

Pharmacovigilance Review Memorandum
Office of Biostatistics and Epidemiology/Division of Epidemiology (OBE/DE)

BLA/Supplement Number: 125389/0

Product Name: Biotest- IgIV (Immune Globulin Intravenous (Human))
10%

Sponsor: Biotest Pharmaceuticals Corporation (BPC)
Indication(s): Primary immune deficiency disorders (PIDD)

Date(s): CBER receipt date: 11/3/2010; Action Due date: 9/3/2011

Review Priority: Routine

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I. Introduction

OBE/DE/TBSB has completed its review of Biotest-IGIV 10% (Immune Globulin Intravenous (Human) 10%). Biotest-IGIV is manufactured from human plasma by a modified Cohn/Oncley cold-alcohol fractionation process and is indicated for the treatment of primary immunodeficiency disorders (PIDD). Information in this review is taken from the Biotest-IGIV BLA, sections 1.12.11 Basis for Submission, 2.7.4.1 Summary of Clinical Safety, 1.16.1 Pharmacovigilance System, and 1.16.2 Risk Management Plan. Information on Polysorbate-80 is drawn from the Nonclinical Pharmacology/Toxicology reviewer's Mid-Cycle Memo by Evi Struble, PhD. Figures and tables in this review are from the Biotest-IGIV BLA. Sections quoted from the BLA appear in *italics*.

II. Product Background

Intravenous immune globulin is derived from human plasma and is used in the treatment of a variety of disorders including immune deficiency disorders and a variety of inflammatory conditions (including autoimmune and inflammatory, neurological, dermatological and other disorders such as chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, myasthenia gravis, relapsing remitting multiple sclerosis, dermatomyositis, polymyositis, toxic epidermal necrolysis, pemphigus vulgaris, hemolytic disease of the newborn, sepsis, and use in renal transplantation)¹. Biotest states that Biotest-IGIV will both increase supply in the market and offers advantages over currently available IGIV preparations: *the introduction of an additional liquid IGIV product with a favorable concentration (10%) and absence of a sugar stabilizer will supplement existing IGIV supply in the US, reducing the risk of IGIV shortages that negatively impact the management of PIDD. Furthermore, a 10% liquid preparation allows for reduced volume load with the corresponding benefit to patients and clinicians of reducing infusion time and its associated costs.* (Biotest-IGIV BLA 1.12.11 Basis for Submission)

Biotest-IGIV is indicated for the treatment of Primary Immune Deficiency Disorders (PIDD). These disorders involve defects in the production of antibodies and include common variable immune deficiency (CVID), severe combined immune deficiency (SCID), X-linked agammaglobulinemia, and other rarer disorders. (Biotest BLA 1.12.11) The purpose of IGIV treatment is to replace IgG antibodies and reduce the number and severity of infections in patients with PIDD.

Biotest-IGIV is a ready-for-use sterile solution containing highly purified and concentrated IgG antibodies with no preservatives. It is prepared from plasma collected from healthy, qualified plasma donors. The plasma is processed using a modified Cohn/Oncley cold-alcohol fractionation process with three viral reduction

¹ Orange J, Hossny E, Weiler C, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma, and Immunology. *J Allergy Clin Immunol*, 2006 Apr;117(4 Suppl):S525-53.

steps. Biotest-IGIV is formulated in sodium chloride, glycine, and polysorbate 80 at pH 4.0 – 4.6. (Biotest-IGIV BLA, 2.3.1 Introduction, p. 1)

III. Clinical Studies

Safety data for Biotest-IGIV is taken from a single study, Nabi-7101. Nabi-7101 is an *open-label, phase III study in 15 centers [that] investigated the safety, efficacy, and pharmacokinetics of Biotest-IGIV 10% in subjects with PIDD.* (Biotest BLA 2.7.4 Summary of Clinical Safety, p. 2) This study consisted of 63 subjects between the ages of 6 and 75 years. Subjects must have a diagnosis of PIDD and documented low IgG antibody levels prior to starting IGIV therapy. In addition, subjects must have been on a stable dose of IGIV for a minimum of 3 months, with adequate antibody trough levels prior to enrollment. (Biotest BLA 2.7.4, p. 3)

Subjects were treated every 3 or 4 weeks (depending on previous schedule). Biotest-IGIV was given up to 12 months with follow-up 3 months after the last infusion. (Biotest BLA 2.7.4, p. 3)

63 subjects were enrolled in the study: 32 women and 31 men with a mean age of 41 years. Most subjects were non-elderly adults (70%) between 18 and 64 years of age, there were 4 children (6.3%) between 6 to 11 years of age, 6 adolescents (9.5%) between 12 and 17 years of age, and 9 (14%) elderly subjects (≥ 65 years of age). The oldest subject was 75 years of age. 17 subjects had a 3-week cycle and 46 a 4-week cycle. There were 51 subjects (81%) with common variable immunodeficiency as their primary diagnosis, followed by X-linked agammaglobulinemia and ‘Other’ (6 subjects each, 9.5% each). (Biotest BLA 2.7.4, p. 3)

Table 2.7.4.3 Demographic and Baseline Characteristics - Safety Population

Parameter	No. of subjects (%) N=63
Gender	
Female	32 (50.8%)
Male	31 (49.2%)
Age (yr)	
Mean (SD)	41.2 (19.68)
Median	44.0
Minimum, Maximum	6, 75
Age group	
6-11 Years	4 (6.3%)
12-17 Years	6 (9.5%)
18-64 Years	44 (69.8%)
65 Years and Older	9 (14.3%)
Primary diagnosis	
X-linked agammaglobulinemia	6 (9.5%)
Common variable immunodeficiency	51 (81.0%)
Other	6 (9.5%)
SBI history	8 (12.7%)
Bacterial pneumonia	7 (11.1%)
Other	1 (1.6%)

N = number of subjects; SBI = serious bacterial infection; SD = standard deviation.

Source: [Clinical Study Report Nabi-7101, Table 11-1](#)

From Biotest BLA 2.7.4, p. 7

Reviewer comment: This small study enrolled only 4 children, 6 adolescents, and 9 elderly patients. Since these groups may respond with different or more severe adverse effects, careful monitoring of these groups will be needed in post-marketing pharmacovigilance.

Reviewer Comment: The population of patients receiving a licensed IGIV may differ from this study population with respect to age and predisposition of adverse events.

Fifty-two (52) subjects (83%) completed this 1-year study. The mean treatment duration was 317.3 days with a range of 66-386 days. Exposure in the study was a total of 53.54 person-years and a total of 19,555 days. (Biotest BLA 2.7.4, p. 4)

Temporally associated adverse events (TAAEs) were defined as *those occurring between the start of the IGIV infusion and occurring up to 72 hours following the infusion, regardless of other factors that may have impacted a possible causal association with product administration.* (Biotest BLA 5.3.5.1.3 Nabi-7101 Clinical Study Report, p.43)

The most frequent (>5% of subjects) TAAEs (headache, fatigue, nausea, infusion site reaction, sinusitis, diarrhea, increased blood pressure, dizziness, and lethargy) were those generally anticipated with any IGIV preparation. The median for TAAEs per

infusion was 0.23. There was only 1 TAAE that resulted in dose change and 4 subjects had 8 TAAEs resulting in infusion interruptions. (Biotest BLA 2.7.4, p. 9)

Table 2.7.4.6 Most Frequent (≥5% of Subjects) TAAEs by Frequency - Safety Population

TAAE	No. of subjects (% of total)	No. of infusions (% of total)
Headache	27 (42.9%)	115 (15.4%)
Fatigue	15 (23.8%)	59 (7.9%)
Infusion site reaction	5 (7.9%)	5 (0.7%)
Nausea	5 (7.9%)	8 (1.1%)
Sinusitis	5 (7.9%)	5 (0.7%)
Blood pressure increased	4 (6.3%)	5 (0.7%)
Diarrhea	4 (6.3%)	4 (0.5%)
Dizziness	4 (6.3%)	4 (0.5%)
Lethargy	4 (6.3%)	4 (0.5%)
Back pain	3 (4.8%)	3 (0.4%)
Blood pressure diastolic decreased	3 (4.8%)	5 (0.7%)
Fibromyalgia ^a	3 (4.8%)	17 (2.3%)
Migraine	3 (4.8%)	8 (1.1%)
Myalgia	3 (4.8%)	4 (0.5%)
Pharyngolaryngeal pain	3 (4.8%)	3 (0.4%)

TAAE = temporally associated (with infusion) adverse event.

Subjects reporting >1 TAAE were counted only once in each level (SOC or PT).

Related TAAEs included 'probably related', 'unknown', or missing.

^a Symptoms occurring under pre-existing fibromyalgia.

Source: [Clinical Study Report Nabi-7101, Table 12-5](#)

From Biotest BLA 2.7.4, p. 10

Approximately half (51%) of patients experienced a TAAE with the first infusion. This decreased to 30 % with the second infusion. For subsequent infusions, the rate of TAAEs remained between 20-30%. (Biotest BLA 2.7.4, p. 11)

Table 2.7.4.9 TAAEs by Infusion - Safety Population

Infusion	N	No. of subjects (%)	
		All TAAEs	Related TAAEs
1	63	32 (50.8%)	24 (38.1%)
2	62	19 (30.6%)	14 (22.6%)
3	61	20 (32.8%)	14 (23.0%)
4	59	16 (27.1%)	11 (18.6%)
5	54	15 (27.8%)	10 (18.5%)
6	52	11 (21.2%)	8 (15.4%)
7	52	9 (17.3%)	8 (15.4%)
8	52	13 (25.0%)	11 (21.2%)
9	52	15 (28.8%)	10 (19.2%)
10	52	11 (21.2%)	9 (17.3%)
11	52	14 (26.9%)	10 (19.2%)
12	52	10 (19.2%)	9 (17.3%)
13	51	12 (23.5%)	6 (11.8%)
14	8	2 (25.0%)	2 (25.0%)
15	8	2 (25.0%)	2 (25.0%)
16	8	3 (37.5%)	2 (25.0%)
17	8	3 (37.5%)	1 (12.5%)

N = number of subjects; TAAE = temporally associated (with infusion) adverse event.

Source: [Clinical Study Report Nabi-7101, Table 12-8](#)

From Biotest BLA 2.7.4, p. 12

A second category of adverse events tracked in Nabi-7101 were Treatment Emergent Adverse Events (TEAEs), defined as *any event which occurred during the observation period and was not present at baseline, or one which represented an exacerbation of a condition present at baseline.* (Biotest BLA 5.3.5.1.3, p. 51) *The most frequent treatment-emergent adverse events (>5.0% of subjects) reflected those to be expected in this population and many of which were potentially related.* (Biotest BLA 2.7.4, p. 17) *About half (52.4%) of the subjects had ≥ 1 severe TEAE. Severe AEs occurring in more than 5% of subjects were: headache (11.1%); sinusitis (9.5%); bronchitis (6.3%); and migraine (6.3%).* (Biotest BLA 2.7.4, p. 19)

**Table 2.7.4.16 Most Frequent (>5% of Subjects) TEAEs by SOC and Preferred Term
Safety Population**

TEAE	Number of Subjects (%) N=63
Ear and labyrinth disorders	
Ear pain	4 (6.3%)
Gastrointestinal disorders	
Diarrhea	13 (20.6%)
Nausea	9 (14.3%)
Vomiting	6 (9.5%)
General disorders and administration site conditions	
Fatigue	18 (28.6%)
Infusion site reaction	5 (7.9%)
Malaise	4 (6.3%)
Pain	7 (11.1%)
Pyrexia	12 (19.0%)
Infections and infestations	
Acute sinusitis	7 (11.1%)
Bronchitis	12 (19.0%)
Gastroenteritis viral	5 (7.9%)
Influenza	4 (6.3%)
Nasopharyngitis	5 (7.9%)
Otitis media	4 (6.3%)
Pharyngitis	7 (11.1%)
Sinusitis	24 (38.1%)
Upper respiratory tract infection	16 (25.4%)
Urinary tract infection	5 (7.9%)
Viral upper respiratory tract infection	6 (9.5%)
Investigations	
Blood pressure increased	4 (6.3%)
Musculoskeletal and connective tissue disorders	
Back pain	7 (11.1%)
Myalgia	4 (6.3%)
Nervous system disorders	
Dizziness	6 (9.5%)
Headache	32 (50.8%)
Lethargy	5 (7.9%)
Migraine	4 (6.3%)
Respiratory, thoracic and mediastinal disorders	
Asthma	5 (7.9%)
Cough	14 (22.2%)
Nasal congestion	5 (7.9%)
Pharyngolaryngeal pain	13 (20.6%)
Sinus congestion	4 (6.3%)
Vascular disorders	
Hypertension	4 (6.3%)
Hypotension	4 (6.3%)

N = number of subjects, SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Subjects reporting >1 TEAE were counted only once.

Source: [Clinical Study Report Nabi-7101, Table 12-15](#)

A third type of adverse event followed in Nabi-7101 was Pre-Determined Adverse Events (PDAEs). These were defined as either:

1. Any AE occurring during the infusion or within 72 h following the infusion with any of the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms known to be anticipated with IGIV treatment (see below);
 2. Any AE occurring during the infusion or within 72 h following the infusion considered by the investigator to be 'probably related' to the study drug (or with 'unknown' or missing relationship). (Biotest BLA 2.7.4, p. 14)
- The MedDRA terms included were: headache, pyrexia, chills, back pain, pain, myalgia, arthralgia, fatigue, dyspnoea, leg cramps, light headedness, urticaria, flushing, blood pressure increased, nausea, vomiting, anaphylactic reaction, hypersensitivity reactions, feeling cold, vertigo, hypotension, pruritus, rash, erythema, generalized erythema, erythema of eyelid, ocular hyperemia, rhinitis, rash maculo-papular, edema peripheral, dermatitis, or meningitis aseptic. (Biotest BLA 2.7.4, p.14-5)

Most PDAEs were those anticipated with any IGIV preparation including all those in >5% of subjects: headache, fatigue, nausea, and increased blood pressure as well as those considered by the investigator to be related to study drug (fatigue and headache) (Biotest BLA 2.7.4, p.15)

Table 2.7.4.12 Most Frequent (>5% of Subjects) PDAEs - Safety Population

PDAEs	No. of subjects (%)	
	All PDAEs	Related PDAEs
Gastrointestinal disorders		
Nausea	5 (7.9%)	3 (4.8%)
General disorders and administration site conditions		
Fatigue	15 (23.8%)	13 (20.6%)
Investigations		
Blood pressure increased	4 (6.3%)	3 (4.8%)
Nervous system disorders		
Headache	27 (42.9%)	24 (38.1%)

PDAE = pre-defined adverse event;

Subjects reporting >1 PDAE are counted only once in each level (SOC or PT).

Related PDAEs - considered by the investigator to be related to the study treatment, included 'probably', 'unknown', or missing.

Source: [Clinical Study Report Nabi-7101, Table 12-11](#)

From Biotest BLA 2.7.4, p. 15

There were no deaths during the study. There were 11 [serious adverse events] (SAEs) in 7 subjects (11.1%) most of which (5 subjects) occurred >72 h post-infusion. The SAEs occurring >72 hours post-infusion included a fall resulting in hip fracture, mental status change secondary to benzodiazepine withdrawal, an episode of hypotension (etiology unclear), two pneumonias (one bacterial), an intestinal obstruction, an episode of colitis, and an acute exacerbation of chronic bronchitis. (Biotest BLA 2.7.4, p. 19-22) Only 2 patients had SAEs within 72 hours of infusion. One patient had acute appendicitis. The second patient had 2 SAEs (mild vomiting and moderate dehydration) which were considered related to the study treatment by the investigator. No SAE resulted in a dose change, dose interruption, or discontinuation from the study, and all of the SAEs resolved. (Biotest BLA 2.7.4, p. 19)

IV. Safety Issues

Hypotension

Biotest-IGIV contains polysorbate-80 at levels higher than all other marketed IGIVs. Polysorbate-80 is used as a stabilizer in Biotest-IGIV, eliminating the need for a sugar stabilizer. Sugar stabilizers, sucrose in particular, have been associated with acute renal failure, renal insufficiency, and osmotic nephrosis.² The concentration of PS80 in Biotest-IGIV is approximately ten times greater than other IGIVs ((b)(4)% for Biotest-IGIV compared to (b)(4)% for next highest product)³. Also, the maximum acceptable daily oral intake of PS80 established by the Food and Agricultural Organization of the United Nations/World Health Organization (WHO) is 25mg/kg. The maximum dose an individual would receive from Biotest-IGIV would be 20 mg/kg (although the effect could differ due to the differing routes of administration).³

Polysorbate-80 is known to cause hypotension in canine models. *In vivo* [canine] studies have shown that polysorbate 80 has an immediate effect on myocardial contractility, with onset occurring within minutes after administration. The effects disappear within 1 h after dosing is stopped. (Biotest BLA 2.7.4, p. 23) According to the protocol for Nabi-7101, blood pressures were measured within 30 minutes of the start of the infusion, every 10 minutes during the infusion, and within 30 minutes of the completion of the infusion. In Nabi-7101, there were no episodes of bradycardia. There were 7 episodes of hypotension, but 3 affected diastolic pressure only (Biotest BLA 2.7.4, p. 23). Two of the remaining 4 episodes occurred >72 hours after infusion. Regarding the two episodes temporally related to the infusion, one subject had a BP of 83/69 1 hour after the start of infusion 8, but the BP increased to 112/78 ten minutes later. Another subject had a BPs of 97/54 and 105/36 during the fifth infusion but [t]he investigator determined that this blood pressure reading was not clinically significant. The next BP was 112/60. While it is unclear if either patient experienced any symptoms, the CRFs clearly document that no action was taken and that both patients recovered. Neither of these 2 patients had recurrent hypotension on re-exposure. (Biotest BLA 2.7.4, p. 23-4)

However, one of the 2 hypotensive episodes documented in the Summary of Clinical Safety as occurring greater than 72 hours after infusion appears to have occurred approximately 68.5 hours after the infusion. This episode refers to the “severe hypotensive crisis” which occurred on June 20, 2008 in patient (b)(6), after infusion number 3 (Biotest BLA 5.3.5.1.24.012 CRF for subject (b)(6)). The dates of this episode have been changed to July 20, 2008 on the form entitled, “3rd Infusion. Infusion Related Adverse Events,” and the July 20th date is carried forward in the data.

Reviewer Comment: The date of this event needs to be clarified. The patient diary indicates it was on the 3rd day after infusion #3, June 20, 2008. If this is correct, the event should be discussed under “Hypotension Related Events.” If the hypotensive crisis did not occur within 72 hours of infusion, it should be

² Shah S. Pharmacy considerations for the use of IGIV therapy. *Amer J Health-System Pharmacy* 2005 Aug;62(16) Suppl3:S5-11.

³ Strubel E, Nonclinical Pharmacology/Toxicology Mid-cycle memo –for Bivigam Immune Globulin Intravenous (Human) 10%, March 11, 2011.

added to the “Other Serious Adverse Events” section of the Summary of Clinical Safety.

Product Class Effects

IGIVs are known to cause thrombotic events, renal failure, and hemolysis. *Physical examination, blood chemistry, hematology, and urinalysis testing were performed at the baseline visit, prior to protocol specified infusions and at the final clinical visit. None of the subjects had signs of thrombotic events, renal failure and hemolysis at any time during the study as demonstrated by stable laboratory values and physical examination findings.* (Biotest BLA 2.7.4, p. 27)

Transmission of Infective Agents

The following viral tests were performed: parvovirus, human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) at screening, prior to Infusions 8 and 12, and at the final safety follow-up visit. There was a single positive finding for parvovirus during the study. However, viral transmission could be excluded as this subject (---(b)(6)---) came in contact with acute Parvo B19 virus from working at a school greeting children where a child was reported to have symptomatic Fifth’s disease. Furthermore there was no cluster (no other cases in other subjects) of Parvo B19 transmission with the IGIV batch concerned. Thus, there was no evidence of any viral transmission by Biotest-IGIV 10%. (Biotest BLA2.7.4, p. 28)

Reviewer Comment: Parvovirus B19 is a common childhood infection and acute transmission would be likely to occur in any environment where large numbers of children are present (schools, daycares, etc.) Therefore, the transmission of Parvovirus B19 to a study subject in a school setting is very plausible.

V. Pharmacovigilance Plan

Biotest AG maintains a global pharmacovigilance system by means of the Corporate Drug Safety (CDS) department that is located at the headquarters of Biotest in Dreieich, Germany. The overall purpose of the company’s pharmacovigilance system is to systematically collect adverse events from all sources, to perform medical assessments of single case and aggregate data, and to perform signal detection activities to enable early detection of potential signals. (Biotest BLA 1.16 Risk Management Plan, p.5) These objectives are carried out through case processing, literature searches, and the compilation of adverse event reports in PSURs. Individual adverse events reports are *recorded, tracked, evaluated and reviewed* so that reporting is *carried out in compliance with worldwide legal requirements.* (Biotest BLA 1.16, p. 8) Literature searches for reports on suspected adverse events are conducted weekly. (Biotest BLA 1.16, p. 8) PSURs are prepared *in accordance with international regulations.* With respect to adverse events, Biotest will *summarize and report the following known immune globulin intravenous (IGIV) class effects in the respective PSURs/aggregate reports on Biotest-IGIV:*

- *Hypersensitivity reactions*
 - *Acute renal failure*
 - *Hyperproteinemia*
 - *Thrombotic events*
 - *Aseptic meningitis*
 - *Hemolysis*
 - *Infusion-related reactions*
 - *Transmission of infective agents*
 - *Impairment of efficacy of live attenuated virus vaccines*
 - *Interference with serological testing*
- (From Biotest BLA 1.16, p. 8-9)

Also, given the risk of hypotension due to polysorbate 80, the sponsor *intends to specifically discuss and address any spontaneous adverse events reported for hypotension in PSURs.* (Biotest BLA 1.16, p. 9)

Biotest uses *validated database queries* to look for safety signals on a quarterly basis. *A batch signal detection procedure is carried out once at least 3 PTCs [Pharmaceutical/ Product Technical Complaint] or ADRs of the same batch have been reported.* (Biotest BLA 1.16, p. 9)

VI. Assessment and recommendations

1. The safety data for Biotest-IGIV is derived from a single trial, Nabi-7101. This study consisted of 63 patients and identified no new safety signals.
2. We concur with the plan for routine pharmacovigilance activities for Biotest-IGIV 10%, as outlined in the BLA, including specifically monitoring and reporting on IGIV class effects and hypotension.
3. The study population may not be representative of the typical patient population receiving IGIV, so at-risk populations such as children, adolescents, pregnant women (who were excluded from the study), and the elderly will need to be monitored in pharmacovigilance activities. We recommend collecting and analyzing the pharmacovigilance data to specifically examine at-risk populations which were studied in small numbers or excluded from pre-marketing safety studies (children, adolescents, pregnant or lactating women, elderly) and reporting these results in the PAER or PSUR.
4. Given the potential for Biotest-IGIV to cause cardiovascular effects (hypotension, bradycardia) due to the increased concentration of polysorbate-80 (used in Biotest-IGIV as a stabilizer), the review team should consider a post-market study or enhanced surveillance to further assess this potential safety issue. An observational study in which a pre-determined sample of Biotest-IGIV treated patients are enrolled, with BP measured at baseline, during, and after infusions, is one option to further assess this issue. The study would assess the frequency and severity of hypotensive events overall and by various factors, such as co-morbidities, concomitant medications, demographics, indication, and dose. Such a study could include

comparison of hypotension frequency and severity to another IGIV product (or historical rates of hypotension following IGIV treatment if available). An alternate plan for enhanced surveillance could involve investigation and reporting passively reported cases of hypotension. In the enhanced surveillance scenario, the sponsor could be required to report all hypotensive AEs as expedited reports (even though hypotension would be a labeled event). Further, the sponsor, as part of their investigation, would attempt to determine and report details of each event, such as the dose, lot number, rate of infusion, onset with respect to the infusion, duration of event, any patient risk factors (co-morbidities, other medications), any treatment instituted, and any sequelae.

VII. Letter Ready Comments

1. We have reviewed the pharmacovigilance plan (PVP) submitted with the BLA for Biotest Immune Globulin Intravenous (Human) 10%. We agree with your plan for routine pharmacovigilance activities for Biotest-IGIV 10%, as outlined in the BLA, for most anticipated AEs for IGIVs, and we note your intention to specifically report on IGIV class effects and hypotension. However, you should conduct a post-market safety study to further assess the risk of hypotension.
2. Polysorbate-80 is associated with hypotension in animal models and is present in Biotest-IGIV at levels higher than any marketed IG product. Although there were no clinically significant cases of hypotension or other cardiac adverse events in the clinical trial for Biotest-IGIV, Nabi-7101 was too limited in size to exclude a lack of excess risk of hypotension with Biotest-IGIV compared to other IGIV treated patients. Please propose a plan for a post-market observational safety study to further assess hypotension risk in Biotest-IGIV-treated patients. Please include in your proposal the sample size to be included and a rationale for this size, as well as information that will be collected at baseline, the frequency and methods for follow-up data collection, and the information to be collected in follow-up.
3. You should also collect and analyze the spontaneously reported pharmacovigilance data to specifically examine at-risk populations which were studied in small numbers or excluded from pre-marketing safety studies (children, adolescents, pregnant or lactating women, elderly) and report these results in PAERs or PSURs.
4. Please consider revising your Pharmacovigilance plan to include submission of all spontaneously reported hypotension events as expedited reports for the first 3 years of marketing in the U.S.