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## Probabilistic forecasting of the global demand for the treatment of hemophilia B

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The objective of this paper is to improve business forecasting practice in modeling the uncertainty of factor IX (FIX) demand for the treatment of hemophilia B (HB) in global production capacity planning. HB is a rare genetic bleeding disorder in which the blood does not clot properly because of the absence or deficiency of FIX, a protein in human blood that is necessary for coagulation. It is difficult to forecast FIX demand for the treatment of HB due to the uncertainty surrounding its epidemiology and treatment, and the economic ability of a country to pay for treatment. Further complicating the forecast is that the global hemophilia market is supply-constrained due to the inherent difficulty in manufacturing a biological drug. A more accurate estimate of demand, derived from epidemiology and treatment modalities, and the economic capacity of a country to pay or FIX treatment, will assist in estimating the global supply of FIX and the national healthcare resources needed to ensure optimal treatment of patients with HB. To estimate global FIX demand we obtained data from the open literature on latent therapeutic demand (LTD) and economic developed status (EDS). LTD is the underlying demand that represents how physicians would prescribe evidence-based treatment and how patients would comply with the prescribed treatment if ample supplies of drugs were available and affordable. EDS is the economic ability of countries to afford HB treatment. Rather than forecasting demand using supply-constrained historical sales data, we model long-term global demand for HB using LTD and EDS. The long-term global forecasted demand for the FIX treatment of HB was 1,700 million international units. This insight is critical for industry when considering whether to expand FIX production capacity to meet the forecasted global demand for the FIX treatment of patients with HB.

*Subject classifications*: application, decision analysis, long-term global forecasting demand, latent therapeutic demand, economic developed status, production capacity planning, hemophilia

# Probabilistic forecasting of the global demand for the treatment of hemophilia B

## 1. Introduction

The objective of this paper is to improve long-term global production capacity planning for the demand uncertainty of treating patients with hemophilia B (HB). To estimate long-term global demand we model latent therapeutic demand (LTD) of HB and the economic ability of countries to afford treatment. LTD is the underlying demand that represents how physicians would prescribe treatment and how patients would comply with the prescribed treatment if ample supplies of drugs were available and affordable. HB is a rare, genetic, life-long bleeding disorder in which the blood does not clot properly because of the absence or deficiency of factor IX (FIX), a protein in human blood that is necessary for coagulation. To treat HB, the deficient or missing FIX protein must be replaced through infusions of FIX into a patient's veins.

This research is motivated by the desire to better understand the demand for FIX in the treatment of HB for planning long-term global production capacity. Forecasting global FIX demand for HB is an important issue for the hemophilia community. The World Health Organization lists FIX drug therapy as an essential medicine (WHO 2011). Unfortunately, HB treatment around the world are often dictated by scarcity of FIX drugs, rationing of care, limitation on reimbursement, and a lack of understanding of patients needs. These shortcomings limit the ability of healthcare professionals to apply the appropriate level of FIX treatment for patients with HB. Most people with HB receive inadequate or no treatment because of unavailable and/or unaffordable FIX treatment (Ayob 2008). Inadequate treatment often results in chronic morbidity (such as joint deformities, disabilities), and no treatment results in death in childhood or early adult life for those with severe HB (Larsson 1985). In the 1960s, there was little difference in HB healthcare among countries (Aledort 1998). Today the gap between the

"have's" and "have not's" has become wider. Trends suggest that the consumption of FIX drugs has been increasing at a faster rate with increasing economic capacity (Stonebraker et al. 2011). As more FIX is produced will it continue to go disproportionately to those countries that already use the most FIX or will increased production allow the rest of the world to catch up?

Answering this question is critical for manufacturers in planning for global production capacity of FIX and for national healthcare agencies to determine realistic budget priorities in planning for an increased allocation of resources required to improve the treatment of patients with HB in their country. The real challenge for industry is forecasting demand in each country over the next ten years to enable improved planning for global production capacity and national healthcare needs. Industry's commitment to providing reliable supplies of the safest possible FIX drug products includes developing a keen understanding of demand. The more we know about the needs of the global hemophilia community, the better industry can respond to the needs of patients and their quality of life, doctors and nurses in the identification of evolving care needs, and public health authorities for a better management and planning of hemophilia care requirements and resources.

The supply-constrained environment of the hemophilia market has reduced the usefulness of traditional historical-sales-based forecasting methods. Industry demand forecasts often use historical sales data to forecast future sales demand (Diebold 2001). The problem with using supply-constrained historical sales to extrapolate future demand is that the demand might have been higher if sufficient supply of FIX drugs were available. Not recognizing that past sales were limited by supply can result in demand forecasts that are underestimated and production capacity planning that is suboptimal (Nahmias 1994). For example, inadequate quantities of FIX drugs caused by supply limitations have hampered efforts by the medical community to define the

optimal treatment for HB (Farrugia 2004). Standard forecasting methods that assume past behavior is predictive of future behavior are often suitable, but offer little guidance for forecasting demand in supply-constrained markets that have been limited by insufficient product availability (Linton 2004) which has been the case in the hemophilia market. This research is novel in forecasting demand for the treatment of HB when the supply of FIX drugs has been limited.

To improve the industry practice of forecasting global FIX demand in the treatment of HB we model LTD for the FIX treatment of HB and the EDS of countries to afford treatment. An increased supply of FIX drugs that moves closer to the LTD for HB should improve the treatment of patients with HB and substantially reduce the costly long-term burden to national healthcare agencies when these patients are inadequately treated. However, an improved estimate of demand would include not only LTD, but also the EDS of countries to afford FIX treatment. The integration of LTD and EDS into a long-term global demand model will assist industry in realistically planning its global production capacity to provide adequate supplies of FIX drugs so that national healthcare resources can meet the needs of HB patients. It is difficult to forecast the global demand for the FIX treatment of HB due to the uncertainty surrounding the prevalence of HB, its treatment, and the economic ability of countries to afford FIX treatment. An improved forecast of long-term (10-year) global demand for the FIX treatment of HB will assist industry in realistically planning its global production capacity to provide adequate supplies of FIX drugs so that national healthcare resources can meet the needs of HB patients.

This paper is organized as follows. Section 2 is a literature review of the previous related work in production capacity planning and demand forecasting. Section 3 describes the research approach. Section 4 discusses the global demand model for the FIX treatment of HB. Section 5

discusses the data obtained and the choices made in modeling the variables in the demand model. Section 6 is the results of the analysis. Section 7 is concluding remarks.

## 2. Previous Related Work

Production capacity planning under uncertainty plays a critical role in improving business performance. Wu et al. (2005) describe the importance of capacity planning in various industries (consumer electronics, telecommunications, pharmaceuticals, and biotechnology) where supply is a limiting factor and there are substantial uncertainties around demand and supply. Geng and Jiang (2009) and Karabuk and Wu (2003) discuss the important role production capacity planning plays in the semiconductor manufacturing industry because of high investment cost, volatile demand structure of products and the high variability of manufacturing yields. Ku (1995) discusses the necessity of capacity planning in the electrical power industry that requires a substantial investment of capital over a long period of time involving a large number of uncertainties. Luss (1982) discusses the importance of planning for the expansion of production capacity in many application areas (e.g., electrical power, water resources, etc.). Stonebraker (2013) discusses whether Bayer should expand production capacity for a biotechnology product.

Forecasting demand is crucial to capacity planning. There is an extensive literature of energy demand forecasting (Jebaraj and Iniyan 2006, Suganthi and Samuel 2012). Forecasting energy demand is an important issue for energy planners and policy makers. Forecasts that underestimate electricity demand lead to potential outages which are devastating to the economy and life. On the other hand, an overestimation of demand leads to idle capacity and wasted financial resources. Models to forecast energy demand often use historical energy consumption and its relationship with macro socio-economic and demographic variables (e.g., GDP, energy price, population, etc.). Ardakani and Ardehali (2014) show that electrical energy consumption

forecasts based on historical socio-economic data are more accurate than forecasts based on historical electrical energy consumption data. Suganthi and Samuel (2012) discuss energy demand forecasting models (e.g., time series, regression, econometric, etc.) that capture uncertainty by considering select-few scenarios to estimate future energy consumption. It is common for these models to have time horizons of 25-50 years to predict the long-term future energy demand (Kydes et al. 1995). There is also considerable literature on forecasting country-specific energy consumption especially for countries in which consumption is growing quickly. For example, Kankal et al. (2011) document 23 studies on energy demand forecasting for Turkey. Besides the energy industry, demand forecasting is critically important in other industries. For example, in the pharmaceutical industry, manufacturers cannot appropriately justify a business case for expanding capacity when forecasts are not reasonable (Levine et al. 2008). In addition, Levine et al. (2008) discuss how national healthcare agencies in developing countries often lack expertise in demand forecasting even though they rely heavily on the forecasts for budgeting. Other examples include long-term global water demand projections (Hejazk et al. 2014), long-term gold price forecasting (Shafiee and Topal 2010), and long-term global fertilizer demand forecasting (Tenkorang and Lowenberg-De-Boer 2009). These examples from industries other than energy use similar models and techniques as discussed in energy demand forecasting.

Rather than forecasting based on supply-constrained historical FIX sales data, we model global demand for the FIX treatment of HB using LTD and EDS. Demand is the potential amount that would be demanded if supply is available. LTD is the amount that would be demanded if supply is available and treatment is affordable. EDS is the economic ability of a country to afford treatment. The focus of this paper is to improve industrial production capacity

planning by forecasting the long-term global FIX demand for the treatment of HB using LTD and EDS.

## 3. Research Approach

We use an approach based on the principles of decision analysis (Stonebraker et al. 2014, Stonebraker and Keefer 2009, and Stonebraker et al. 2004) to assess the uncertainty of treatment-related and epidemiological-related variables for LTD and economically-related variables for EDS. For LTD, we model the uncertainty associated with the epidemiology of HB and its treatment modalities. Epidemiology describes the disease occurrence (prevalence) and its distribution within the demographics of a patient population (e.g., severity of disease). Treatment includes the percentage of patients with HB that are prescribed treatment (dosage and frequency of administration) and the percentage of patients that are compliant with the prescribed treatment. The basic idea of LTD is to use the estimates of epidemiological-related variables to determine the number of potential patients with HB available for FIX treatment and to use the estimates of treatment-related variables to determine the volume of FIX treatment consumed per patient, and multiply the number of patients and volume of treatment together to forecast LTD. For EDS, we forecast, over 10 years, the economic ability of countries to afford FIX treatment by investigating relationships between historical FIX usage and macroeconomic indicators. To model long-term global FIX demand (LTD and EDS) for the treatment of HB, we:

1) Reviewed the medical literature on the epidemiology of HB and its treatment and obtained data on the epidemiological-related and treatment-related variables impacting LTD.
2) Obtained longitudinal data on observed FIX sales and macro health-economic indicators. Explored country-by-country relationships between historical FIX sales and macro

health-economic indicators and determined the indicator with the largest correlation to FIX sales. Modeled the economic-related variables impacting EDS.

3) Integrated LTD and EDS into a long-term global demand model that forecasts the FIX treatment of HB (number of FIX international units or IUs) that would be demanded if supply were not constrained.
4) Constructed an influence diagram to model the probabilistic and functional interrelationships of the epidemiology, treatment, and economic variables that impact the long-term global demand by considering the uncertainties in, and dependencies among these discrete and continuous random variables.
5) Conducted one-way sensitivity analysis of the variables using a tornado diagram to rank-order variables in terms of their impact on long-term global FIX demand for the treatment of HB.
6) Modeled the uncertainty surrounding the most sensitive random variables. Random variables can be discrete (binary and categorical), continuous, or mixed. For continuous random variables with substantial amount of data, we constructed an empirical probability distribution from data collected (Clemen 1996) and used discrete approximations methods (Keefer and Bodily 1983 and Hammond and Bickel 2013). These discrete approximations methods included the extended Pearson-Tukey (EPT) and the extended Swanson-Megill (ESM). The EPT uses a three-point discrete approximation of the 5th, 50th, and 95th percentiles from a probability distribution which are assigned probabilities of 0.185, 0.63, and 0.185, respectively. The ESM uses a three-point discrete approximation of the 10th, 50th, and 90th percentiles from a probability distribution which are assigned probabilities of 0.3, 0.4, and 0.3, respectively. For continuous random

variables with limited data, we used Monte Carlo simulation (e.g., uniform, triangular) to represent the data collected.

7) Generated probability distribution of long-term global demand of the FIX treatment of HB in terms of million international units and international units per capita.

## 4. Demand Model

The demand model consists of epidemiology, treatment, and economic variables, and their corresponding interrelationships. Table 1 shows the epidemiology-related variables, treatment-related variables, and economic-related variables. The influence diagram (Fig. 1) structures the interrelationships of the variables in Table 1. LTD models the population-based epidemiology of HB and its treatment modalities. Economic developed status (EDS) models the percentage of patients in a country over time that would have the economic ability to afford FIX treatment. EDS includes the initial EDS and an annual growth rate. Fig. 1 shows that there are 14 random variables in the long-term global demand model for the FIX treatment of HB. Five of these variables are dependent on other random variables. For example, prophylaxis treatment, prophylaxis compliance, and number of bleeding episodes each depend on severity. The remaining 9 random variables are independent.

The demand model in Fig. 1 was implemented in Excel and DPL (Syncopation Software, Inc. 2013). Excel organized the variables and their estimated values; specified the logical relationships between the variables; and computed demand. Demand is calculated from LTD and EDS. LTD is calculated from the number of patients, treatment volume per patient, and patient weight. The number of patients is calculated based on the prevalence, inhibitor prevalence, and severity. The treatment volume per patient is calculated based on prophylaxis treatment, prophylaxis compliance, on-demand treatment, number of bleeding episodes, prophylaxis dose,

prophylaxis frequency, immune tolerance induction treatment, immune tolerance induction dose, and immune tolerance frequency. EDS is calculated based on the values of initial economic developed status and annual growth rate. DPL provided the probabilistic structure used in modeling the uncertainty around the random variables (Fig. 1), generated the tornado diagram from the range estimates obtained, and used Monte Carlo simulation to generate a probability distribution for the global FIX demand of HB.

## 5. Data Obtained and Probabilistic Modeling

Data were obtained from the open literature since access to experts was not available. Rather than obtaining data from the opinions of experts the standard practice in medical decision making is to obtain data from the open literature. For example, published data from random-controlled trials are at the top of the hierarchy of medical evidence and data obtained from the opinions of medical experts are at the bottom of the hierarchy (Coyle et al. 2010). We restricted our search of epidemiology-related variables to high-income countries because diagnostic procedures are often not available and data-collection and reporting methods are often lacking in lower income countries (Stonebraker et al. 2011, 2012). HB data were also limited in the open literature since HB data is often combined with hemophilia A data.

In this research, data for the epidemiological-related, treatment-related, and economic-related variables were obtained from three sources: (1) specialized hemophilia medical journals, (2) the registries of the World Federation of Hemophilia (WFH 2002, 2004, 2005, 2006, 2007, 2008, 2009, 2011a, 2011b, 2012, 2013), Canada (AHCDC 2013), Italy (AICE 2012), and United States (CDC 2011); and (3) the World Bank's World Development Indicators (World Bank 2013). We searched specialized hemophilia medical journals (e.g., *Haemophilia*, *Blood,* etc.) and MedLine PubMed® using the key words, "hemophilia B", "epidemiology," "prevalence," and

"treatment." The World Bank's World Development Indicators (2013) provide cross-country comparable statistics on 1,234 macro socio-health-economic indicators that are organized into the following general categories: Economic Policy & Debt Balance of Payment, Economic Policy & Debt External Debt, Economic Policy & Debt National Accounts, Education, Environment, Financial Sector, Health, Infrastructure, Labor & Social Protection, Poverty, Private Sector & Trade, and Public Sector. In the remainder of this section, we discuss data collection for the epidemiology, treatment, and economic variables.

### 5.1. Epidemiology-Related Variables

#### 5.1.1. Prevalence

Prevalence is the number of diagnosed male patients with HB per 100,000 male population (UN 2013). We obtained prevalence data from high-income countries (AHCDC 2013, AICE 2012, CDC 2011, Linden et al. 2003, Mirchandani et al. 2011, Soucie et al. 1998, Stonebraker et al. 2012, Tagliaferri et al. 2008a, WFH 2011b, WFH 2012, WFH 2013). The prevalence estimates were determined by dividing the number of patients with HB in the country by its male population (UN 2013). We used the most-recent prevalence data for each high-income country in our analyses. Estimates used in the one-way sensitivity analysis ranged from 1.59 to 4.13 per 100,000 male population. In the probabilistic analysis, the uncertainty about HB prevalence was modeled as a continuous random variable using the EPT (Table 2).

#### 5.1.2. Inhibitor Prevalence

Inhibitor prevalence is the percent of severe HB patients with inhibitors. We obtained data from the open literature (AHCDC 2013, Astermark et al. 2006, Berntorp et al. 2012, Castaman et al. 2013, CDC 2011, Kamiya et al. 1995, Katz 1996, Monahan et al. 2010, Puetz et al. 2014, Recht et al. 2011, Roth et al. 2001, Shapiro et al. 2005, Sultan 1992, WFH 2012, WFH 2011, Zappa et

al. 2012). Estimates used in the one-way sensitivity analysis ranged from 1.7% to 8.4%. In the probabilistic analysis, the uncertainty about inhibitor prevalence was modeled as a continuous random variable using the EPT (Table 2).

### 5.1.3. Severity

Patients with HB are classified as severe if FIX activity level is <1% of normal, moderate: 1-5% of normal, and mild: >5% and <40% of normal (White et al. 2001). We obtained data from the open literature (AHCDC 2013, AICE 2012, CDC 2011, Linden et al. 2003, Soucie et al. 1998, Tagliaferri et al 2008a, WFH 2011, WFH 2012, Zappa et al. 2012). Estimates used in the one-way sensitivity analysis ranged from 20% severe, 41% moderate, and 39% mild for the United Kingdom (WFH 2013) to 60% severe, 29% moderate, and 11% mild for South Korea (WFH 2013). In the probabilistic analysis, the uncertainty about severity was modeled as a discrete (categorical) random variable using the average of the data for percent severe, percent moderate, and percent mild from the high-income countries (WFH 2013) (Table 2).

### 5.1.4. Patient Weight

Since the FIX dosage to treat a patient with HB is weight-dependent, we obtained the weight distribution data on the United States population from the Centers for Disease and Control (CDC) (Fryar et al. 2012). We obtained age grouping data for HB patients with and without inhibitors (AHCDC 2013, AICE 2012, Puetz et al. 2014). We addressed the differences in age groupings for the United States population (Fryar et al. 2012) and patients with HB (AHCDC 2013, AICE 2012, Puetz et al. 2014) by dividing the age-specific counts in Fryar et al. (2012) by the total counts in that age group (Klein and Schonborn 2001). An empirical probability distribution for patient weight was derived for HB patients without inhibitors and with inhibitors. The 10th and 90th percentiles were determined from this distribution and were used in the one-

way sensitivity analysis. In the probabilistic analysis, the uncertainty about patient weight was modeled as a continuous random variable using the ESM (Table 2).

### 5.2. Treatment-Related Variables

#### 5.2.1. Prophylaxis Treatment

Prophylaxis treatment is whether physician would prescribe prophylaxis for a given level of severity. We obtained data from the open literature (Aznar et al. 2011, Blanchette et al. 2003, Bliss et al. 2008, Tagliaferri et al. 2008b, Taki and Shirahata 2009, Zappa et al. 2012).Since prophylaxis treatment has binary outcomes, the percentage of HB patients treated prophylactically was varied from 0% to 100% in the one-way sensitivity analysis. In the probabilistic analysis the uncertainty about prophylaxis treatment was modeled as a discrete binary random variable (Table 2).

#### 5.2.2. Prophylaxis Dose

Prophylaxis dose is the prophylaxis dose size prescribed by physician (IU per kilogram of patient bodyweight). We obtained data from the open literature (Ahnström et al. 2004, Biss et al. 2008, Björkman 2003, Coppola et al. 2008, Fischer et al. 2002, Fischer and Van den Berg 2003, Löfqvist et al. 1997, Monahan et al. 2010, Nilsson et al. 1992, Roth et al. 2001, Tagliaferri et al. 2008b, Van den Berg and Fischer 2003). Estimates used in the one-way sensitivity analysis ranged from 25 to 50 IUs per kilogram. The uncertainty about prophylaxis dose was modeled as a continuous random variable using the uniform distribution in the probabilistic analysis (Table 2).

#### 5.2.3. Prophylaxis Frequency

Prophylaxis Frequency is the number of prophylactic infusions administered per patient per year. We obtained data from the open literature (Ahnström et al. 2004, Biss et al. 2008, Björkman

2003, Coppola et al. 2008, Fischer et al. 2002, Fischer and Van den Berg 2003, Löfqvist et al. 1997, Monahan et al. 2010, Nilsson et al. 1992, Roth et al. 2001, Tagliaferri et al. 2008b, Van den Berg and Fischer 2003). Estimates used in the one-way sensitivity analysis ranged from 52 times per year (once weekly) to 182 times per year (every other day). In the probabilistic analysis the uncertainty about prophylaxis frequency was modeled as a discrete (categorical) random variable (Table 2).

#### 5.2.4. Prophylaxis Compliance

Prophylaxis compliance is whether patients would adhere to the prophylaxis prescription for a given level of severity. We obtained data from the open literature (Zappa et al. 2012). Since prophylaxis compliance has binary outcomes, the percentage of HB patients compliant with prophylaxis was varied from 0% to 100% in the one-way sensitivity analysis. In the probabilistic analysis the uncertainty about prophylaxis compliance was modeled as a discrete binary random variable (Table 2).

#### 5.2.5. On-Demand Treatment

On-demand treatment is the amount of treatment (IU per kg) administered per bleeding episode. We obtained data from the open literature (Monahan et al. 2010, Roth et al. 2001, Shapiro et al. 2005, Zappa et al. 2012). Estimates used in the one-way sensitivity analysis ranged from 30 to 130 IUs per kilogram. In the probabilistic analysis the uncertainty about on-demand treatment was modeled as a continuous random variable using the uniform distribution (Table 2).

#### 5.2.6. Number of Bleeding Episodes

The number of bleeding episodes is the annual number of bleeding episodes for a given level of severity and whether patients are compliant with prophylaxis. We obtained data from the open literature (Monahan et al. 2010, Panicker et al. 2003, Tagliaferri et al. 2008a). Estimates used in

the one-way sensitivity analysis ranged from 0 to 16 for severe HB patients treated on-demand, 0 to 3.2 for moderate HB patients treated on-demand, 0 to 9 for severe HB patients treated by prophylaxis. In the probabilistic analysis the uncertainty about the number of bleed episodes was modeled as a mixed random variable using the uniform distribution (Table 2).

### 5.2.7. Immune Tolerance Induction Treatment

Immune tolerance induction treatment is whether physicians would prescribe immune tolerance induction when a HB patient has inhibitors. We obtained data from the open literature (Astermark et al. 2006, Castaman et al. 2013, Zappa et al. 2012). Since immune tolerance induction treatment has binary outcomes, the percentage of HB patients treated with immune tolerance induction was varied from 0% to 100% in the one-way sensitivity analysis. In the probabilistic analysis the uncertainty about immune tolerance induction treatment was modeled as a discrete binary random variable (Table 2).

### 5.2.8. Immune Tolerance Induction Dose

Immune tolerance induction dose is the dose size prescribed by physicians (IU per kg) for immune tolerance induction. We obtained data from the open literature (Astermark et al. 2006, Castaman et al. 2013, DiMichele 2009). Estimates used in the one-way sensitivity analysis ranged from 25 to 200 IUs per kilogram. In the probabilistic analysis the uncertainty about immune tolerance induction dose was modeled as a continuous random variable using the triangular distribution (Table 2).

### 5.2.9. Immune Tolerance Induction Frequency

Immune tolerance induction frequency is the number of infusions administrated for immune tolerance inductions per patient per year. We obtained data from the open literature (Astermark et al. 2006, Castaman et al. 2013, DiMichele 2009). Estimates used in the one-way sensitivity

analysis ranged from 5 to 365 times per year. In the probabilistic analysis the uncertainty about immune tolerance induction frequency was modeled as a continuous random variable using the triangular distribution (Table 2).

### 5.3. Economic-Related Variables

Similar to global energy demand forecasting, we investigated a proxy for economic develop status (EDS) by examining the correlation among historical FIX sales (Stonebraker et al. 2004) and socio-health-economic indicators (World Bank 2013). Data were obtained on FIX sales (WFH 2002, 2004, 2005, 2006, 2007, 2008, 2009, 2011a, 2011b, 2012, 2013) for 97 countries for the years 2002 to 2012 and on 1,234 country-specific macro socio-health-economic indicators for 204 countries from the World Bank (2013) for the years 1960-2012. We determined that GDP per capita (constant 2005 US dollars) (World Bank 2013) had a strong correlation with IG sales (R = 0.76) and used GDP per capita as a proxy for EDS. Of the 204 countries, 14 countries did not have GDP per capita data so we removed them from our analysis resulting in 190 countries. The EDS of country $i$ at time $t$, $EDS_{i,t}$, to afford IG treatment was determined using the country's initial economic-developed status, $EDS_{i,t=0}$, and its annual growth rate, $g_i$:

$$EDS_{i,t} = EDS_{i,t=0} \times (1 + g_i)^t .$$

#### 5.3.1. Initial Economic Developed Status (EDS)

GDP per capita data were normalized from 0% to 100% since the initial EDS is a percentage of HB patients in a country that have the economic ability to afford FIX treatment. For each year, we determined the minimum and maximum GDP per capita of the 190 countries considered in this research. The initial EDS of the country with the minimum GDP per capita was set to 0% whereas the initial EDS of the country with the maximum GDP per capita was set to 100%. For

all other countries, the initial EDS of country $i$ at time $t = 0$, $EDS_{i,t=0}$, is determined using its GDP per capita, $x_i$, and the minimum and maximum values of GDP per capita. Estimates for initial EDS are given in Table 3.

### 5.3.2. Annual Growth Rate

The GDP per capita was used as proxy to determine the future annual growth rate of EDS. Pritchett (2000) shows that year-to-year variability becomes less when the time period is extended. Williams (2003) finds that the annual growth pattern has extremely large fluctuation whereas long-term growth patterns are stable. Similarly, we found substantial year-to-year fluctuations for the GDP per capita data from 1960-2012 (World Bank 2013) especially in lower income countries, and more stability (less fluctuations) as the time period is extended. Since we are forecasting global demand in the next 10 years, we used 10-year moving interval for the GDP per capita of each country for the years 1960 to 2012 to determine the compound annual growth rate. For example, when GDP per capita data are available for a country over that entire time period (1960-2012) we computed 43 compound annual growth rates. The first 10-year moving interval is 1960-1970 and the last 10-year moving interval is 2002-2012. The annual growth rate over a 10-year interval is adjusted to a compound annual growth using the following equation:

$$g_i = \left(1 + \frac{GDP\ per\ capita_{i,t} - GDP\ per\ capita_{i,t-10}}{GDP\ per\ capita_{i,t-10}}\right)^{\frac{1}{10}} - 1,$$

where $GDP\ per\ capita_{i,t}$ is the GDP per capita for country $i$ at time $t$ and $GDP\ per\ capita_{i,t-10}$ is the GDP per capita for country $i$ at time $t-10$.

We constructed an empirical CDF (Clemen 1996) for the calculated annual growth rate data of each country and applied the EPT approximation for these continuous distributions. Probabilistic estimates for the annual growth rate are given in Table 3. As shown in Fig. 1, the

global demand at time $t$ of IG treatment for CVID, $Demand_t$, is determined from LTD and the EDS of country $i$ at time $t$ and is giving in the following equation:

$$Demand_t = \sum_{i=1}^{N} LTD \times EDS_{i,t}$$

where $N$ is the number of countries in the analysis.

## 6. Results

### 6.1. Sensitivity Analysis

As is common in decision analysis practice, we used deterministic analysis to determine the most-sensitive variables to global demand (McNamee and Celona 2005). The sensitive random variables of demand were determined using a tornado diagram as calculated by DPL (Syncopation Software, Inc. 2013). Specifically, a tornado diagram was constructed to show the changes in demand that result from varying each random variable over its range of estimates while leaving the other variables set at their base-case values. The impact on the long-term global demand for HB of the random variables was determined by varying each variable sequentially over its range of possible (low and high) values while keeping the other variables set at their base-case value. The length of the bar for each variable in Fig. 3 represents how sensitive each is to the long-term global demand for HB. The tornado diagram is arranged that the variable with the greatest impact on demand is the longest bar and it is located at the top whereas the least sensitive is shown at the bottom of Fig. 3. For the binary discrete random variables (prophylaxis treatment, prophylaxis compliance, and immune tolerance induction treatment) the values ranged from 0% to 100%. For example, for prophylaxis treatment, we used the range from 0% (no one treated with prophylaxis) to 100% (all patients treated with prophylaxis). The most sensitive random variable from the tornado diagram was prophylaxis treatment (Fig. 3).

### 6.2. Probabilistic Analysis

Probabilistic analysis was used to evaluate the impact of uncertainty on the long-term global demand for the FIX treatment of HB. Using the probability models for the variables (Tables 2 and 3) resulted in a mean and standard deviation of 1,700 ± 1,292 million IUs for the global FIX demand in the treatment of HB (Fig. 4). The mean of 0.213 IUs per capita is less than the mean LTD of 0.958 IUs per capita. The FIX demand forecast for the high-income countries is greater than lower income countries.

### 6.3. Business Implications

The results of this research provide the hemophilia industry insights of the long-term global demand of the FIX treatment for HB. This insight is crucial for gaining commitment of the hemophilia industry on whether to expand production capacity of FIX for the treatment of HB. From a business perspective, FIX manufacturers need accurate global demand forecasts to determine whether to expand capacity since building a new FIX manufacturing plant to expand capacity is expensive. The capital costs are $70-110 million, timeframe to construct the facility is 3-4 years, and annual operating costs are $74 million (Goss and Curling 2013). The key question from hemophilia industry is whether the FIX demand forecasts in this research are accurate? The inputs used in modeling LTD have been critically reviewed in the hemophilia medical community through a presentation at the 2014 World Federation of Hemophilia World Congress in Melbourne, Australia. Our model to forecast EDS follows the well-documented energy demand forecasting models that estimate the long-term global energy demand using macro-economic variables (e.g., GDP per capita). These demand models are often used in the energy industry in planning for capacity expansion. However, unlike these models, we do not use select-few scenarios to model uncertainty. Instead we use probability models for the variables that

influence the long-term global demand for the FIX treatment of HB

## 7. Concluding Remarks

Forecasts are important for effective implementation of industrial production capacity planning and national healthcare policy planning. Accurate forecasts of FIX demand for the treatment of HB are vital when the market has been supply-constrained. The aim of this study is to forecast the long-term global FIX demand for HB by modeling LTD and EDS to improve production capacity planning in the hemophilia industry. These forecasts would also guide national healthcare agencies to take necessary policy actions to ensure the proper treatment for patients with HB. The modeling of long-term FIX demand will help industrial manufacturers determine the right level of their production capacity to ensure that adequate supplies of drugs are available and help national healthcare agencies plan and allocate its resources to improve patient outcomes. The forecasted long-term global demand for the FIX treatment of HB is expected to be greater than the historical supply-constrained sales. This insight is critical for the hemophilia industry to expand production capacity to meet the forecasted global demand for the FIX treatment of FIX.

The broader impacts of this research will be manifested in several ways. This is a problem of great practical importance, and it will lead to: (1) deeper understanding of the global long-term demand for the FIX treatment of HB, (2) improved resource-allocation decisions for national healthcare planning and global production capacity planning, and (3) move the HB community closer to the World Federation of Hemophilia's strategic goal of "Treatment for All" (Skinner 2006, 2010, 2012). The evolution of HB healthcare is of great importance in allocating resources, particularly in developing countries where the priority is to secure treatment levels ensuring not only patient survival, but good musculoskeletal health to allow an independent and

high-quality productive life.

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**Table 1**
Variables that influence the demand for FIX in hemophilia B (HB).

| Variable | Description | Influences |
|---|---|---|
| Epidemiology-Related Variables (Latent Therapeutic Demand – LTD) | | |
| Prevalence | number of diagnosed male patients with HB per 100,000 male population | |
| Inhibitor Prevalence | percent of severe HB patients with inhibitors | |
| Severity | severe: <1% of normal<br>moderate: 1-5% of normal<br>mild: >5% and <40% of normal | Prophylaxis Treatment<br>Prophylaxis Compliance<br>Number of Bleeding Episodes |
| Patient Weight | kilogram of body weight | |
| Treatment-Related Variables (Latent Therapeutic Demand – LTD) | | |
| Prophylaxis Treatment | whether physician would prescribe prophylaxis for a given level of severity | Number of Bleeding Episodes<br>On-Demand Treatment |
| Prophylaxis Dose | prophylaxis dose size prescribed by physician (IU per kg) | |
| Prophylaxis Frequency | number of prophylactic infusions administered per patient per year | |
| Prophylaxis Compliance | whether patients would adhere to the prophylaxis prescription for a given level of severity | On-Demand Treatment |
| On-Demand Treatment | amount of treatment (IU per kg) administered per bleeding episode | |
| Number of Bleeding Episodes | annual number of bleeding episodes for a given level of severity and whether patients are compliant with prophylaxis | |
| Immune Tolerance Induction Treatment | whether physicians would prescribe immune tolerance induction | |
| Immune Tolerance Induction Dose | immune tolerance induction dose size prescribed by physicians (IU per kg) | |
| Immune Tolerance Induction Frequency | number of immune tolerance inductions administrated per patient per year | |
| Economic-Related Variables (Economic Developed Status – EDS) | | |
| Initial Developed Status | Macro-economic ability of a country to pay for treatment | |
| Annual Growth Rate | Annual growth rate for a country's economic developed status | |

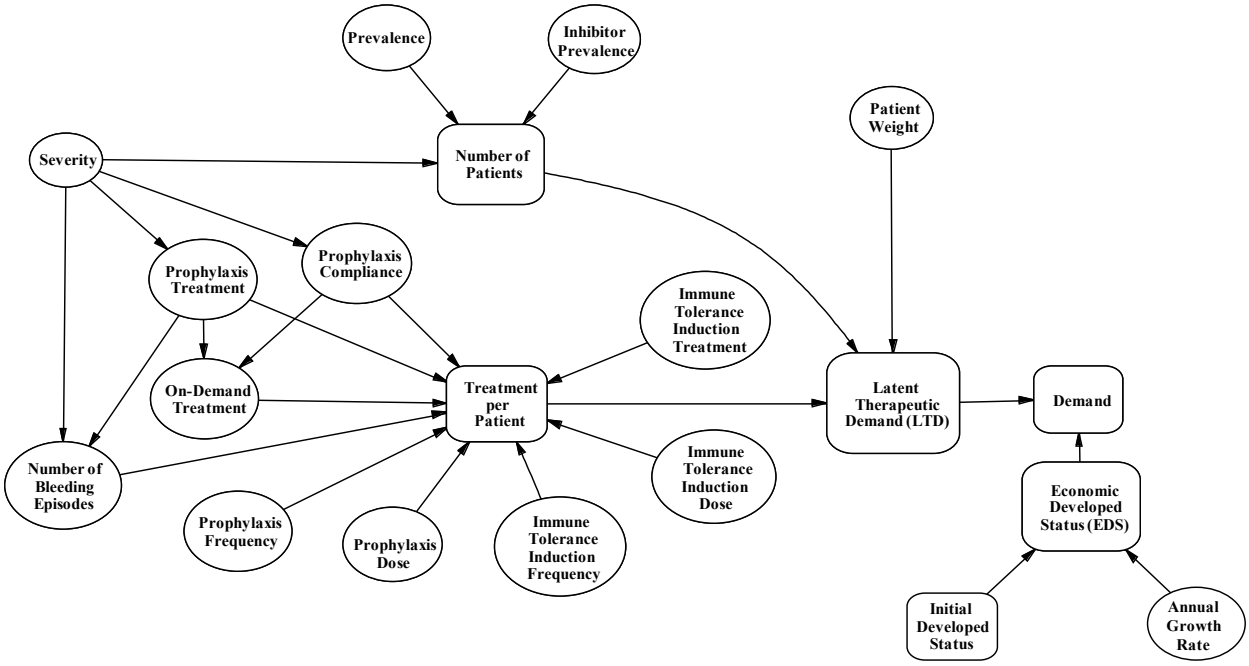



**Fig. 1** Modeling the variables that influence demand for hemophilia B (HB).

**Table 2**
Modeling the variables that influence demand for hemophilia B (HB).

| Variable | Type | Model |
|---|---|---|
| Prevalence | Continuous | EPT(1.59, 2.83, 4.13) |
| Inhibitor Prevalence | Continuous | EPT(1.7%, 3.9%, 8.4%) |
| Severity | Discrete (Category) | Severe: 35.3%<br>Moderate: 32.4%<br>Mild: 32.3% |
| Patient Weight | Continuous | EPT(17.7, 77.9, 117.6) without inhibitors<br>EPT(11.8, 56.2, 116.2) with inhibitors |
| Prophylaxis Treatment | Discrete (Binary) | Probability of Prophylaxis Treatment for Severe = 53%<br>Probability of Prophylaxis Treatment for Moderate = 10% |
| Prophylaxis Dose | Continuous | U(25, 50) |
| Prophylaxis Frequency | Discrete (Category) | Once Weekly: 24%<br>Twice Weekly: 57%<br>Every Other Day: 19% |
| Prophylaxis Compliance | Discrete (Binary) | Probability of Complying with Prophylaxis = 78% |
| On-Demand Treatment | Continuous | U(30, 130) |
| Number of Bleeding Episodes | Mixed | Severe On-Demand: Probability of No Bleeds 36%, Bleeds U(8, 16)<br>Moderate On-Demand: Probability of No Bleeds 77%, Bleeds U(1.3, 3.2)<br>Severe on Prophylaxis: Probability of No Bleeds 57%, Bleeds U(1, 9) |
| Immune Tolerance Induction Treatment | Discrete (Binary) | Probability of Immune Tolerance Induction Treatment = 67% |
| Immune Tolerance Induction Dose | Continuous | T(25, 100, 200) |
| Immune Tolerance Induction Frequency | Continuous | T(5, 150, 365) |

EPT is the Extended Pearson Tukey (5th, 50th, and 95th percentiles with the following probabilities of 0.185, 0.630, and 0.185)
ESM is the Extended Swanson Megill (10th, 50th, and 90th percentiles with the following probabilities of 0.3, 0.4, and 0.3)
U(low, high) = uniform distribution
T(low, most-likely, high) = triangular distribution

**Table 3**
Modeling the economic-related variables for 190 countries that influence long-term global demand of the factor IX (FIX) treatment for hemophilia B (HB).

| | | | Initial Economic Developed Status | Annual Growth Rate | | |
|---|---|---|---|---|---|---|
| Country Name | Income | Region | | 5th percentile | 50th percentile | 95th percentile |
| Afghanistan | (5) | Asia | 0.4% | 3.5% | 7.2% | 15.4% |
| Albania | (3) | Europe | 3.6% | -0.1% | 12.7% | 18.1% |
| Algeria | (3) | Africa | 4.9% | -5.2% | 8.9% | 19.3% |
| Angola | (3) | Africa | 5.1% | -6.1% | 10.3% | 24.4% |
| Antigua and Barbuda | (2) | Caribbean | 12.1% | 2.5% | 5.9% | 16.8% |
| Argentina | (3) | Latin America | 10.9% | -6.1% | 5.9% | 11.0% |
| Armenia | (4) | Asia | 3.0% | 0.9% | 15.5% | 19.8% |
| Aruba | (2) | Caribbean | 15.4% | 1.8% | 3.1% | 3.8% |
| Australia | (1) | Oceania | 65.0% | 1.4% | 6.4% | 12.5% |
| Austria | (1) | Europe | 44.8% | 1.2% | 8.1% | 16.9% |
| Azerbaijan | (3) | Asia | 6.7% | -5.6% | 19.7% | 25.9% |
| Bahamas | (2) | Caribbean | 20.9% | 0.3% | 6.0% | 11.8% |
| Bahrain | (2) | Asia | 13.7% | -0.2% | 2.9% | 6.9% |
| Bangladesh | (5) | Asia | 0.5% | 0.8% | 3.3% | 8.0% |
| Barbados | (2) | Caribbean | 14.2% | 3.2% | 7.2% | 15.3% |
| Belarus | (3) | Europe | 6.2% | -3.1% | 10.2% | 17.2% |
| Belgium | (1) | Europe | 41.6% | 1.2% | 6.6% | 16.3% |
| Belize | (3) | Latin America | 2.7% | 3.1% | 5.9% | 10.4% |
| Benin | (5) | Africa | 0.5% | -0.5% | 3.9% | 10.7% |
| Bhutan | (4) | Asia | 2.1% | 2.6% | 5.8% | 10.9% |
| Bolivia (Plurinational State of) | (4) | Latin America | 2.2% | -2.2% | 3.7% | 13.4% |
| Bosnia and Herzegovina | (3) | Europe | 4.2% | 10.9% | 14.3% | 20.7% |
| Botswana | (3) | Africa | 6.7% | 2.0% | 10.1% | 20.1% |
| Brazil | (3) | Latin America | 10.7% | 0.9% | 7.8% | 16.3% |
| Brunei Darussalam | (2) | Asia | 39.5% | -3.2% | 5.0% | 28.2% |
| Bulgaria | (3) | Europe | 6.5% | -7.1% | 3.2% | 15.7% |
| Burkina Faso | (5) | Africa | 0.4% | -2.3% | 4.4% | 11.6% |
| Burundi | (5) | Africa | 0.0% | -4.5% | 0.7% | 12.2% |
| Cambodia | (5) | Asia | 0.7% | -4.5% | 4.3% | 10.8% |
| Cameroon | (4) | Africa | 0.9% | -4.9% | 4.8% | 14.4% |
| Canada | (1) | Northern America | 50.2% | 1.0% | 6.7% | 10.6% |
| Cape Verde | (4) | Africa | 3.3% | 2.9% | 8.5% | 11.8% |
| Central African Republic | (5) | Africa | 0.2% | -5.4% | 4.5% | 10.6% |
| Chad | (5) | Africa | 0.8% | -2.8% | 2.8% | 16.5% |
| Channel Islands | (2) | Europe | 43.1% | 0.0% | 0.0% | 0.0% |
| Chile | (1) | Latin America | 14.7% | 0.0% | 6.2% | 13.1% |
| China | (3) | Asia | 5.6% | 3.8% | 6.5% | 16.6% |
| China, Hong Kong SAR | (2) | Asia | 35.3% | 1.3% | 10.2% | 18.6% |
| China, Macao SAR | (2) | Asia | 75.3% | 2.7% | 10.7% | 16.3% |
| Colombia | (3) | Latin America | 7.2% | 0.4% | 6.2% | 13.5% |
| Comoros | (5) | Africa | 0.6% | -3.5% | 4.2% | 7.5% |
| Congo | (4) | Africa | 2.8% | -3.5% | 7.7% | 16.3% |
| Costa Rica | (3) | Latin America | 8.8% | 2.8% | 6.1% | 13.4% |
| Cote d'Ivoire | (4) | Africa | 1.0% | -3.1% | 3.5% | 14.5% |
| Croatia | (2) | Europe | 13.2% | 1.3% | 10.0% | 11.9% |
| Cuba | (3) | Caribbean | 3.6% | -0.7% | 3.8% | 9.4% |
| Cyprus | (2) | Asia | 24.9% | 3.4% | 7.7% | 16.4% |
| Czech Republic | (1) | Europe | 17.8% | 6.8% | 9.4% | 12.9% |
| Democratic Republic of the Congo | (5) | Africa | 0.0% | -9.0% | -0.4% | 9.7% |
| Denmark | (1) | Europe | 54.1% | 1.5% | 7.0% | 14.9% |
| Djibouti | (4) | Africa | 0.5% | -0.6% | 0.4% | 3.3% |
| Dominican Republic | (3) | Caribbean | 5.3% | -0.2% | 6.5% | 13.0% |
| Ecuador | (3) | Latin America | 5.0% | -3.3% | 4.9% | 16.8% |
| Egypt | (4) | Africa | 2.9% | 2.6% | 6.0% | 9.3% |
| El Salvador | (4) | Latin America | 3.4% | 1.5% | 6.3% | 9.7% |
| Equatorial Guinea | (2) | Africa | 23.0% | -3.7% | 21.1% | 39.9% |
| Eritrea | (5) | Africa | 0.2% | 1.8% | 3.4% | 10.3% |
| Estonia | (1) | Europe | 15.9% | 12.4% | 14.0% | 16.2% |
| Ethiopia | (5) | Africa | 0.2% | -6.9% | -1.6% | 10.9% |
| Fiji | (3) | Oceania | 4.1% | 0.0% | 4.3% | 15.1% |
| Finland | (1) | Europe | 43.9% | 0.8% | 7.4% | 14.9% |
| France | (1) | Europe | 38.2% | 0.5% | 6.9% | 13.6% |
| French Polynesia | (2) | Oceania | 17.5% | 1.5% | 8.0% | 13.4% |
| Gabon | (3) | Africa | 10.6% | -3.5% | 3.2% | 23.8% |
| Gambia | (5) | Africa | 0.3% | -5.4% | 3.4% | 12.5% |

| | | | | | | |
|---|---|---|---|---|---|---|
| Georgia | (4) | Asia | 3.1% | -6.6% | 10.2% | 16.0% |
| Germany | (1) | Europe | 40.2% | 0.4% | 5.6% | 12.6% |
| Ghana | (4) | Africa | 1.3% | -2.6% | 2.2% | 16.9% |
| Greece | (1) | Europe | 21.1% | 2.3% | 7.6% | 14.6% |
| Grenada | (3) | Caribbean | 6.8% | 3.9% | 8.5% | 9.9% |
| Guatemala | (4) | Latin America | 3.0% | -0.5% | 4.7% | 12.3% |
| Guinea | (5) | Africa | 0.2% | -4.4% | -0.5% | 3.7% |
| Guinea-Bissau | (5) | Africa | 0.2% | -0.1% | 3.7% | 9.1% |
| Guyana | (4) | Latin America | 3.2% | -2.6% | 4.9% | 11.5% |
| Haiti | (5) | Caribbean | 0.5% | 0.6% | 3.6% | 6.9% |
| Honduras | (4) | Latin America | 2.0% | -2.1% | 6.2% | 10.1% |
| Hungary | (3) | Europe | 11.9% | 4.5% | 7.6% | 13.6% |
| Iceland | (1) | Europe | 40.7% | 1.9% | 7.2% | 16.7% |
| India | (4) | Asia | 1.2% | 1.5% | 5.6% | 11.6% |
| Indonesia | (4) | Asia | 3.2% | 1.1% | 5.5% | 20.3% |
| Iran (Islamic Republic of) | (3) | Asia | 4.0% | -9.1% | 7.9% | 21.4% |
| Iraq | (3) | Asia | 6.0% | -14.3% | 14.9% | 24.8% |
| Ireland | (1) | Europe | 44.1% | 6.2% | 9.8% | 14.3% |
| Israel | (1) | Asia | 20.3% | 1.3% | 7.2% | 11.7% |
| Italy | (1) | Europe | 31.7% | 0.0% | 9.3% | 12.7% |
| Jamaica | (3) | Caribbean | 5.0% | -1.4% | 5.8% | 9.8% |
| Japan | (1) | Asia | 44.9% | -0.6% | 10.6% | 18.2% |
| Jordan | (3) | Asia | 4.5% | -3.7% | 5.2% | 15.2% |
| Kazakhstan | (3) | Asia | 11.5% | -1.2% | 14.6% | 22.3% |
| Kenya | (5) | Africa | 0.7% | -1.9% | 4.7% | 10.5% |
| Kiribati | (4) | Oceania | 1.4% | -10.0% | 4.3% | 9.0% |
| Kuwait | (2) | Asia | 31.5% | -5.9% | 7.6% | 14.8% |
| Kyrgyzstan | (5) | Asia | 0.9% | -6.6% | 3.2% | 13.7% |
| Lao People's Democratic Republic | (4) | Asia | 1.1% | -4.2% | 4.5% | 14.8% |
| Latvia | (2) | Europe | 13.3% | 0.6% | 12.0% | 17.7% |
| Lebanon | (3) | Asia | 9.1% | 2.0% | 5.8% | 17.9% |
| Lesotho | (4) | Africa | 0.9% | 0.4% | 5.8% | 13.3% |
| Liberia | (5) | Africa | 0.2% | -15.2% | 4.2% | 9.0% |
| Libya | (3) | Africa | 6.7% | -5.6% | 1.9% | 9.4% |
| Lithuania | (2) | Europe | 13.5% | 2.0% | 13.3% | 15.5% |
| Luxembourg | (1) | Europe | 100.0% | 3.1% | 7.9% | 15.0% |
| Madagascar | (5) | Africa | 0.2% | -5.2% | 1.8% | 8.4% |
| Malawi | (5) | Africa | 0.0% | -2.4% | 3.8% | 10.8% |
| Malaysia | (3) | Asia | 9.8% | 2.7% | 6.4% | 15.4% |
| Maldives | (3) | Asia | 6.1% | 8.4% | 9.5% | 15.1% |
| Mali | (5) | Africa | 0.4% | -1.3% | 5.3% | 13.2% |
| Malta | (2) | Europe | 19.9% | 3.3% | 7.0% | 15.2% |
| Mauritania | (4) | Africa | 0.8% | -0.7% | 4.6% | 9.4% |
| Mauritius | (3) | Africa | 7.6% | 3.3% | 6.6% | 11.5% |
| Mexico | (3) | Latin America | 9.2% | 1.5% | 7.3% | 11.9% |
| Micronesia (Fed. States of) | (4) | Oceania | 2.8% | 1.6% | 2.8% | 4.2% |
| Mongolia | (4) | Asia | 3.3% | -12.3% | -1.2% | 19.6% |
| Montenegro | (3) | Europe | 6.6% | 13.0% | 14.4% | 15.1% |
| Morocco | (4) | Africa | 2.6% | 1.4% | 5.3% | 12.4% |
| Mozambique | (5) | Africa | 0.3% | -7.0% | 4.7% | 8.9% |
| Namibia | (3) | Africa | 5.3% | -1.0% | 3.3% | 11.7% |
| Nepal | (5) | Asia | 0.4% | 1.2% | 4.2% | 9.5% |
| Netherlands | (1) | Europe | 44.1% | 2.3% | 6.8% | 16.7% |
| New Caledonia | (2) | Oceania | 15.1% | -0.5% | 7.2% | 12.9% |
| New Zealand | (1) | Oceania | 36.2% | 1.3% | 6.1% | 10.9% |
| Nicaragua | (4) | Latin America | 1.5% | -6.6% | 4.4% | 12.3% |
| Niger | (5) | Africa | 0.1% | -5.0% | 1.7% | 9.0% |
| Nigeria | (4) | Africa | 1.3% | -9.4% | 7.2% | 18.3% |
| Norway | (1) | Europe | 95.9% | 3.5% | 8.1% | 15.6% |
| Oman | (2) | Asia | 14.1% | 0.1% | 7.9% | 34.3% |
| Pakistan | (4) | Asia | 1.0% | 1.5% | 4.4% | 9.8% |
| Panama | (3) | Latin America | 9.0% | 1.2% | 6.2% | 11.0% |
| Papua New Guinea | (4) | Oceania | 1.9% | -5.7% | 4.1% | 13.8% |
| Paraguay | (4) | Latin America | 3.4% | -2.5% | 5.3% | 18.8% |
| Peru | (3) | Latin America | 6.3% | -0.9% | 6.3% | 11.4% |
| Philippines | (4) | Asia | 2.3% | -0.2% | 4.5% | 13.0% |
| Poland | (1) | Europe | 12.0% | 7.1% | 9.0% | 10.9% |
| Portugal | (1) | Europe | 19.2% | 2.5% | 8.6% | 14.9% |
| Puerto Rico | (2) | Caribbean | 26.5% | 4.9% | 6.9% | 10.1% |
| Qatar | (2) | Asia | 55.0% | -7.1% | 6.0% | 23.9% |
| Republic of Korea | (1) | Asia | 21.6% | 4.7% | 12.6% | 20.8% |
| Republic of Moldova | (4) | Europe | 1.7% | -8.0% | 7.5% | 16.9% |
| Romania | (3) | Europe | 8.5% | -0.7% | 10.7% | 17.5% |
| Russian Federation | (2) | Europe | 13.3% | -7.4% | 8.6% | 20.4% |
| Rwanda | (5) | Africa | 0.4% | -4.9% | 5.2% | 15.3% |

| | | | | | | |
|---|---|---|---|---|---|---|
| Saint Lucia | (3) | Caribbean | 6.4% | 3.4% | 5.3% | 10.4% |
| Saint Vincent and the Grenadines | (3) | Caribbean | 6.0% | 4.3% | 7.9% | 12.9% |
| Samoa | (4) | Oceania | 3.3% | 1.2% | 7.3% | 9.3% |
| Sao Tome and Principe | (4) | Africa | 1.1% | 7.5% | 8.3% | 9.5% |
| Saudi Arabia | (2) | Asia | 24.0% | -7.0% | 3.0% | 31.3% |
| Senegal | (4) | Africa | 0.7% | -3.7% | 3.4% | 8.6% |
| Serbia | (3) | Europe | 4.8% | 7.2% | 10.8% | 18.8% |
| Seychelles | (3) | Africa | 12.2% | 2.8% | 8.2% | 19.1% |
| Sierra Leone | (5) | Africa | 0.4% | -5.5% | 2.8% | 10.0% |
| Singapore | (2) | Asia | 49.7% | 2.4% | 10.3% | 17.1% |
| Slovakia | (1) | Europe | 16.0% | 8.6% | 10.9% | 12.8% |
| Slovenia | (1) | Europe | 21.0% | 3.6% | 7.9% | 9.2% |
| Solomon Islands | (4) | Oceania | 1.5% | -4.7% | 4.9% | 11.2% |
| Somalia | (5) | Africa | 0.1% | -2.1% | 3.4% | 8.7% |
| South Africa | (3) | Africa | 7.0% | -1.4% | 6.1% | 11.9% |
| South Sudan | (5) | Africa | 0.7% | 0.0% | 0.0% | 0.0% |
| Spain | (1) | Europe | 27.4% | 1.0% | 8.4% | 16.0% |
| Sri Lanka | (4) | Asia | 2.6% | 2.7% | 5.7% | 10.7% |
| State of Palestine | (4) | Asia | 0.9% | -0.7% | -0.7% | -0.7% |
| Sudan | (4) | Africa | 1.3% | -6.2% | 5.5% | 14.5% |
| Suriname | (3) | Latin America | 8.8% | -7.9% | 8.6% | 15.3% |
| Swaziland | (4) | Africa | 2.7% | -0.2% | 6.2% | 12.2% |
| Sweden | (1) | Europe | 52.9% | -0.2% | 6.6% | 12.5% |
| Switzerland | (1) | Europe | 76.0% | 0.1% | 5.6% | 9.6% |
| Syrian Arab Republic | (4) | Asia | 2.9% | -5.4% | 6.7% | 15.0% |
| Tajikistan | (5) | Asia | 0.6% | -10.5% | 8.6% | 17.5% |
| TFYR Macedonia | (3) | Europe | 4.2% | -2.8% | 5.9% | 10.7% |
| Thailand | (3) | Asia | 5.0% | 0.3% | 8.6% | 14.0% |
| Timor-Leste | (4) | Asia | 0.8% | 6.9% | 7.1% | 8.3% |
| Togo | (5) | Africa | 0.3% | -3.6% | 2.7% | 9.9% |
| Tonga | (3) | Oceania | 4.1% | 2.1% | 7.0% | 11.9% |
| Trinidad and Tobago | (2) | Caribbean | 16.6% | -4.5% | 9.0% | 20.1% |
| Tunisia | (3) | Africa | 3.8% | 2.1% | 5.9% | 14.9% |
| Turkey | (3) | Asia | 10.1% | 1.1% | 7.3% | 13.1% |
| Turkmenistan | (3) | Asia | 6.3% | -3.8% | 10.0% | 22.1% |
| Uganda | (5) | Africa | 0.3% | -3.1% | 3.6% | 9.2% |
| Ukraine | (4) | Europe | 3.5% | -8.7% | 5.0% | 16.6% |
| United Arab Emirates | (2) | Asia | 23.8% | -4.1% | 1.8% | 4.5% |
| United Kingdom | (1) | Europe | 37.5% | 3.6% | 7.2% | 13.5% |
| United Republic of Tanzania | (5) | Africa | 0.3% | 4.2% | 5.5% | 7.8% |
| United States of America | (1) | Northern America | 49.7% | 3.1% | 5.8% | 9.1% |
| United States Virgin Islands | (2) | Caribbean | 21.9% | 5.9% | 8.0% | 16.2% |
| Uruguay | (2) | Latin America | 14.0% | -1.5% | 5.3% | 14.3% |
| Uzbekistan | (4) | Asia | 1.4% | -4.2% | 0.7% | 14.2% |
| Vanuatu | (4) | Oceania | 2.8% | 0.7% | 3.7% | 8.7% |
| Venezuela (Bolivarian Republic of) | (3) | Latin America | 12.0% | -5.4% | 4.9% | 13.2% |
| Viet Nam | (4) | Asia | 1.5% | -2.9% | 11.4% | 14.7% |
| Yemen | (4) | Asia | 1.2% | 1.4% | 9.4% | 11.8% |
| Zambia | (4) | Africa | 1.2% | -4.6% | 2.5% | 14.2% |
| Zimbabwe | (5) | Africa | 0.4% | -5.1% | 0.6% | 9.2% |

Income levels: (1) High Organisation for Economic Co-operation and Development (OECD), (2) High non-OECD, (3) Upper Middle, (4) Lower Middle, (5) Low

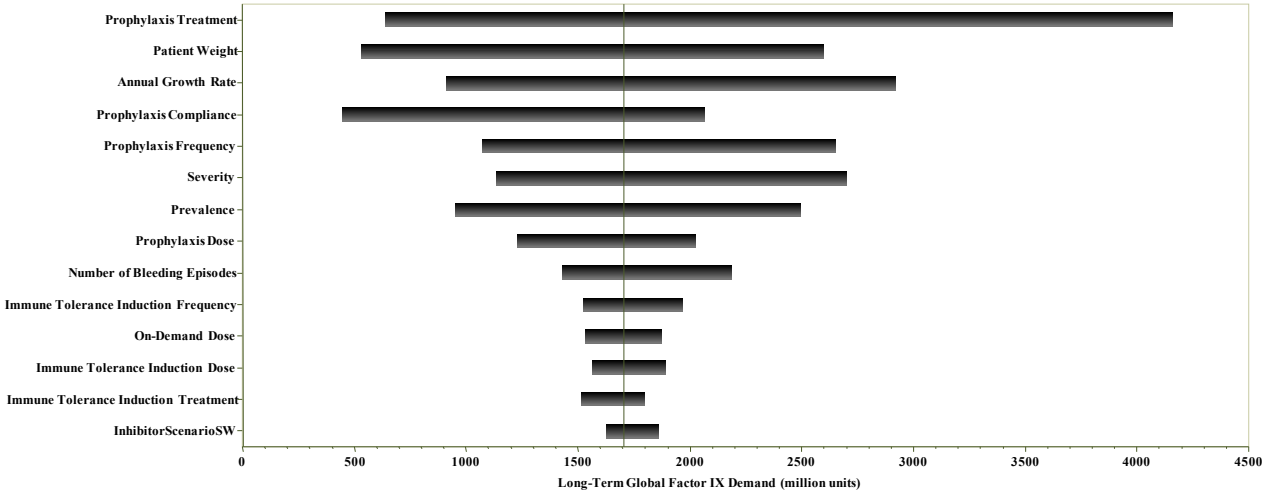
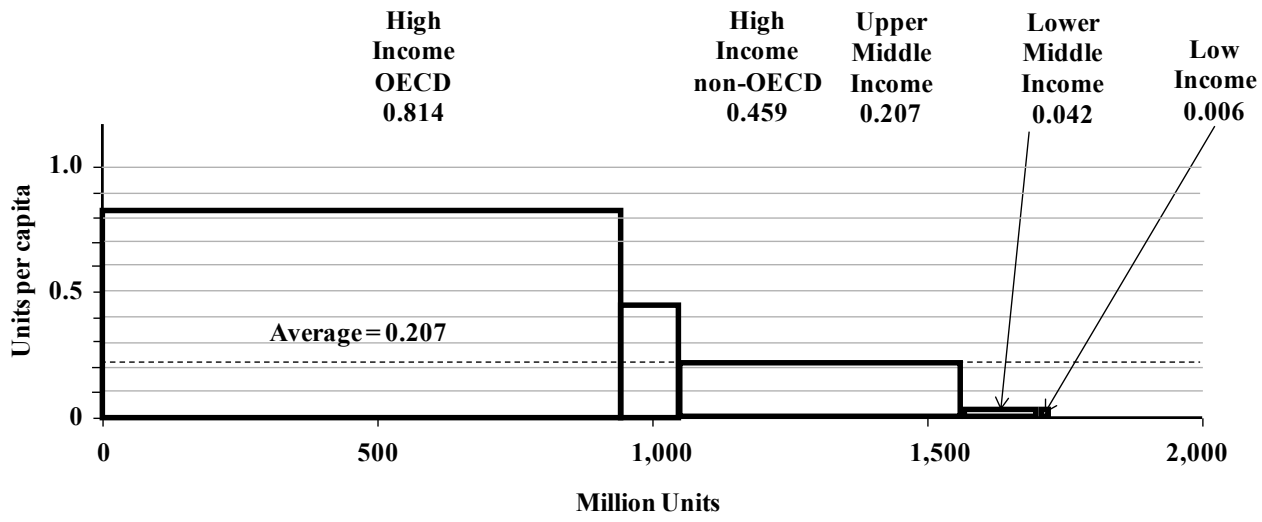



**Fig. 3**. Tornado diagram for long-term global demand of factor IX in the treatment of hemophilia B.




| Forecasted Demand | All | High OECD | High non-OECD | Upper Middle | Lower Middle | Low |
|---|---|---|---|---|---|---|
| Million units | 1,700 | 910 | 110 | 552 | 122 | 6 |
| Units per capita | 0.207 | 0.814 | 0.459 | 0.207 | 0.042 | 0.006 |
| Number of Countries | 190 | 31 | 28 | 50 | 47 | 34 |

OECD – Organisation for Economic Co-operation and Development.

**Fig. 4**. Forecast for the long-term global demand for the factor IX (FIX) treatment of hemophilia B (HB) by national income level.

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