of >10% band neutrophils; leukopenia; hypoxemia (PaO₂ < 60 mm Hg on room air); positive blood culture; Gram stain and culture of deep expectorated sputum^e, positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with BAL or protected brush sampling,▪ <i>Imaging studies:</i> Pulmonary infiltrate with consolidation on chest X-Ray (new in comparison with baseline chest X-Ray)
<p>Infection: Visceral Abscess</p> <ul style="list-style-type: none">▪ <i>Symptoms:</i> abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present)▪ <i>Physical findings:</i> intermittent fevers (temperature >38°C oral or >39°C rectal); abdominal tenderness; palpable mass; hepatomegaly; jaundice▪ <i>Laboratory tests:</i> positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen; positive blood culture; leukocytosis with accompanying left shift; differential white blood cell count of >10% immature (band) neutrophils elevated serum amylase concentration (pancreatic abscess); elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess▪ <i>Imaging studies:</i> typical findings on ultrasound, CT scan, MRI scan, or radionuclide scan

Note: Items in bold are considered essential diagnostic features.

^d For the diagnosis of pneumonia in adults, commonly at least 2 of the listed symptoms and/or signs should be present in conjunction with at least one laboratory and one imaging studies diagnostic element. However, for the purposes of counting serious infection episodes in a clinical trial of IGIV, the finding of a new pulmonary infiltrate with consolidation on CXR is considered sufficient. To establish the diagnosis of bacterial pneumonia for *pediatric* patients, most of the same diagnostic criteria listed may be used, with the following exceptions: Because pediatric patients may not produce a sputum specimen for culture, blood cultures or serology may be substituted to identify the etiologic bacterial pathogen. In infants age 3 to 24 months, who tend to have a higher baseline temperature, fever is defined as a rectal temperature >38.3°C (101°F). In children >2 years, fever is more commonly defined as a rectal temperature >38°C (100.4°F). In pediatric patients, elevations of WBC counts >15,000/mm³ are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count <5000/mm³ may be observed, usually associated with severe infection

^e We recommend a deep expectorated sputum gram stain demonstrate the presence of microorganisms on examination of 10-20 oil immersion microscopic fields and <10 squamous epithelial cells and >25 polymorphonuclear leukocytes at 10X low power magnification to determine suitability of sputum culture.