Inherited Orphan Blood Disorders Therapeutics Market to 2019

Breakthrough Drugs Remain Elusive Against Backdrop of High Unmet Need

GBI Research
Global Business Intelligence

GBI Research Report Guidance

- Chapter three gives an overview of each disease covered in the report (sickle cell anemia, thalassemia and HAE), comprising etiology, epidemiology, symptoms and treatment. Additionally, a geographical overview of the revenues and Annual Cost of Therapies (ACoTs) of the disease therapeutics market in the US, the top five countries of Europe and Japan (Japan is not included for the sickle cell anemia market) are given. It also outlines the major marketed products used in the treatment of the respective indications, as well as the characterization of the market revenues and ACoTs forecast until 2019. Lastly, the section describes the major drivers and barriers in each market. Each section also provides an overview of the current developmental pipelines and detailed analysis of key pipeline products and the most promising drugs for each indication.
- Chapter four provides an overview of M&A, R&D licensing agreements and co-development agreements since 2005. This section also includes analysis of the geography, value and year for each of the deal types.

Inherited Orphan Blood Diseases - Executive Summary

This report reviews the therapeutic markets for three inherited orphan blood diseases and provides forecasts to 2019. The indications covered are sickle cell anemia, thalassemia and Hereditary Angioedema (HAE). As orphan diseases they have very low rates of prevalence and incidence and may disproportionately affect groups of genetic similarity due to their trends of inheritance. Many orphan diseases have high unmet clinical needs and premium pricing potential for successful new market entries. This is the case for all three of the indications covered.

During the forecast period, the sickle cell anemia market will be the fastest growing of the three markets with a Compound Annual Growth Rate (CAGR) of XX%, reaching $XXm in 2019. The thalassemia market will grow at a CAGR of XX% to reach $XXm in 2019. HAE represents the largest but slowest growing market at a CAGR of XX%, expected to reach $XX billion by 2019.

The sickle cell anemia pipeline is weak due to its lack of innovative disease-modifying therapies. There is a high unmet need for these types of therapies as the market is currently served by generic drugs. Whilst there are drugs within the pipeline that are likely to affect the sickle cell anemia market, their similarity to existing treatments makes it unlikely that they will make a significant difference to revenues and market competition.

There is a level of high unmet need in the thalassemia therapeutics market, as the treatments currently available only manage disease symptoms and the effects of treatments such as blood transfusions. Many are also generic, and the pipeline contains only a few promising therapies, none of which are expected to make an impact on the market during the forecast period.

The HAE market is currently strong and is dominated by drugs that treat edemas in emergency situations. The HAE pipeline, however, is very weak with no novel therapies in late-stage development, meaning that there is very little likelihood of significant impact on the market in the near future. The level of unmet need for HAE is moderate, as the treatment required by patients varies greatly. For those with regular HAE attacks, unmet need is high and more options for treatment are required.

GBI Research
Global Business Intelligence

1 Table of Contents

1.1 List of Tables

1.2 List of Figures

2 Inherited Orphan Blood Diseases - Introduction

2.1 Overview

What treatments do exist for rare diseases are often limited to symptom management, life expectancy extension and improvement of quality of life rather than curative treatments

Orphan diseases are also known as rare diseases and affect only a small minority of a country's population. In Europe, a disease is considered rare if it affects five or fewer than five per XX people. In the US, a disease is considered rare if it affects fewer than XX (or around XX people per XX people) individuals within the population, or within a certain subpopulation. In Japan, a disease is considered rare if it affects fewer than XX individuals within the population, around four people per XX people.

The prevalence and therefore status of a disease is likely to vary over time and differ according to country and subpopulation. For example, Acquired Immunodeficiency Syndrome (AIDS) used to be a very rare disease in the US, affecting a disproportionate number of individuals within the homosexual community, intravenous drug users, hemophiliacs and the Haitian immigrant subpopulation. Today, AIDS is classified as an epidemic by the World Health Organization (WHO) with the highest prevalence's among populations of the countries of Sub-Saharan Africa and South and South East Asia.

Rare diseases are usually serious and often life-threatening. They may present during childhood, although more than XX% of rare diseases only develop during adulthood. Due to their rarity and medical practitioners' resulting unfamiliarity, sufferers are often misdiagnosed or left undiagnosed. What treatments do exist for rare diseases are often limited to symptom management, life expectancy extension and improvement of quality of life rather than curative treatments. It is these failings that make the orphan disease drug market such a good opportunity for drug discovery and development.

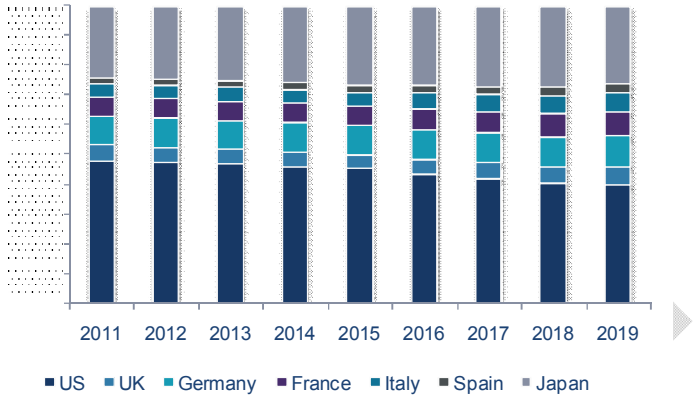
In this report, the markets for the treatment of three inherited orphan blood disorders will be examined in the US, the top five EU countries (the UK, France, Germany, Italy and Spain) and in Japan. The diseases covered will be sickle cell anemia, thalassemia and Hereditary Angioedema (HAE).

3.1.4 Annual Cost of Therapy

While the market for penicillin is expected to remain static, the market share held by hydroxyurea is expected to decrease as new, more expensive branded drugs enter the market

The following graph shows, by percentage, the variation in the average ACoT for the treatment of sickle cell anemia:

Figure 11: Sickle Cell Anemia, Total Market, Average Annual Cost of Therapy, 2011–2019



Source: GBI Research's Marketed Products database [accessed November 1, 2012]

Table 2: Sickle Cell Anemia, Total Market, CAGR of Average Annual Cost of Therapy

	US	UK	France	Germany	Italy	Spain
CAGR of ACoT						

Source: GBI Research's Marketed Products database [accessed November 1, 2012]

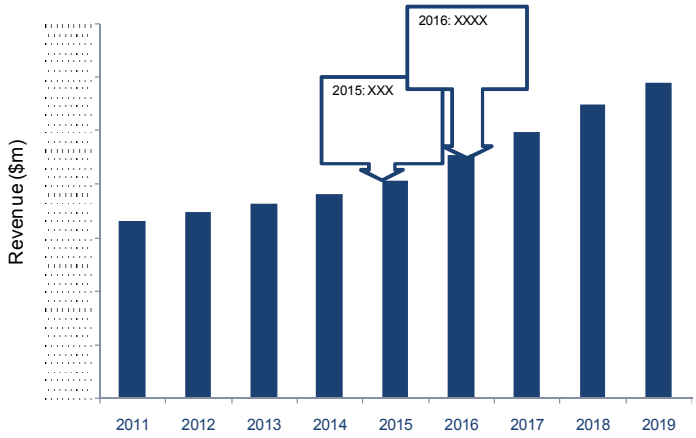
The graph shows that there has been very little change in the ACoT in most markets over the 2011–2019 period. The ACoT in the US saw the highest increase over the forecast period, which correlates with the expected launch dates of the promising pipeline products. This is most noticeable for sickle cell anemia as all previous treatment has been with generic drugs such as hydroxyurea and penicillin. While the market for penicillin is expected to remain static, the market share for hydroxyurea is expected to decrease as new and more expensive branded drugs enter the market. This will happen first in the US market and is not likely to significantly impact the European market until after the forecast period.

3.3.2 Revenues

Over the period, 2011–2019 the market is expected to grow at a CAGR of XX% and reach $XXm by 2019

Below is the cumulative market forecast, for all markets covered in the report, of pharmaceutical treatments indicated for α- and β-Thalassemia (HbH and β-thalassemia intermedia and major only). Over the 2011–2019 period the market is expected to grow at a CAGR of XX% to reach $XXm.

Figure 24: Thalassemia, Total Market, Revenue Forecast ($m), 2011–2019



Source: GBI Research's Marketed Products database [accessed November 1, 2012]

The growth of this market is driven by several factors, mainly the expected launches of promising late-stage pipeline products Sotatercept and HQK-XX; which are expected to be launched in the US and Japan in 2015 and in the EU in 2016.

5 Inherited Orphan Blood Disorders Therapeutics - Appendix

5.1 Market Definitions

5.2 Abbreviations

- AAEE: Associazione Italiana Angoedema Ereditario
- ACoT: Annual Cost of Therapy
- AIDS: Acquired Immune Deficiency Syndrome
- C1-INH: C1 Esterase Inhibitor
- CAGR: Compound Annual Growth Rate
- CBC: Complete Blood Count
- FDA: Food and Drug Administration
- HAE: Hereditary Angioedema
- HAEA: Hereditary Angioedema Association
- HbF: Fetal Hemoglobin
- HDAC: Histone Deacetylase
- HSCT: Hematopoietic Stem Cell Therapy
- MSCS: Mean Symptom Complex Severity
- TGF-β: Transforming Growth Factor Beta
- TOS: Treatment Outcome Score
- WHO: World Health Organization

5.3 Sources

- Fowkes FJI, Allen SJ, Allen A, et al. (2008) Increased Microerythrocyte Count in Homozygous α+-Thalassaemia Contributes to Protection against Severe Malarial Anaemia. PLoS Med 5(3): Available from: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0050056#close [Accessed September 19, 2012].
- Galanello R and Origa R (2011). Delta-beta thalassemia. Orphanet. Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=231237. [Accessed November 6, 2012].
- HemaQuest Pharmaceuticals (2012). Hemoglobin disorders. Available from: http://www.hemaquest.com/indications/hemoglobin.asp. [Accessed September 19, 2012].
- Human Genome Project Information (2005). Genetic Disease Profile: Sickle Cell Anemia. Available from: http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/sca.shtml. [Accessed September 19, 2012].
- McAuley CF, et al. (2010) High mortality from Plasmodium falciparum malaria in children living with sickle cell anemia on the coast of Kenya. Blood; 116(10): 1663–1668.
- Modell B and Darlinson M (2008). Global Epidemiology of Haemoglobin Disorders and Derived Service Indicators. Bulletin of the World Health Organization; 86(6): 480–487.
- National Heart, Lung and Blood Institute (2011) What Is Sickle Cell Anemia? Available from: http://www.nhlbi.nih.gov/health/health-topics/topics/sca/. [Accessed September 17, 2012].
- National Heart, Lung and Blood Institute (2002). The Management of Sickle Cell Disease. Available from: http://www.nhlbi.nih.gov/health/prof/blood/sickle/. [Accessed September 20, 2012].
- National Organization for Rare Diseases (2010) The Physician's Guide to Hereditary Angioedema Available from: http://www.rarediseases.org/docs/HAE_3_8.pdf [Accessed 17th September 2012].

- Piel FB, et al. (2010). Global Distribution of the Sickle Cell Gene and Geographical Confirmation of the Malaria Hypothesis. Nature Communications; 1(104).
- RSCB PDB (2012) Protein Data Bank. Available from: http://www.rcsb.org/pdb/explore/images.do?structureId=4HHB (Deoxyhemoglobin). http://www.rcsb.org/pdb/explore/images.do?structureId=2HBS (Deoxyhemoglobin S). [Accessed 17th September 2012].
- Uniprot, 2012. UniProtKB [databse] Available from: http://www.uniprot.org/uniprot/P02042
- Wang WC (2009). Sickle Cell Anemia and other Sickling Syndromes. In Greer JP, et al., eds. Wintrobe's Clinical Hematology, 12th ed., pp. 1038–1082. Philadelphia: Lippincott Williams and Wilkins.
- Weatherall D, et al. (2006). Inherited Disorders of Hemoglobin. In Jamison DT, et al. Disease Control Priorities in Developing Countries, 2nd ed., pp. 663–680. World Bank. Available from: http://files.dcp2.org/pdf/DCP/DCP34.pdf.
- Williams TN, et al. (2005). An Immune Basis for Malaria Protection by the Sickle Cell Trait. PLoS Medicine; 2(5): e128.

5.4 Research Methodology

GBI Research's dedicated research and analysis teams consist of experienced professionals with marketing, market research and consulting backgrounds in the pharmaceutical and medical devices industry as well as advanced statistical expertise.

GBI Research adheres to the codes of practice of the Market Research Society (www.mrs.org.uk) and the Strategic and Competitive Intelligence Professionals (www.scip.org).

All GBI Research databases are continuously updated and revised.

5.4.1 Coverage

The objective of updating GBI Research coverage is to ensure that it represents the most up to date vision of the industry possible.

Changes to the industry taxonomy are built on the basis of extensive research of company, association and competitor sources.

Company coverage is based on three key factors: market capitalization, revenues and media attention/innovation/ market potential.

- An exhaustive search of 56 member exchanges is conducted and companies are prioritized on the basis of their market capitalization;
- The estimated revenues of all major companies, including private and governmental, are gathered and used to prioritize coverage; and
- Companies which are making the news, or which are of particular interest due to their innovative approach are prioritized.

GBI Research aims to cover all major news events and deals in the medical industry, updated on a daily basis.

The coverage is further streamlined and strengthened with additional inputs from GBI Research Expert Panel (see below).

5.4.2 Secondary Research

The research process begins with exhaustive secondary research on internal and external sources being carried out to source qualitative and quantitative information relating to each market.

The secondary research sources that are typically referred to include, but are not limited to:

- Company websites, annual reports, financial reports, broker reports, investor presentations and SEC filings.
- Industry trade journals, scientific journals and other technical literature;
- Internal and external proprietary databases;

- Relevant patent and regulatory databases;
- National government documents, statistical databases and market reports;
- Procedure registries; and
- News articles, press releases and web-casts specific to the companies operating in the market.

5.4.3 Primary Research

GBI Research conducts hundreds of primary interviews a year with industry participants and commentators in order to validate its data and analysis. A typical research interview fulfills the following functions:

- It provides first-hand information on the market size, market trends, growth trends, competitive landscape and future outlook
- It helps in validating and strengthening the secondary research findings; and
- It further develops the analysis team's expertise and market understanding.

Primary research involves email interactions and telephone interviews as well as face-to-face interviews for each market, category, segment and sub-segment across geographies.

The participants who typically take part in such a process include, but are not limited to:

- Industry participants: CEOs, VPs, marketing/product managers, market intelligence managers and national sales managers;
- Hospital stores, laboratories, pharmacies, distributors and paramedics;
- Outside experts: Investment bankers, valuation experts, research analysts specializing in specific medical equipment markets;
- Key Opinion Leaders: Physicians and surgeons specializing in different therapeutic areas corresponding to different kinds of medical equipment.

5.4.4 Therapeutic Landscape

- Revenue for each indication by geography is arrived at by utilizing the GBI Research market forecasting model. The global revenue for each indication is the sum value of revenues of all seven regions.
- The annual cost of therapy for each indication is arrived at by considering the cost of the drugs, the dosage of the drugs and the duration of the therapy.
- The generic share of the market for each indication is obtained by calculating the prescription share for generic drugs and the respective cost of treatment.
- The treatment usage pattern which includes quantitative data on the diseased population, treatment-seeking population, diagnosed population and treated population for an indication, is arrived at by referring to various sources as mentioned below.
- The marketed drugs section contains an overview of the drugs, their mechanism of action, efficacy and safety issues related to the drugs. The drugs profiled in this section are chosen based on estimated revenues and their mechanism of action.

GBI Research uses the epidemiology-based treatment flow model to forecast market size for therapeutic indications.

5.4.4.1 Epidemiology-based Forecasting

The forecasting model used at GBI Research makes use of epidemiology data gathered from research publications and primary interviews with physicians to represent the treatment flow patterns for individual diseases and therapies. The market for any disease segment is directly proportional to the volume of units sold and the price per unit.

Sales = Volume of Units Sold X Price per Unit

The volume of units sold is calculated on the average dosage regimen for that disease, duration of treatment and number of patients who are prescribed drug treatment (prescription population). Prescription population is calculated as the percentage of population diagnosed with a disease (diagnosis population). Diagnosis population is the population diagnosed with a disease expressed as a percentage of the population that is seeking treatment (treatment-seeking population). Prevalence of a disease (diseased population) is the percentage of the total population who suffer from a disease/condition.

Data on treatment seeking rate, diagnosis rate and prescription rate, if unavailable from research publications, are gathered from interviews with physicians and are used to estimate the patient volumes for the disease under consideration. Therapy uptake and compliance data are fitted in the forecasting model to account for patient switching and compliance behavior.

To account for differences in patient affordability of drugs across various geographies, macroeconomic data such as inflation and GDP; and healthcare indicators such as healthcare spending, insurance coverage and average income per individual are used.

Annual cost of treatment is calculated using product purchase frequency and the average price of the therapy. Product purchase frequency is calculated from the dosage data available for the therapies and drug prices are gathered from public sources.

The epidemiology-based forecasting model uses a bottom-up methodology and it makes use of estimations in the absence of data from research publications. Such estimations may result in a final market value which is different from the actual value. To correct this 'gap' the forecasting model uses 'triangulation' with the help of base year sales data (from company annual reports, internal and external databases) and sales estimations.

Analogous Forecasting Methodology

Analogous forecasting methodology is used to account for the introduction of new products, patent expiries of branded products and subsequent introduction of generics. Historic data for new product launches and generics penetration are used to arrive at robust forecasts. Increase or decrease of prevalence rates, treatment seeking rate, diagnosis rate and prescription rate are fitted into the forecasting model to estimate market growth rate.

The proprietary model enables GBI Research to account for the impact of individual drivers and restraints in the growth of the market. The year of impact and the extent of impact are quantified in the forecasting model to provide close-to-accurate data sets.

Diseased Population

The diseased population for any indication is the prevalence. The prevalence rates are usually obtained from various journals, online publications, sources such as the World Health Organization (WHO) or associations and foundation websites for that particular disease.

Diagnosis Population

Out of the patients who undergo diagnostic tests to confirm a disease, only a few people get diagnosed with the disease. This number as a percentage of the treatment seeking population is the diagnosis rate. The diagnosis population is primarily driven by the sensitivity of the diagnostic tests, state-of-the-art technology, patient access to these diagnostic tests and cost of the diagnostic tests.

Prescription Population

For any disease, multiple treatment options exist. For example, in cancer treatment various treatment options such as surgery, radiation therapy, and drug therapy are available. Prescription population is defined as the number of patients who are prescribed drug therapy. This is calculated as a percentage of the diagnosis population. The prescription population is primarily driven by the age at which the disease is diagnosed, the disease stage, patient health and cost of drug treatment.

5.4.4.2 Market Size by Geography

The treatment usage pattern and annual cost of treatment in each country has been factored in while deriving the individual country market size.

Forecasting Model for Therapeutic Areas

Figure 62: GBI Research Market Forecasting Model

GBI Research Market Sizing Model				
Disease Population				
	General Population			743,535,048
		Qualifying condition 1 (Age/Sex/Occupation etc)		
		Qualifying condition 2 (Age/Sex/Occupation etc)		
	Prevalence tissue valve disease		0.2%	1,784,484
		Qualifying condition (complication, severity)		
		DISEASED POPULATION		1,784,484
Treatment Flow Patterns				
	Treatment Seeking Rate (Symptoms/Dis Awareness)		89%	1,588,191
	Diagnosis Rate (Clinical and Diagnostic Tests)		75%	1,191,143
	Prescription Rate (Physician Perception, Treatment Effectiveness)			
		Tissue Valve	70%	833,800
		Other Treatments for Valve (Surg/Med/None)		-
	Fulfillment			
		Availability	NA	
		Willingness to Use (Patient Perceptions)	NA	
		Ready to Use (Surgery eligibility, Reuse etc)	NA	
	Affordability at Price			
		HE as % of GDP spend		
		Average Income (per individual)		
		Patient Out-of-pocket Budget (Annual)		
		Budget allocation to one-time surgery		
		Budget allocation to other health needs		
		Average Payor Coverage		
		Patient Liability		
		Target Price (@20% pat liab)		
		ASP for Cost of Therapy		
		TOTAL PATIENT VOLUMES		
	Product Purchase Frequency		1	
		TOTAL UNIT VOLUMES		
Pricing per Unit			$ 18,000	
		Inflation		
		Price Decrease due to competition		
Market Value				

Source: GBI Research

The above figure represents a typical forecasting model followed in GBI Research. As discussed previously, the model is built on the treatment flow patterns. The model starts with the general population, then diseased population as a percentage of the general population and then follows the treatment seeking population as a percentage of the diseased population and diagnosed population as a percentage of the treatment seeking population. Finally, the total volume of units sold is calculated by multiplying the treated population by the average dosage per year per patient.

Articles from research journals and agency publications such as the British Medical Journal, New England Journal of Medicine, Oxford Journal, National Institute of Health and clinicaltrials.gov are used in the above model. The marketed drugs section is taken from company websites and internal databases

5.4.5 Geographical Landscape

GBI Research analyzes only seven major geographies: the US, the top five countries in Europe (the UK, Germany, France, Spain, and Italy) and Japan. The total market size for each country is provided which is the sum value of the market sizes of all the indications for that particular country.

5.4.6 Pipeline Analysis

This section provides a list of molecules at various stages in the pipeline for various indications. The list is sourced from internal database and validated for the accuracy of phase and mechanism of action at ClinicalTrials.gov and company websites. The section also includes a list of promising molecules which is narrowed down based on the results of the clinical trials at various stages and the novelty of mechanism of action.

5.4.7 Competitive Landscape

Profiles of leading players are provided along with an overview of key products marketed by the companies for various indications. An analysis of strengths, weaknesses, opportunities and threats of each company with respect to various indications is also listed.

GBI Research aims to cover all major M&A, licensing deals and co-development deals related to the market. This section is sourced from the companies' websites and internal databases.

5.4.8 Expert Panel Validation

GBI Research uses a panel of experts to cross-verify its databases and forecasts.

GBI Research's expert panel comprises marketing managers, product specialists, international sales managers from medical device companies, academics from research universities, KOLs from hospitals, consultants from venture capital funds and distributors/suppliers of medical equipment and supplies.

Historic data and forecasts are relayed to GBI Research's Expert Panel for feedback and adjusted in accordance with their feedback.

5.6 Disclaimer