Guidance for Industry

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

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For questions on the content of this guidance, contact the Division of Blood Applications, Office of Blood Research and Review at 301-827-3543.

U.S. Department of Health and Human Services
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I. INTRODUCTION

We, FDA, are providing you, Investigational New Drug Application (IND) sponsors and Biologics License Application (BLA) applicants, recommendations 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 of investigational IGIV products and is intended to assist you in the preparation of the clinical/biostatistical and human pharmacokinetic sections of a BLA. This guidance does not address evidence of clinical efficacy for other indications, or other sections of a BLA such as chemistry, manufacturing, and controls and preclinical toxicology.

This guidance finalizes the draft guidance of the same title dated November 2005 (70 FR 72124, December 1, 2005).

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 infectious agents.

To date, all IGIV products licensed by FDA carry an FDA approved indication for use in primary humoral immunodeficiency. Some IGIV products have additional approved indications, such as elevation of platelet counts to prevent and/or to control bleeding in immune/idiopathic thrombocytopenic purpura.

At the FDA Blood Products Advisory Committee (BPAC) meeting held in March, 1999 (Ref. 1), we presented our preliminary recommendations for designing a pivotal clinical trial to evaluate the safety and efficacy of a new IGIV product for treatment of primary humoral immunodeficiency. The presented design involved a prospective, randomized, double-blind, parallel, positive control, non-inferiority study in 80 subjects with a documented history of such immunodeficiency, 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 have determined that alternative clinical trial design proposals involving testing in smaller numbers of subjects with primary humoral immunodeficiency in an open-label, single-arm trial compared to a statistically modeled historical control might be sufficient to provide evidence of safety and efficacy. At the March, 2000 BPAC meeting (Ref. 2), we presented an alternate approach to clinical trial design to evaluate IGIV safety and efficacy in primary humoral immunodeficiency, and we describe a similar approach in Section III below. Other approaches may also satisfy applicable requirements.

Other FDA guidance documents contain helpful information for you to consider as you prepare BLAs. These documents are available at http://www.fda.gov/cber/guidelines.htm.

III. GENERAL PRINCIPLES CONCERNING CLINICAL TRIAL DESIGN TO EVALUATE SAFETY, EFFICACY, AND PHARMACOKINETICS

A. Safety

1. General Principles Pertaining to Safety

   Historically, the observed incidence of adverse experiences (AEs) reported to occur in clinical trials of IGIV products has varied widely by product, maximal infusion rate, and patient population/indication being studied. For this reason, the safety profile of each IGIV product should be determined independently. In previous experience, 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 based on the totality of pertinent safety findings and analyses.

- We recommend a minimum of 30 subjects be studied at the highest dose to be recommended in the product's labeling. For adverse events that occur with a frequency of 10%, the probability of observing at least one event in this sample size is approximately 0.95. If an adverse event were not observed in this sample, then the probability of seeing that event is no more than 0.1 (i.e., the upper limit of 95% confidence interval for the observed rate of 0/30 is 0.1).

- For purposes of this guidance, an AE is a treatment-emergent AE associated with the use of the IGIV, whether or not the AE is determined to be product related.

- Under 21 CFR 312.32(a), a serious adverse drug experience (SAE) is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, 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 in this definition. 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 not be independent. Methodology for these analyses should be described in the statistical analysis plan.

- 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) 72

hours following an infusion of test product, regardless of other factors that may impact a possible causal association with product administration. The ADVERSE REACTIONS section of the product's draft package insert submitted with any IGIV BLA should summarize: (a) the total number of AEs that occur during or within 72 hours of an infusion, (b) the total number of infusions, and (c) the mean number of such temporally-associated AEs per infusion (i.e., (a)/(b)) that were seen in the clinical trial(s).

- 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 your 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. The methodology for computing such confidence limits should be described in the statistical analysis plan. It may be appropriate to modify this target as experience with various IGIV products further increases.

- According to the available literature, the intensity (i.e., severity) of many AEs associated with infusion of IGIV is dependent on the rate of infusion (Ref. 3). For this reason, 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 provisions 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) AEs. Protocols should provide for the systematic evaluation of AEs as a function of infusion rate.

- For AEs that occur during infusion, it is important that the protocol and the case report form (CRF) are designed to capture: (1) the infusion rate in effect at the time of onset of AEs; (2) the time of onset of AEs; and (3) the time AEs change materially in intensity and/or resolve.

- We consider subject diaries kept in "real time" to be important source documents for the complete collection of AE data. 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 the safety of trial subjects. In such

instances, you should record the use of any premedications and their possible impact on the study data and evaluate their possible impact in the final study report.

- Routine hematology[1] and serum chemistry[2] tests, and urinalysis[3] should be obtained at baseline and periodically during the period of test product administration.

- We recommend laboratory measurements intended to aid the detection/evaluation of intravascular hemolysis during and after the period of test product administration. In addition to the routine hematology, chemistry, and urinalysis testing noted above, measurements of serum haptoglobin, plasma-free hemoglobin, urine hemosiderin, and direct anti-globulin (DAT, Coombs) testing should be obtained at baseline and follow-up. We recommend that study protocols specify measurement of specific eluted antibodies in the event of positive Coombs test measurements, in addition to retesting. A drop in hemoglobin of 2 g/dL or greater, in conjunction with both a drop in serum haptoglobin to below the lower limit of normal and a rise in serum LDH from baseline, would suggest intravascular hemolysis.

- 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 AEs that occur during infusion, you should report and analyze: (1) the infusion rate in effect at the time of onset of AEs; (2) the time of onset of AEs; and (3) the time AEs change materially in intensity and/or resolve. It is important to our review that you also provide listings of SAEs, AEs by severity, AEs by body system, and your determination of which AEs were product-related, and which were not.

    - The mean number of AEs temporally associated with infusions per infusion. As previously noted, this is given by (a)/(b) where: (a) equals the total number of AEs that occur during or within 72 hours of an infusion, and (b) equals the total number of infusions.

[1] Includes complete blood count with white blood cell differential and platelet count.
[2] Includes serum electrolytes, glucose, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and total bilirubin.
[3] Includes microscopic examination of urine sediment.

- 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.

- For each AE, indicate which infusion of investigational product this occurred with or followed (i.e., 1st infusion, 2nd infusion, etc.). The AE 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.

- 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. In addition to reporting the verbatim AE terminology as entered on the case report forms, we recommend you report and analyze AEs according to a set of standard AE terms using a coding dictionary, such as the Medical Dictionary for Regulatory Activities (medDRA).[4]

- 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 not be independent. Methodology for these analyses should be described in the statistical analysis plan.

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 hypogammaglobulinemia and agammaglobulinemia due to primary humoral immunodeficiency experienced approximately four or more

[4] http://www.meddramsso.com/MSSOWeb/faq/meddra.htm

serious acute bacterial infections per year (Ref. 4). That number contrasts with an observed serious infection frequency of less than 0.5 per year during periods of regular (generally every 3 to 4 weeks) administration of IGIV, 200 to 600 mg/kg per infusion. The available data do not permit identification of a trough total immunoglobulin G (IgG) level (pre-next-dose) or pathogen-specific plasma IgG level which, if achieved and maintained, would ensure optimal protection from the risk of serious bacterial infection. Preliminary data from clinical trials suggest that, within the commonly prescribed IGIV dosage range, subjects with higher trough levels may experience greater protection from bacterial infections. We encourage you to study the relationships among dose of your product, trough level, and risk of serious and non-serious bacterial infections.

More data are needed to better understand the quantitative relationships among trough total and pathogen-specific plasma IgG levels and serious infection risk. We encourage you to initiate exploratory analyses of your clinical trial data to evaluate the relationship of both serious and non-serious infections to the pharmacokinetic parameters, the total IgG levels, the levels of the various subclasses of IgG and, if possible, the levels of selected specific antibodies such as anti-pneumococcal capsular polysaccharide and anti-*Haemophilus influenzae* antibodies.

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 in adult and pediatric subjects for 12 months (to avoid seasonal biases) and compare the observed infection rate to a relevant historical standard, as discussed in this same section, or to a concurrent control group.

- In ensuring compliance with the requirements of the Pediatric Research Equity Act of 2007 (Title IV of the Food and Drug Administration Amendments Act of 2007), we recommend that you discuss with the reviewing division at the IND stage your plans for pediatric studies.

- 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 Appendix outlines diagnostic criteria for each of the serious infection types that should be included in the analysis.

- 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.

- 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, 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 in this same section. 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.

- 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. Additional information important to our review includes a frequency table giving the number of subjects with 0, 1, 2… serious infections, a description of each serious infection, and summary statistics for the length of observation of each subject.

- We recommend that you obtain and analyze secondary endpoints, including candidate surrogate efficacy endpoints. Secondary endpoints would normally include trough total IgG and specific antibody levels, all infections of any kind/seriousness, non-serious infections (total and by category, including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc.), time to resolution of infections, antibiotic treatment (oral, parenteral, oral plus parenteral, prophylactic, and therapeutic), hospitalizations due to infection, episodes of fever, days lost from school and/or work due to infections and their treatment, and additional quality of life measures. You should prospectively define these secondary endpoints and their corresponding statistical analyses in the study protocol.

C. Pharmacokinetic Studies of IGIV

1. Guidance for Pharmacokinetic (PK) Studies

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

We recommend that you obtain PK data from at least 18-20 adult subjects with primary humoral 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 compared with 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 levels obtained 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 ($AUC_{0\text{-}t}$; $AUC_{0\text{-}infinity}$), volume of distribution, concentration maximum (C_{max}), and elimination rate constant(s). The serum samples for these antibody measurements should be made after a "washout" period lasting 3 to 5 estimated half-lives, during which time subjects receive the investigational IGIV on a regular basis. You should justify the choice of PK model used to derive the PK parameters.

- You should measure the trough total IgG levels prior to each infusion during the study. IgG subclass levels should be measured at least once after steady state is estimated to have been achieved (i.e., after approximately 5 half lives have elapsed during regular periodic administration of the test product). It may be appropriate to identify in the study protocol and provide justification for the minimum trough level value that is acceptable. 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. If you elect

not to include a concurrent control for your PK study/sub-study design, we recommend you compare and relate your observed trough IgG level data to that of currently licensed historical control IGIV products.

- 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.

2. PK Studies in the Pediatric Population

The following definitions of pediatric populations are described in the FDA guidance entitled "General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products" (Ref. 5).

- Neonate: birth to 1 month
- Infant: 1 month to 2 years
- Child: 2 to 12 years
- Adolescent: 12 years to <16 years

If possible and needed, the PK study of an IGIV product should be conducted across all pediatric age groups. An appropriate PK study could involve administering either a single dose in "naïve" subjects who have not been receiving regular IGIV replacement therapy, or multiple doses of the test IGIV over a time period of 3 to 5 terminal elimination half-lives, with PK sampling following the last dose. The sample size should consist of 6 to 12 subjects in a given pediatric age group. Two methods can be used for the estimation of PK parameters:

- The standard 2-stage PK approach (model-independent and/or model-dependent approach) (Refs. 6 through 8)

  The standard 2-stage PK approach is the usual approach for the estimation of PK parameters. In this approach, frequent blood sampling is required. Blood samples should be collected over specified intervals depending on the elimination half-life of the drug. It is important in this approach to include enough subjects (e.g., 6 to 12) to give a reasonable estimate of variability.

- The population PK approach (Refs. 9 and 10)

  An alternate approach in many pediatric situations is the population PK approach. This approach involves sparse blood sampling from a larger population than would be used in a standard PK study to estimate PK parameters. The population PK approach is more practical in pediatric populations (especially neonates and very young children) than the 2-stage PK approach because it allows for infrequent sampling, sometimes as few as 2 to 4 samples per subject. Because a relatively large number of subjects is studied, estimates of both population means and individual values (POSTHOC Bayesian)[5], as well as estimates of intra- and inter-subject variability can be obtained if the population PK study is properly designed (Refs. 11 through 13).

  More details for conducting PK studies in pediatric populations can be found in the FDA guidance entitled, "General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products" (Ref. 5).

[5] The term "POSTHOC Bayesian" refers to individual subject estimates of PK parameters.

IV. APPENDIX Diagnostic Criteria for Serious Infection Types

Infection: Bacteremia/sepsis[a] ▪ *Symptoms:* chills, rigors ▪ *Physical findings:* 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 ▪ *Laboratory tests*: **positive blood culture[b]**, leukocytosis (white blood cell (WBC) count > 12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis
Infection: Bacterial Meningitis ▪ *Symptoms*: headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures ▪ *Physical findings*: Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38 °C oral or >39°C rectal ▪ *Laboratory tests:* **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
Infection: Osteomyelitis/Septic Arthritis ▪ *Symptoms*: pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults.) ▪ *Physical findings*: 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 ▪ *Laboratory tests*: 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 *Imaging studies*: **positive X-ray, nuclear medicine bone scan, magnetic resonance imaging (MRI) scan, or computed tomography (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 $PaCO_2$ <32 mm Hg; WBC count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms (Ref. 14). For pediatric subjects, we recommend you employ the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis (Ref. 15).

[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 decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis (Ref. 16).

Infection: Bacterial Pneumonia[d] ▪ *Symptoms*: productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias ▪ *Physical findings*: 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) ▪ *Laboratory tests*: leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO_2 < 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 bronchoalveolar lavage (BAL) or protected brush sampling, ▪ *Imaging studies*: **Pulmonary infiltrate with consolidation on chest X-Ray (CXR)** (new in comparison with baseline CXR)
Infection: Visceral Abscess ▪ *Symptoms:* abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present) ▪ *Physical findings:* intermittent fevers (temperature >38°C oral or >39°C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice ▪ *Laboratory tests:* **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 WBC count of >10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess), elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess ▪ *Imaging studies:* **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/mm^3 are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count <5000/mm^3 may be observed, usually associated with severe infection (Ref. 17).

[e] We recommend a deep expectorated sputum gram stain to 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 (Ref. 17).

V. REFERENCES

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