Healthcare Observer Jan 2013

The Hemophilia Market: Steep but Surmountable Barriers for New Entrants

Since the 1990s, the hemophilia market has been dominated by recombinant proteins from Baxter, Bayer, and Pfizer. However, pipelines are maturing and longer-acting versions of factors VIII and IX from firms including Novo Nordisk and Biogen-Idec are approaching the market. In this report, we break down the key growth drivers for the broader hemophilia market, including improved emerging market penetration and global gains in prophylaxis use. We also detail the growth potential of the biggest hemophilia market—hemophilia A—using a bottom-up market model as well as a top-down product-by-product sales forecast.

Overall, we think the broader hemophilia market will grow at an average 5.9% rate over the next five years, from $8.5 billion in 2011 to $11.4 billion in 2016. In conjunction with this report, we have raised our assumed probability of approval for Biogen's hemophilia products from 75% to 100%, and we are therefore raising our fair value estimate from $138 per share to $142. We are also increasing Bayer's fair value estimate to $86 from $84 based on increased expectations for Bayer's new hemophilia drugs.

Damien Conover, CFA
Director, Pharmaceuticals
(312) 696-6052
damien.conover@morningstar.com

Alex Morozov, CFA
Director, Devices
(312) 696-6159
alex.morozov@morningstar.com

Karen Andersen, CFA
Senior Analyst, Biotechnology
(312) 384-4826
karen.andersen@morningstar.com

Morningstar Healthcare Observer Analyst Team

Matthew Coffina, CFA
Senior Analyst,
Managed Care/PBMs
(312) 696-6864
matthew.coffina@morningstar.com

David Krempa
Associate, Pharmaceuticals
(312) 696-6633
david.krempa@morningstar.com

Lauren Migliore, CFA
Analyst, Biotechnology
(312) 244-7048
lauren.migliore@morningstar.com

Charlie Miller
Analyst, Life Sciences/Diagnostics
(312) 696-6568
charlie.miller@morningstar.com

Julie Stralow, CFA
Senior Analyst, Credit/Devices
(312) 696-6278
julie.stralow@morningstar.com

Debbie Wang
Senior Analyst, Devices
(312) 384-3937
debbie.wang@morningstar.com

Michael Waterhouse
Analyst, Specialty Pharmaceuticals
(312) 696-6742
michael.waterhouse@
morningstar.com

MORNINGSTAR®

Hemophilia Therapeutic Area Moat: Wide, but Negative Trend

Investment Takeaway

While **Bayer** BAYRY (FV: $86), **Novo Nordisk** NVO (FV: $156), and leading player **Baxter** BAX (FV: $65) will likely continue to innovate, preventing erosion of their markets with new pipeline products, we think **Biogen Idec** BIIB (FV: $142) stands to build significant hemophilia drug sales over time. Overall, we think barriers to entry in hemophilia A are highest, as no firm has been able to extend the half life of the natural factor VIII protein by more than roughly 60%. However, longer half-life extensions in hemophilia B could lead to significant convenience benefits for new products that differentiate them from established brands. Overall, we think this puts Baxter in a strong position to defend its lucrative hemophilia A franchise despite numerous new products in late-stage development.

Karen Andersen, CFA

Patients with hemophilia have inherited a genetic mutation that gives them a low or non-existent supply of one of the blood factors needed for blood clotting. Without a functioning gene, patients are vulnerable to serious bleeds and associated degenerative joint disease. Typical treatment can be on-demand (when a bleed occurs) or prophylaxis (to prevent bleeds and any associated joint damage). Patients are more likely to begin prophylaxis regimens as children, and adult patients are more likely to use on-demand treatment. Overall, with increased recombinant and prophylaxis use among diagnosed patients, as well as improved diagnosis globally (and particularly in emerging markets), we expect the broader hemophilia market to grow from $8.5 billion in 2011 to $11.4 billion in 2016, representing an average 5.9% growth rate over this period.

Table 1 Total Hemophilia Market (in millions of USD)

Area	2011	2012E	2013E	2014E	2015E	2016E
Hemophilia A	5,207	5,478	5,765	6,197	6,682	6,988
Hemophilia B	1,218	1,313	1,421	1,529	1,679	1,854
Inhibitors	1,822	1,867	1,904	1,971	2,023	2,125
von Willebrand disease	300	315	331	347	389	436
Total	**8,547**	**8,973**	**9,420**	**10,044**	**10,773**	**11,402**
5-Year CAGR						**5.9%**

Sources: Morningstar Estimates, Company Data

We see high barriers to successful entry into the hemophilia market for new players. First, manufacturing difficulties abound in this therapeutic area. For example, factor VIII (for hemophilia A) is the largest protein that has been produced using recombinant technology, and it is considered relatively unstable as an independent protein (usually found in the body linked to von Willebrand factor). Therefore, it can be difficult to produce at consistent, good yields. Baxter's Advate, for example, is produced using a continuous perfusion system[1], which carries long processing times and risks of contamination. Players with marketed products have cultivated their manufacturing techniques for years, and some of their methods are not patents but trade secrets. In addition, even current players have difficulty safely

Source

[1] *Shapiro, Amy. Anti-hemophilic factor (recombinant), plasma/albumin-free method (octocog-alpha; Advate) in the management of hemophilia A. Vascular Health and Risk Management, 2007: 3(5)*

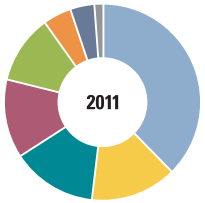
improving on their current products; Novo Nordisk recently discontinued development of a modified version of inhibitor treatment NovoSeven due to the safety concerns. We think these challenges will keep biosimilar competition at bay, at least until the more lucrative, easier to produce biologic targets have been addressed and proved profitable investments.

Second, all of the entrenched hemophilia players have global, specialist-focused marketing teams that have established strong relationships with physicians. We think this gives incumbents the upper hand in final treatment decisions, particularly if new products don't show meaningful benefits. Many new products could be limited by their "me-too" status, making them virtually branded biosimilars. Strong global sales forces and brand power could be particularly important in emerging markets; Baxter has successfully signed an exclusive Advate contract in Brazil, and Bayer is seeing strong double-digit growth in emerging markets (25% in 2011). Because Biogen and partner SOBI do not have significant experience marketing products in geographies outside of the U.S. and Europe, they could be at a distinct disadvantage reaching international hematologists versus global players like Bayer, Baxter, and Novo Nordisk.

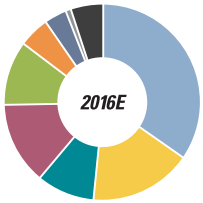
Finally, there is a very low switch rate among hemophilia therapies. Many patients have been on products like Baxter's Recombinate or Bayer's Kogenate for more than a decade. This low switch rate among hemophilia patients could make it difficult to encourage current patients to move to Biogen's products without a compelling convenience benefit. We think the low switch rate will persist despite the relative similarity among treatment options, as issues such as inhibitor development can be difficult to pinpoint in pivotal trials. This should limit patient confidence in new therapies entering the market.

We think Recombinate illustrates patient loyalty to their chosen therapy, when incremental improvements are not significant. While conversion from plasma-derived factor VIII to Recombinate was quite rapid, conversion from Recombinate to Advate has been a much longer process. Biogen noted at its analyst day in June that the switch rate in hemophilia is less than 10%. Patients who were happy on Recombinate often opted to stick with the therapy, while new, previously untreated patients—often children—were put on Advate. In the U.S., after almost 10 years of Advate marketing, Recombinate still comprises about 25% of Baxter's recombinant factor VIII sales. Therefore, while new products could slowly erode the dominance of current hemophilia market players, we think this more of a long-term threat than a near-term one.

Figure 1 2011 & 2016E Hemophilia Market, Share by Company



Company	2011 %
Baxter	38
Novo Nordisk	14
Pfizer	14
Bayer	13
CSL	11
Grifols	5
Octapharma	4
Kedrion	1



Company	2016E %
Baxter	35
Novo Nordisk	17
Pfizer	10
Bayer	14
CSL	11
Grifols	5
Octapharma	4
Kedrion	1
Biogen Idec	5

Sources: Morningstar, Company Data

Hemophilia A

2011 Market: $5.2 Billion
2011–2016 Market Growth: 6%
2016 Market: $7 Billion

The hemophilia A market stands at $5.2 billion by our estimates, and we think the market could grow to reach $7 billion by 2016, representing a 6% average growth rate over the next five years. While Bayer and Baxter dominate the market today with recombinant versions of the factor VIII protein, we expect Biogen Idec and Novo Nordisk to bring new, longer-acting factor VIII proteins to the market beginning in early 2014, with Bayer and Baxter defending their franchises with longer-acting proteins of their own shortly thereafter. We think market growth will stem from a combination of increased prophylaxis use among diagnosed patients in developed markets, price premiums for newer products, and increased treatment rates and volumes per patient in emerging markets. We think this growth will be partly countered by negotiated discounts on recombinant therapies in emerging markets as well as the continued popularity of lower-priced plasma-derived therapy in emerging markets. This overall weight on global pricing among both recombinants and plasma-derived factor VIII treatments brings our sales forecast slightly below the 8% five-year historical growth rate for recombinant factor VIII treatments.

Patients with hemophilia A have a defective factor VIII gene, which resides on the X chromosome (making this generally a disease among males). Approximately 400,000 patients are believed to have the disease globally, but only about one-third are diagnosed and receive treatment. The quality of this treatment can also vary significantly; patients in developed markets are more likely to receive prophylaxis factor replacement therapy two to three times a week, while many emerging markets are almost exclusively "on-demand" (when a bleed occurs). Recombinant therapies tend to be used in developed markets (for example, 80% of factor VIII volumes in Europe are recombinant[2]), and are the preferred method of prophylaxis therapy. Plasma-derived factor VIII products—originally available to patients in the 1950s—from firms such as Baxter and **Grifols** GRFS (FV: $30) are still popular, lower-priced alternatives, particularly in emerging markets.

While almost 40% of patients diagnosed with severe hemophilia A receive prophylaxis treatment, only 14% of moderate patients and less than 10% of mild patients do, yielding an average prophylaxis rate of about 25% globally. Focusing in on developed markets, overall prophylaxis rates are higher, at roughly 30%–35% in the U.S. and 50% in Western Europe.[3] Prophylaxis rates also vary by a patient's

Source

[2] *Conversation with Helena Rudberg, Head of Hemophilia, SOBI, December 6 2012*
[3] *Estimates from Bayer, SOBI.*

age. About 90% of children with severe hemophilia A in the U.S. receive prophylaxis, and this drops to 60% for severe cases among adults in the U.S. According to Biogen, prophylaxis generally drops with age, partly due to patients becoming more independent and less compliant as they reach adulthood, and partly due to the fact that prophylaxis did not become a popular option until the 1990s, creating a large bucket of older adults who were not familiar with prophylaxis as children and are unlikely to be receiving such treatment as adults. For example, prophylaxis levels among 18-year-olds stand around 80%, while only about 20% of patients over age 40 receive prophylaxis therapy.

Changes in prophylaxis rates are critical to our estimates of global market growth, Biogen estimates that U.S. patients on prophylaxis consume 75% of units sold, and Bayer estimates that 65% of all factor VIII consumption on a global level is for prophylaxis use. As recombinant products tend to be used for prophylaxis, we expect the dollar percentage of the market to be even higher than this. According to Bayer, 75% of sales in developed markets are from prophylaxis use. We expect growth in prophylaxis use globally to be a one of the key market drivers (as detailed on page 12).

Table 2 Hemophilia A (Factor VIII) and von Willebrand Disease, Sales from Marketed Products and Late-Stage Pipeline

Firm	Product	2011	*2012E*	*2013E*	*2014E*	*2015E*	*2016E*
Recombinant Marketed							
Baxter	Advate (octocog alpha)	1,659	*1,715*	*1,863*	*1,879*	*1,846*	*1,782*
Baxter	Recombinate	553	*540*	*520*	*500*	*480*	*460*
Bayer	Kogenate FS-(full length)	1,108	*1,225*	*1,275*	*1,325*	*1,275*	*1,175*
CSL (Bayer)	Helixate FS (full length)	506	*560*	*582*	*605*	*582*	*537*
Pfizer (Wyeth)	Refacto/Xyntha	506	*560*	*582*	*605*	*582*	*537*
Total		**4,332**	***4,600***	***4,823***	***4,914***	***4,766***	***4,490***
Recombinant Pipeline							
Bayer	BAY81-8973				*50*	*75*	*100*
Octapharma	Human-cl rhFVIII				*25*	*50*	*75*
Novo Nordisk	NN7008 (N8) turoctocog alfa			*50*	*100*	*150*	*175*
Novo Nordisk	NN7088, N8-GP				*75*	*200*	*325*
Biogen Idec	rFVIIIFc				*100*	*250*	*375*
CSL Behring	CSL627 rFVIII					*50*	*100*
Bayer	BAY94-9027					*100*	*200*
Baxter	BAX 855					*100*	*200*
Baxter	BAX 111 (rVWF)				*30*	*60*	*90*
Total		—	—	***50***	***380***	***1,035***	***1,640***
Total Recombinant Sales		**4,332**	***4,600***	***4,873***	***5,294***	***5,801***	***6,130***
Recombinant Market Growth		—	***6%***	***6%***	***9%***	***10%***	***6%***
2011–2016 CAGR							***7.2%***
Plasma-Derived Sales							
Grifols	Alphanate/Koate ex US	225	*248*	*272*	*299*	*320*	*343*
Baxter	Hemofil M	300	*296*	*300*	*300*	*300*	*300*
CSL Behring	Humate-P, Haemate-P/Monoclate-P/Beriate	350	*350*	*350*	*350*	*350*	*350*
Kedrion	Koate US	100	*100*	*100*	*100*	*100*	*100*
Octapharma	Wilate	100	*100*	*100*	*100*	*100*	*100*
Octapharma	Octanate	100	*100*	*100*	*100*	*100*	*100*
Total Plasma-Derived Sales		**1,175**	***1,194***	***1,222***	***1,249***	***1,270***	***1,293***
Plasma-Derived Market Growth			***2%***	***2%***	***2%***	***2%***	***2%***
2011–2016 CAGR							***1.9%***
Total Hemophilia A and von Willebrand Sales		**5,507**	***5,793***	***6,095***	***6,544***	***7,071***	***7,423***
Annual Growth		—	***5%***	***5%***	***7%***	***8%***	***5%***
2011–2016 CAGR							***6.2%***

Source: Company Reports, Morningstar

**CSL 2011 numbers are for fiscal year ending in June 2012*

***sales of some plasma-derived factor VIII include sales for von Willebrand disease*

****Helixate ingredient sales to CSL are removed from our Kogenate sales numbers*

Hemophilia B

2011 Market: $1.2 billion
2011–2016 Market Growth: 9%
2016 Market: $1.8 Billion

We expect the $1.2 billion hemophilia B market to grow at an average rate of 9% over the next five years to reach more than $1.8 billion, as **Pfizer's** PFE (FV: $27) BeneFIX sees new recombinant competition from several firms, including a similar product from Baxter and potentially longer-acting (i.e., dosed less frequently) versions from NovoNordisk, Biogen-Idec, and **CSL** CSL ($44 AUD). Baxter is aiming to have the first prophylaxis label among recombinant FIX products, which could be a slight short-term marketing advantage. However, we think significant convenience benefits with begin to sway patients from BeneFIX when longer-acting FIX products hit the market, and that this will also draw patients new to prophylaxis therapy. We think increased uptake of premium-priced novel products as well as better prophylaxis penetration will drive market growth above historical rates, which have averaged roughly 6% annually over the last five years for BeneFIX.

Patients with hemophilia B (or Christmas disease) have a defective factor IX gene, which resides on the X chromosome (making it almost exclusively a disease in men). Factor IX is a serine protease that is necessary for normal blood clotting. In the 1960s, plasma-derived concentrates of the factor IX protein became available for patients, dramatically increasing lifespans to near-normal levels. About 80,000 people are believed to have hemophilia B globally, but only roughly 30% of them are diagnosed and treated.

Today's therapy involves injections 2–3 times per week with factor IX, either plasma-derived or recombinant. In the U.S, usage is almost exclusively recombinant, as patients rapidly switched to Pfizer's BeneFIX when it became available in 1997 due to a shortage of plasma-derived factor IX (in Europe, roughly 50% of the volume of factor IX sales remain plasma-derived).[4] As in hemophilia A, patients can be treated on-demand (when a bleed occurs) or chronically as a prophylaxis measure. Globally, while roughly one-third of patients diagnosed with severe hemophilia B receive prophylaxis therapy, patients with mild to moderate disease typically still receive on-demand treatment, so average prophylaxis rates globally stand at about 15%. In the U.S., approximately 27% of patients are on a prophylaxis regimen, accounting for 75% of unit consumption. Prophylaxis use goes as high as 46% among severe patients in the U.S. Prophylaxis rates are slightly lower in hemophilia B compared to hemophilia A, partly due to the fact that hemophilia B patients tend to bleed less. However, we think this provides greater upside to sales growth, particularly as much more convenient products reach the market.

Source

[4] *Conversation with Helena Rudberg, Head of Hemophilia, SOBI. December 6, 2012.*

Table 3 Hemophilia B (Factor IX), Marketed Products and Late-Stage Pipeline

Firm	Product	2010	2011	*2012E*	*2013E*	*2014E*	*2015E*	*2016E*
Recombinant								
Pfizer	BeneFIX	643	693	762	792	750	650	550
NovoNordisk	N9-GP, NN7999						100	225
Biogen Idec	rFIXFc					50	125	200
CSL Behring	CSL654 rIX-FP					50	75	100
Baxter	BAX 326				50	100	150	200
Total		**643**	**693**	***762***	***842***	***950***	***1,100***	***1,275***
Plasma-Derived								
CSL Behring	Mononine/Berinin		110	*116*	*121*	*121*	*121*	*121*
Baxter	Immunine		100	*90*	*90*	*79*	*82*	*76*
Grifols	AlphaNine SD		175	*186*	*197*	*208*	*221*	*234*
Octapharma	Octanine		140	*160*	*171*	*170*	*155*	*147*
Total		**500**	**525**	***551***	***579***	***579***	***579***	***579***
Total Hemophilia B Market		**1,143**	**1,218**	***1,313***	***1,421***	***1,529***	***1,679***	***1,854***
Market Growth			**7%**	***8%***	***8%***	***8%***	***10%***	***10%***
2011–2016 CAGR								***9%***

Source: Company Reports, Morningstar

Inhibitors

2011 Market: $1.8 Billion
2011–2016 Market Growth: 3%
2016 Market: $2.1 Billion

We expect the $1.8 billion inhibitor market to grow to $2.1 billion by 2016, with novel therapies from Baxter and Bayer potentially entering the market near the end of this timeframe. While better market penetration rates in hemophilia A will likely increase the number of patients needing inhibitor treatment, we think the developed world market is well penetrated already, and emerging market potential is smaller than in the hemophilia A and B factor protein markets.

Some patients with hemophilia A or B develop antibodies to their factor replacement therapy, making them unresponsive to therapy and putting them in a dangerous situation if a bleed occurs. There are roughly 5,000 patients globally with inhibitors, and the vast majority (90% according to the WFH Global Survey 2010) are hemophilia A patients. For some patients, simply giving them high-dose treatment with their replacement factor, such as Grifols' Alphanate, will allow them to regain benefits. For example, one published study showed that using immune tolerance induction or therapy (ITI or ITT) yielded tolerance (elimination of the inhibitors) in 70% of patients who entered with high-titre antibodies to the factor, after a period of four months of treatment.[5]

However, depending on the severity of a patient's antibodies, bypass therapy such as Baxter's Feiba, Novo Nordisk's NovoSeven, or a combination of the two products can be required. Novo Nordisk cur-

Source

[5] *Haemophilia. 2009 May;15(3):718–26. Epub 2009 Feb 27.*

rently holds about 70% of the global market in dollar share. Such bypass treatments can be quite costly, averaging roughly $300,000 per year.[6]

Baxter and Bayer are the two key players looking to benefit from regulatory approvals over the next few years. For patients with inhibitors to factors VIII or IX, prophylaxis rates with NovoSeven or Feiba stand at 35–40%, but Baxter hopes to gain supplementary Feiba approval in this indication—dosing every 2 days—in 2014. Published data show that prophylaxis reduces bleeds by 62%, and we think Feiba could continue to see strong growth that is further boosted by a prophylaxis label. Baxter also has its own recombinant factor VIIa product—akin to NovoSeven—poised to reach the market in 2016. Bayer is attempting to develop a modified recombinant factor VIIa product with an improved half-life, which we think could also reach the market in 2016 and could have a significant convenience advantage over other products.

However, safety will be the key hurdle for innovative products to pass. Novo Nordisk's own efforts to improve on NovoSeven with vatreptacog have resulted in safety issues (some patients developed inhibitors, a serious side effect for patients who are already on a back-up treatment after developing inhibitors to factor VIII or IX). We think modifications to factor VIIa could be difficult to achieve without provoking an immune response from patients, and therefore we're keeping our estimates for Bayer's launch quite conservative. Overall, we think the market is poised to grow at a 3% CAGR over the next five years, well below NovoSeven's 11% five-year historical CAGR. NovoSeven already has high penetration in the U.S. and Europe (where it sees 80% of its sales), and copycat biosimilar versions of the expensive therapy are taking over markets in developing countries like Iran and Russia.

Source

[6] *Alnylam RNAi Roundtable, Dec 14 2012.*

Table 4 The Inhibitor Market: Products and Pipeline (in millions of USD)

Firm	Treatment	Status	Our Take	2011	*2012E*	*2013E*	*2014E*	*2015E*	*2016E*
Baxter	Feiba (plasma derived activated prothrombin complex)	Marketed	While plasma-derived, Feiba is a unique combination of factor proteins that has been the market for decades with no significant competition	608	*641*	*665*	*720*	*760*	*800*
Novo Nordisk	NovoSeven (eptacog alfa, recombinant FVIIa)	Marketed (patents expired)	Market penetration already high, price power in US countered by EU austerity and emerging market copycats	1,214	*1,226*	*1,239*	*1,251*	*1,263*	*1,200*
Novo Nordisk	vatreptacog alfa (NN1731)	Ph 2 data positive, moved to Ph 3 in 2011. discontinued in 2012 as patients developed antibodies	Vatreptacog's failure signals potential difficulty in development of other modified versions of factor VIIa	0	*0*	*0*	*0*	*0*	*0*
Baxter	rFVIIa	2016 launch	Aims to be similar to NovoSeven						*50*
Novo Nordisk	NN7128/NN7129 (Neose PEGylation technology, subcu long-acting rFVIIa derivative)	Discontinued in Q3 2011, due to dose determination difficulties	Failure could signal difficulty for next-generation products	0	*0*	*0*	*0*	*0*	*0*
Bayer	BAY86-6150, modified recombinant Factor VIIa	Ph 2/3 started summer 2012, to complete 2015	5–7 hour half life looks 2–3x longer than NovoSeven, but current study will be needed to accurately compare						*75*
CSL	rVIIa-FP	Orphan drug status, Ph I start in 2012	Fused to albumin to extend half life, but little data to date						
Total Inhibitor Market				**1,822**	***1,867***	***1,904***	***1,971***	***2,023***	***2,125***
Annual Growth				—	***2%***	***2%***	***4%***	***3%***	***5%***
2011–2016 CAGR									***3.1%***

Source: Company Reports, Morningstar Estimates

Von Willebrand Disease

2011 Market: $300 Million
2011–2016 Market Growth: 8%
2016 Market: $440 Million

Von Willebrand disease is believed to be the most common inherited bleeding disorder, with roughly 1% of the population impacted. However, the market is only roughly $300 million today, mostly owing to the fact that 80% of patients have a relatively mild form of the disorder that does not typically require factor replacement therapy, and fewer than 1% of patients have a complete inability to produce the protein. Roughly 16,000 patients are treated today, half of them in the U.S., and all patients are taking a plasma-derived therapy that combines factor VIII with von Willebrand factor (VWF). However, due to the fixed proportions of these proteins in the therapy, it is difficult to customize treatment. Baxter's BAX111 is a recombinant form of pure VWF, which will allow for customized treatment and could also have a longer half life. Baxter hopes that this product will allow for increased prophylaxis use, which according to a recent UDC (universal data collection) report released by the CDC, stands at roughly 1% in the U.S. today. Approval of BAX111 could also raise awareness among the 20% of von Willebrand patients who have VWF defects and have moderate disease, but are currently undertreated (only 30% on factor replacement). We expect Baxter's product to reach the market in 2014, and to see as much as $90 million in sales by 2016.

Key Growth Drivers for the Global Hemophilia Market

Investment Takeaway

There are several factors influencing our 6% hemophilia market growth assumption through 2016. First, diagnosis rates should continue to grow, albeit at a slower rate than in the past due to high developed market penetration rates. Second, we expect factor replacement usage per patient to increase as treatment for those already diagnosed gradually becomes more aggressive, particularly in emerging markets which see a wide discrepancy from factor replacement volumes per patient in the U.S. and Europe. Third, we think the improved convenience of three-day-dosing with Advate and longer-acting therapies in the pipeline could begin to encourage more patients, particularly adults, to consider chronic prophylaxis therapy. Because this requires two to three times the volume of Advate—and new products will likely be sold at a price premium to current options—this will slowly expand sales. Finally, we expect uptake of low-priced plasma-derived therapies in emerging markets, as well as lower negotiated prices for recombinant therapies in these markets, to slightly weigh on pricing. Overall, we think recombinant regimens could see steady pricing per unit (new entrants canceling price pressure from growing emerging market sales) but average plasma-derived therapy prices could see steady 2% annual erosion (as most growth will be centered in emerging markets).

Karen Andersen, CFA

1. Diagnosis and Improved Treatment in Emerging Markets

Only 30% of hemophilia patients are diagnosed. We expect diagnosis and treatment rates to increase as more treatment options reach the market, thanks in part to new marketing efforts from firms such as Biogen-Idec and Novo Nordisk that could boost patient awareness globally. Roughly 40% of hemophilia cases are categorized as severe, meaning that these patients are vulnerable to several bleeds per month without treatment.[7] While mild patients can go undiagnosed for years and moderate hemophilia patients have variable bleed rates, we would expect hemophilia diagnosis rates to slowly approach 40% in the long run.

While global diagnosis rates have increased roughly 4% annual over the past 10 years according to numbers from the WFH global survey, we expect 2% annual growth over the next five years, given the high penetration of developed markets and our expectations for slow but steady progress in emerging markets.

Breaking down diagnosis rates geographically, we estimate that developed markets have diagnosis rates closer to 34%, and emerging market diagnosis rates appear much lower, closer to 24%. In addition, a large number of hemophilia patients are predicted to exist in key emerging markets. In hemophilia A, for example, about 40% of the global prevalence is tied to the BRIC nations, Mexico, and Turkey. As funding for critical care in developing markets becomes more available, we expect diagnosis and treatment rates to approach developed market levels in the long run. While global diagnosis rates have increased roughly 4% annual over the past 10 years according to numbers from the WFH global survey, we expect 2% annual growth over the next five years, given the high penetration of developed markets and our expectations for slow but steady progress in emerging markets.

Volume of factor replacement also varies geographically. The World Federation of Hemophilia reported that upper income countries (by World Bank rankings) saw an average per capita use of factor VIII of 5.0 IU in 2010, translating to almost 100,000 IU per patient. The U.S. stands at 5.16 per capita. These numbers fall dramatically for upper middle income countries (40,000 IU per patient, or 2.0 IU per capita) and lower middle income countries (well below 10,000 IU per patient, or less than 0.5 IU per

Source

[7] *Canadian Hemophilia Society.*

capita). For Factor IX, upper income usage is above 0.8 IU per capita (more than 60,000 IU per patient), and similar differences exist for emerging markets. Overall, we think these numbers imply a combination of lower diagnosis rates as well as less aggressive treatment for diagnosed patients in emerging markets.

Some emerging markets are in a position to advance more rapidly than others, in our opinion. We note that upper-middle income Russia and low middle income Brazil already have very high per capita treatment levels for hemophilia A (4.3 and 2.4 IU per capita, respectively, according to Baxter), and are not necessary representative of developing markets as a whole. With high diagnosis rates and high rates of on-demand factor replacement, we think Russia and Brazil could be models for China, which also has a centralized drug market. Advate was approved in China in 2012, and less than 20% of hemophilia patients are currently treated. Overall, increasing treatment rates—from 30% to 32% of patients globally from 2011 to 2016—account for roughly one third of our estimated hemophilia A market growth.

With high diagnosis rates and high rates of on-demand factor replacement, we think Russia and Brazil could be models for China, which also has a centralized drug market.

2. The Standards of Care: Recombinants and Prophylaxis

The wide discrepancy between volume of factor replacement used per capita in developed and emerging markets is not only due to lower diagnosis rates in emerging markets, but also minimal usage of prophylaxis regimens. We think prophylaxis use could become more common globally as treatment regimens become more convenient and as emerging markets are able to spend more on healthcare. We expect increased prophylaxis to be the biggest driver for the hemophilia market in developed markets. The price premium that recombinants hold to their plasma-derived counterparts could also serve to accelerate market growth beyond demand growth, as more patients move to recombinant therapies in emerging markets. However, we note that in emerging markets, some of the growth potential from increasing prophylaxis and recombinant use will be tempered by negotiated lower prices.

Recombinants: Standard in Developed Markets and Growing in Emerging Markets

Baxter's Recombinate, approved in 1992, was the first approved recombinant factor VIII therapy. Recombinate is the full-length protein, making the key active ingredient no different in amino acid sequence from the natural human version in plasma-derived therapies like Baxter's Hemofil M. However, as the risk of transmission of viruses emerged, like hepatitis in the 1970s/1980s and HIV in the 1980s/1990s, patients became fearful of plasma-derived factor VIII, and Baxter's Recombinate saw strong uptake. By 2001, more than 40% of global FVIII sales were recombinant products, either Recombinate or Bayer's Kogenate (approved in 1993), and this grew to almost 70% by 2008.

Baxter's Advate was approved in 2003, the firm's second recombinant Factor VIII protein. Advate improved on Recombinate's safety and convenience; Advate does not contain any animal or human plasma or albumin (bovine-derived trace proteins and human-derived albumin as a stabilizer in Recombinate and Kogenate could in theory lead to viral transmission, or transmission of mad cow disease),

and it is offered at a higher potency yet lower volume (thereby shortening infusion times to only 5 minutes via an IV push).

Plasma-derived factor VIII, however, still carries a substantial portion of the market, with 31% of the 1.6 billion units of factor VIII consumed in the U.S. in 2010 derived from plasma.[8] In Europe, this number is closer to 20%, but several developing markets are exclusively plasma-based, owing to price. We estimate that about one-third of the 120,000 patients diagnosed with hemophilia A are in emerging markets, opening up an avenue for market growth as patients switch to more expensive recombinant products. While recombinant penetration of emerging markets will likely be achieved via lower prices agreed upon with large centralized buyers, akin to Baxter's recent exclusive contract in Brazil, we see this as a significant opportunity. Simply converting plasma-derived patients to Advate in key BRIC nations would given Baxter more than 1 billion incremental units of sales, which we estimate at a $400 million opportunity. If treatment rates improve, and if these countries were to see the same rates of prophylaxis use as the UK (more than 7 IU per capita), this potential would be closer to 20 billion units according to Baxter, or $8 billion by our estimates.

Simply converting plasma-derived patients to Advate in key BRIC nations would given Baxter more than 1 billion incremental units of sales, which we estimate at a $400 million opportunity.

Prophylaxis: Efficacy a Clear Winner, but Cost Remains an Issue

Prophylaxis regimens not only reduce the average number of annual bleeds, but also reduce the likelihood of permanent and disabling joint damage. For example, 93% of prophylaxis patients in a landmark 2007 study of hemophilia A patients showed no signs of joint damage versus only 55% using on-demand treatment.[9] Prophylaxis has increased since the introduction of recombinant proteins that lack the risk of viral contamination.

However, much more protein is required for prophylaxis than for on-demand treatment (when a bleed occurs), and it therefore entails a higher cost. In one study, patients in the prophylaxis group used 350,000 units on average over a 4-year period (less than one bleed per year), versus only 113,000 for the on-demand group (almost 5 bleeds per year). In keeping with these numbers, Baxter estimates that volumes for prophylaxis are typically 2–3 times that of on-demand use. Researchers noted that 90% of the cost of hemophilia A care is tied to recombinant factor VIII, and that by the age of 6, the average prophylaxis patient was getting 6000 IU of factor VIII per kilogram each year, versus 2500IU for on-demand patients.[10] Assuming a cost of $1 per unit and using the average weight of a 6-year-old boy (21 kg), this would bring the annual cost to more than $120,000. The researchers noted that the cost of prophylaxis in factor VIII could go as high as $300,000 per year for a 50-kilogram child. Regardless of weight, the cost of prophylaxis will be at least twice as expensive as on-demand care and will increase as a patient grows into adulthood.

Source

[8] *World Federation of Hemophilia Global Survey 2010*

[9] *Manco-Johnson, Marilyn J, et al. Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia. New England Journal of Medicine, August 9, 2007.*

[10] *Manco-Johnson, Marilyn J, et al. Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia. New England Journal of Medicine, August 9, 2007.*

Given the steeper costs of both recombinant and prophylaxis therapy, we expect pricing pressure could remain an issue. Prices for recombinants like Advate vary significantly, with average price points of roughly 70 cents per unit in the U.S. and 50 cents per unit in the UK. On the other hand, plasma-derived versions sell for only 20–25 cents per unit in emerging markets.[11] Costs are likely to factor into future international tenders in hemophilia despite its rare disease status, given the numerous (and growing) treatment alternatives. For example, it costs between EUR 40,000–120,000 per year to treat an individual with hemophilia in Germany, for example, compared to EUR 2,500 for the average German.[12] The UK began a tender system in 2006 for recombinant factor VIII products via a reverse auction, significantly shifting market share in favor of the most affordable products and lowering the overall price paid by 50%.[13] However, several countries (like Sweden and the Netherlands) are still willing to pay more for treatments for rare diseases.

Increasing rates of prophylaxis therapy account for almost one third of hemophilia A market growth through 2016 in our bottom-up model, and we only assume rates increase relatively modestly, from 25% in 2011 to 29% in 2016.

We still think that prophylaxis has the potential to be a significant growth driver for the hemophilia market, despite costs. In terms of market growth, it doesn't take much of an increase in global prophylaxis rates to impact our assumptions. For example, increasing rates of prophylaxis therapy account for almost one third of hemophilia A market growth through 2016 in our bottom-up model, and we only assume rates increase relatively modestly, from 25% in 2011 to 29% in 2016. If we were to assume that overall global prophylaxis rates could grow as high as 35% in 2016, this would boost our five-year growth rate for hemophilia A sales from 5.9% to 8.3%, and our 2016 market size from $7.3 billion to $8.2 billion.

Source

[11] *Baxter meeting with CFO, November 2012.*

[12] *Johnson, Kathleen A. and Zheng Yi-Zhou. Cost of Care in Hemophilia and Possible Implications of Health Care Reform. ASH documents, Hematology 2011. P.413.*

[13] *Mannucci, Pier Mannuccio, et all. How we choose factor VIII to treat hemophilia. Blood. March 12, 2012.*

Table 5 Hemophilia A Market 2011–2016

	2011	2012E	2013E	2014E	2015E	2016E
Patients Globally, Estimated	400,000	*404,000*	*408,040*	*412,120*	*416,242*	*420,404*
Prevalence Growth		*1%*	*1%*	*1%*	*1%*	*1%*
Identified Patients Globally	120,000	*122,400*	*124,848*	*127,345*	*129,892*	*132,490*
Growth in Identified Patients		*2%*	*2%*	*2%*	*2%*	*2%*
Percentage of Patients Diagnosed	30%	*30%*	*31%*	*31%*	*31%*	*32%*
Prophylaxis Patients						
Patients on Prophylaxis	30,000	*31,212*	*32,460*	*34,383*	*36,370*	*38,422*
As Percentage of Treated Patients	25%	*26%*	*26%*	*27%*	*28%*	*29%*
Average cost/unit, Prophylaxis	$0.80	*$0.80*	*$0.80*	*$0.80*	*$0.80*	*$0.80*
Prophylaxis Adult						
Prophylaxis Adults, number of patients	15,000	*15,684*	*16,393*	*17,535*	*18,730*	*19,979*
As Percentage of all Prophylaxis Patients	50%	*50%*	*51%*	*51%*	*52%*	*52%*
Assumed IU/kg per year	3,000	*3,050*	*3,100*	*3,150*	*3,200*	*3,250*
Average cost/yr, Prophylaxis Adult (75kg)	$180,000	*$183,000*	*$186,000*	*$189,000*	*$192,000*	*$195,000*
Prophylaxis Adult Sales	$2,700,000,000	*$2,870,177,490*	*$3,049,012,886*	*$3,314,190,787*	*$3,596,237,971*	*$3,895,992,012*
Prophylaxis Children						
Prophylaxis Children, number of patients	15,000	*15,528*	*16,068*	*16,848*	*17,639*	*18,443*
As Percentage of all Prophylaxis Patients	50%	*50%*	*50%*	*49%*	*49%*	*48%*
Assumed IU/kg per year	3000	*3050*	*3100*	*3150*	*3200*	*3250*
Average cost/yr, Prophylaxis Child (25kg)	$60,000	*$61,000*	*$62,000*	*$63,000*	*$64,000*	*$65,000*
Prophylaxis Children Sales	$900,000,000	*$947,206,170*	*$996,212,131*	*$1,061,407,507*	*$1,128,916,127*	*$1,198,766,773*
Global Prophylaxis Market	**$3,600,000,000**	***$3,817,383,660***	***$4,045,225,018***	***$4,375,598,295***	***$4,725,154,097***	***$5,094,758,785***
On-Demand Patients						
Patients using on-demand treatment	90,000	*91,188*	*92,388*	*92,962*	*93,522*	*94,068*
As Percentage of Treated Patients	75%	*75%*	*74%*	*73%*	*72%*	*71%*
Average cost/unit, On Demand	$0.31	*$0.30*	*$0.30*	*$0.29*	*$0.29*	*$0.28*
On-Demand Adult						
On-Demand Adults, number of patients	77,143	*78,161*	*79,189*	*79,682*	*80,162*	*80,629*
As Percentage of all On Demand Patients	86%	*86%*	*86%*	*86%*	*86%*	*86%*
Assumed IU/kg per year	1,000	*1,050*	*1,100*	*1,150*	*1,200*	*1,250*
Average cost/yr, On-Demand Adult (75 kg)	$23,250	*$23,924*	*$24,562*	*$25,165*	*$25,734*	*$26,270*
On-Demand Adult Sales	1,793,571,429	*1,869,946,722*	*1,945,065,870*	*2,005,196,124*	*2,062,890,358*	*2,118,151,466*
On-Demand Children						
On Demand Children, number of patients	12,857	*13,027*	*13,198*	*13,280*	*13,360*	*13,438*
As Percentage of all On Demand Patients	14%	*14%*	*14%*	*14%*	*14%*	*14%*
Assumed IU/kg per year	1,000	*1,050*	*1,100*	*1,150*	*1,200*	*1,250*
Average cost/yr, On Demand Child (25kg)	$7,750	*$7,975*	*$8,187*	*$8,388*	*$8,578*	*$8,757*
On Demand Children Sales	$99,642,857	*$103,885,929*	*$108,059,215*	*$111,399,785*	*$114,605,020*	*$117,675,081*
Global On-Demand Market	**$1,893,214,286**	***$1,973,832,651***	***$2,053,125,085***	***$2,116,595,909***	***$2,177,495,378***	***$2,235,826,547***
Global Hemophilia A market	**$5,493,214,286**	***$5,791,216,311***	***$6,098,350,103***	***$6,492,194,203***	***$6,902,649,475***	***$7,330,585,332***
Market Growth	—	***5%***	***5%***	***6%***	***6%***	***6%***
Market CAGR						***5.9%***

Source: Morningstar, Company Data

3. Safety: Inhibitors and Product Selection

Patient switching in hemophilia is generally low. In the past, patients were worried about the development of viral infections, but no cases of blood-borne virus transmission have been seen over the past two decades, mostly due to improved testing of donor plasma and viral inactivation. The key safety concern today relates to developing inhibitors, or neutralizing antibodies. While recent evidence seems to indicate that previously treated patients (PTPs) do not see a higher rate of inhibitor development when switching, we think uncertainty regarding the long-term inhibitor rates with newer products will cause physicians and patients to favor current treatment regimens. We also expect physicians to be even more conservative with previously untreated patients (PUPs), as inhibitors are more likely to develop in such patients. For example, the cumulative rate of inhibitor development is 30% in hemophilia A and much lower—between 1.5% and 3%—in hemophilia B.[14] On the other hand, in PTPs, the rate is closer to 2 or 3 per 1,000 patient years.[15] We think this dynamic could make it challenging for newer products to quickly erode share of standards of care such as Advate in hemophilia A. However, if inhibitor rates with new therapies among PUPs are eventually shown to be comparable to Advate, we think more convenient therapies could see stronger uptake, even in pediatric markets. This is partly owing to the fact that children under the age of two typically have to go to a clinic three to four times per week to receive prophylaxis therapy, and children between ages of 2 and 5 can perhaps do IV dosing at home, but this might also be needed three to four times per week.

While recent evidence seems to indicate that previously treated patients do not see a higher rate of inhibitor development when switching, we think uncertainty regarding the long-term inhibitor rates with newer products will cause physicians and patients to favor current treatment regimens.

Plasma-derived vs. Recombinant

There is conflicting data regarding inhibitor risk with plasma-derived versus recombinant factor replacement, making it unclear whether one could be safer than the other.[16] Rates of inhibitor development with the various treatment options are quite difficult to compare, given the heterogeneous nature of studies conducted to date. The independent SIPPET study comparing Grifols' Alphanate to Baxter's Advate is a 300-patient study that should have results in 2014. The study aims to determine whether plasma-derived proteins show a 50% reduction in rate of inhibitor development as compared to recombinant factor proteins among patients previously untreated with recombinants. Baxter is also conducting a study of once-weekly Advate in previously untreated patients to see if it can reduce inhibitor formation; the EPIC study, in 100 patients under the age of 1, began enrolling in 2011 and should read out in 2016.

Generally speaking, recombinant proteins tend to be less immunogenic than plasma-derived ones, which would support the premium pricing of the recombinant proteins. However, modifications that are made to proteins after the amino acids are linked in a chain—including glycosylation and sulphation—could differ for recombinant factor proteins, which are not made in human cells.[17]

The SIPPET study represents one of the biggest downside risks for the recombinant hemophilia A market, for both marketed and pipeline products. If data support Alphanate's safety over Advate's, we

Source

[14] *Br J Haematol. 2007 Aug;138(3):305–15.*

[15] *Blood First Edition paper, June 12, 2012; DOI 10.1182/blood-2012-03-378927*

[16] *Franchini, Massimo. Plasma-derived versus recombinant Factor VIII concentrates for the treatment of haemophilia A: recombinant is better. Blood Transfus 2010;8:292–6*

[17] *Mannucci, Pier Mannuccio, et all. How we choose factor VIII to treat hemophilia. Blood. March 12, 2012.*

think this could serve to increase the volume share of plasma-derived hemophilia A therapies from the 20–30% level we see today in the U.S. and Europe, particularly given their lower price tags.

However, even if plasma-derived products do produce lower rates of inhibitors, contamination fears will likely remain an issue for patients and prescribers. For example, while viral inactivation during plasma processing is effective, other infectious diseases—like Creutzfeldt-Jakob (a prion disease better known as mad cow disease) can be transmitted through plasma. While Alphanate is processed with three steps specifically designed to eliminate prions—and has received FDA labeling to this effect—the long incubation time for prions could still make this a theoretical concern.

Even if plasma-derived products do produce lower rates of inhibitors, contamination fears will likely remain an issue for patients and prescribers.

We also think recombinant products would still have a significant market to serve among patient switches. Because inhibitor rates are much lower overall with switching patients, we think this is less of an issue for this population, and that adults will likely be willing to switch to achieve the convenience benefits of long-acting versions as they increasingly opt for prophylaxis therapy. Because adults require higher doses of factor proteins to maintain prophylaxis, these patients are among the most expensive to treat, and the most lucrative for drug firms.

Full-Length vs. B-Domain-Deleted

Among recombinant products, efforts have been made in recent years to create fragments of the factor proteins, with the theory that they would yield fewer potential sites for immunogenicity. B-domain-deleted versions of factor VIII were created with recombinant technology for two additional reasons: 1) Bayer and Baxter had already created a strong IP position around full-length versions, limiting competition and 2) a shorter protein is easier to manufacture. Because the protein is naturally cleaved to a B-domain-deleted version at the site of the bleed (and only full length in circulation), there was strong rationale for the potential of shorter versions of FVIII. However, recent data indicate that B-domain-deleted proteins like Pfizer's ReFacto (Xyntha) appear have a rate of inhibitor development that is 7-times higher than for full-length recombinants like Advate.[18] For example, the average rate of inhibitor development for Advate is 0.29%, while the rate seen with Xyntha in its key pivotal trial was roughly 2%, and more than 2.6% for pooled data from numerous studies.

We will learn more about inhibitor rates with B-domain deleted proteins from two key sources: the UK market migration and future trials of novel therapies.

We will learn more about inhibitor rates with B-domain deleted proteins from two key sources. First, the UK has moved a large number of patients onto ReFacto (Xyntha) due to price, and we will see data on inhibitor development released over time. According to SOBI (a Swedish firm which receives manufacturing and royalty income from Pfizer for ReFacto and also markets the product in Nordic countries), data so far does not indicate any increase in inhibitors among patients who switched to ReFacto. However, we note that inhibitors are generally an issue among patients who are new to therapy, so switch studies will be among the hardest to monitor for changes in inhibitor rates.

Source

[18] *Aledort LM, Navickis RJ, Wilkes MM. Can B-domain deletion alter the immunogenicity of recombinant factor VIII? A metaanalysis of prospective clinical studies. J Thromb Haemost 2011; 9: 2180–92.*

There are also several B-domain deleted proteins in late-stage development, and we will eventually see data for these products in untreated patients. For example, SOBI and Biogen-Idec's recombinant fusion Factor VIII and IX proteins (rFVIIIFc and rFIXFc) and Bayer's pegylated FVIII, BAY94-9027, all fall into this category. While initial studies will be in previously-treated adults and children, we expect to see data in the long run stemming from use in previously untreated children. Until that time, we do not expect these products to receive a prescribing label for new patients, which will prevent them from fully participating in market growth, in our opinion.

Prophylaxis use has been tied to better joint health, which would lead to better outcomes for patients.

4. Convenience as a Driver of Switching and Prophylaxis Use

Long-acting replacement factors could provide several benefits to current regimens. The simple convenience of less-frequent administration is itself a benefit, which could lead patients established on prophylaxis regimens to switch to these new therapies. However, we think adult patients currently only using factor replacement on-demand could also be more likely to consider prophylaxis treatment as treatment frequency improves significantly. For example, SOBI noted that patients using on-demand treatment already require roughly 50 injections a year to treat their bleeds on average, and if long-acting products are successful, patients could see dramatic reductions in bleed rates with a similar number of yearly injections. Prophylaxis use has been tied to better joint health, which would lead to better outcomes for patients. While prices of recombinant therapies are already quite high, we think there could be a low-double-digit price premium for these novel therapies in the U.S. Other developed markets, such as Europe, could be willing to support premiums as well, but we think cost effectiveness data (i.e., showing that convenience leads to increased prophylaxis and less crippling joint damage) will be required to support price premiums.

Long-Acting Alternatives a Modest Improvement in Hemophilia A

Human factor VIII has a half-life of 10–12 hours,[19] and therefore must be administered frequently (two to three times a week) for effective prophylaxis. Long-acting replacement factors are aiming to achieve a once-per-week frequency in hemophilia A, which would be a significant improvement over Advate's benchmark of every-three-day dosing, in our opinion (85–90% of patients are eligible for every-three-day dosing of Advate, versus the standard three–four times weekly factor VIII treatment).

Biogen-Idec is poised to be the first to launch into this next generation of hemophilia A therapy. The firm's rFVIIIFc is a recombinant, truncated (B-domain-deleted) version of factor VIII, fused to the Fc domain of an antibody to extend half life in the bloodstream. This fusion protein technology is well-recognized, and has been used in products including Amgen's Enbrel and Nplate. As these modifications are large enough to deem Biogen and SOBI's products new biologic entities, Biogen is forced to perform extensive clinical trials, and initial data is only in adults who have switched from other regimens. In fact, the initial approval is likely to be likely to patients age 12 and up. Therefore, we will require future data—first in pediatric patients and then in previously untreated patients—before we can gain a clearer picture of the safety profile of this product. While its longer half life could give it a better

Source

[19] *The use of PEGylated liposomes in the development of drug delivery applications for the treatment of hemophilia. International Journal of Nanomedicine, 5 August 2010.*

[20] *Fogarty, Patrick F. Biological Rationale for New Drugs in the Bleeding Disorders Pipeline. ASH education book, 2011.*

Given that dosage only improved to a median of every 3.5 days with individualized rFVIIIFc over Advate's 3 days in the A-LONG study—and that only 30% of patients in the individualized arm of the rFVIIIFc study were treated on the five-day dosing schedule by the end of the study—we don't think Biogen offers a significant impact on convenience for patients.

safety profile than Xyntha, inhibitor development will remain a question in the near term. In addition, Fc fusion proteins do not provide a shield from the patient's immune system, a benefit enjoyed by the other long-acting technologies from Bayer and Baxter.[20] Marketing authorization for new products will be delayed in Europe, as companies are now required to have pediatric data before the initial filing. While we expect Biogen's long-acting factor VIII to reach the U.S. market in 2014, these pediatric study requirements should push back launch in Europe and other geographies to 2016.

Table 6 Comparing Advate and rFVIIIFc

Category	Advate	rFVIIIFc
type of molecule	protein-free full-length rFVIII	B-domain-deleted rFVIII covalently linked to human IgG1 Fc domain
patients studied in trials	5 completed studies in previously treated patients and one ongoing study in previously untreated patients	A-LONG 165 patients 12 and older, all switches (on-demand, weekly, and individualized arms)
median ABR (annualized bleed rate)	1.0 (both standard prophylaxis and PK-driven prophylaxis), vs 44 for on-demand patients	1.6 individualized, 3.6 weekly, 33.6 on demand (patients previously only on episodic care put on weekly or on demand—see weekly as alternative for episodic, not those already on prophylaxis)
zero bleeds	42% of patients on prophylaxis (0% on demand)	
dosing frequency	every three days	individualized: median was every 3.5 days. 30% of patients had every 5 day mean dosing in last three months on study
anaphylaxis/hypersensitivity	can occur (trace mouse proteins)	no anaphylaxis
otheradverse reactions	more than 10% of patients saw pyrexia, headache, cough, nasopharyngitis, vomiting, arthralgia, and limb injury	more than 5% of patients saw nasophyaryngitis, arthraligia, headache and upper respiratory tract infection
immunogenicity	3/182 pts saw upward trend in CHO antibodies, 10/182 upward trend in mulgG (mouse immunoglobulin) antibodies. Could lead to urticaria, pruritus, rash, and slight eosinophil count elevations, but repeat admin without recurrence of side effects.	—
inhibitors	0.3% overall inhibitor rate. 5/25 previously untreated patients developed antibodies in median 11 exposure days, 4 high titer 1 low titer. In previously treated patients, 1 of 198 older than age 10 developed low-titer antibody in 26 exposure days, or 0.51% frequency (no longer detectable after 8 weeks). none of 53 pediatric (<6) previously treated patients developed inhibitors	no inhibitors
half life	12.4 hours (A-LONG)	19 hours (A-LONG)—50–60% improvement
marketing	access to vast majority of hemophilia market	access to 2/3 of hemophilia market globally
status	approved for every 3-day prophylaxis	to file H1 2013

Source: Morningstar, Company Data

Source

[20] *Fogarty, Patrick F. Biological Rationale for New Drugs in the Bleeding Disorders Pipeline. ASH education book, 2011.*

Given that dosage only improved to a median of every 3.5 days with individualized rFVIIIFc over Advate's 3 days in the A-LONG study—and that only 30% of patients in the individualized arm of the rFVIIIFc study were treated on the five-day dosing schedule by the end of the study—we don't think Biogen offers a significant impact on convenience for patients. We think initial use of Biogen's hemophilia A offering will be focused on switches, and that Biogen will only be able to slowly penetrate both the pediatric market (due to inhibitor concerns) and the adult market (due to a lack of compelling convenience improvement and expected high cost). Below is a table comparing Advate and rFVIIIFc. The speed of Biogen's market penetration is important not only for incumbents, but also because several other firms are working on long-acting versions of factor VIII. Baxter analyzed roughly 100 modifications of Advate before settling on BAX 855. A PEGylated version of the recombinant protein, BAX 855 was designed to have the same immune system recognition and clearance from the body as Advate, but with a 60–70% longer half-life. The polyethylene glycol (PEG) polymers are attached to the protein and lengthen the time it can circulate without being degraded. With only minor PEGylation (1–2 sites) necessary, the product is similar enough to Advate to allow for accelerated development of BAX 855, and it is moving to Phase III development in 2013. This could lead to a filing in 2014 and a 2015 launch. Assuming Biogen-Idec files for approval of its new therapies in the first half of 2013 and receives approval in early 2014, we think this puts Baxter almost two years behind Biogen. Baxter also has another long-acting version of factor VIII ready to enter development, based on polysialic acid technology. There are no approved products that use this technology, but preclinical work has been promising (low immunogenicity potential and significantly longer half life), and this could be an important addition to Baxter's hemophilia portfolio in the long run.

Given data so far, we do not expect rapid uptake of new hemophilia A entrants from Biogen-Idec, Baxter, Bayer, and Novo Nordisk. No one has been able to tweak the half life of factor VIII proteins by more than roughly 60%.

Bayer also has a PEGylated recombinant FVIII in development, BAY94-9027, which entered Phase III clinical trial PROTECT VIII in 2012. The study aims to test administration of the protein in four arms; three arms of the study are prophylaxis, with initial administration twice a week and ultimate administration schedules after 10 weeks of therapy ranging from twice a week to as little as once per week. The trial should complete at the end of 2013, with data in early 2014. Because this is a trial in previously-treated patients over the age of 12, Bayer will likely need to complete an additional pediatric trial before gaining approval in Europe. It is important to note that this product is B-domain-deleted, which has led to higher rates of inhibitor development with Pfizer's Xyntha. However, in trials to date, this product has not shown immunogenicity, and it is possible that the PEGylation (at only one site on the molecule) is preventing the immune system from developing antibodies to it.[21]

Finally, Novo Nordisk's N8-GP is also in Phase III development, and given its half life extension and data produced to date, we think it is capable of matching Biogen's data, perhaps achieving every four-day dosing. According to Dr. Riedel, Chief Scientific Officer at Baxter, no one has been able to tweak the half life of factor VIII proteins by more than roughly 60%. Given data so far, we do not expect rapid uptake of new entrants from Biogen-Idec, Baxter, Bayer, and Novo Nordisk.

Below, we compare the various pipeline candidates in hemophilia A.

Source

[21] *Fogarty, Patrick F. Biological Rationale for New Drugs in the Bleeding Disorders Pipeline. ASH education book, 2011.*

Table 7 Detailing the Hemophilia A Late-Stage Pipeline

Firm	Recombinant FVIII Product Pipeline	Type	Phase	Launch Estimate	Our Take
Bayer	BAY81-8973	FLP	III (LEOPOLD I to complete in 2013)	2014	No half life advantage to Bayer's Kogenate, but manufactured without human and animal proteins.
Octapharma	Human-cl rhFVIII	Human-like	III (two trials complete, PUP trial to start)	2014	First recombinant with human-like modifications to protein, and no residual hamster proteins. No expected half life improvement.
Novo Nordisk	NN7008 (N8) turoctocog alfa	BDD	Filed 4Q 12	2013	Similar to Advate, but BDD status and lack of track record should slow uptake
Novo Nordisk	NN7088, N8-GP	LA (glycopegylated)	III (start Q1 12)	late 2014/ early 2015	With roughly 1.6-fold the half life of plasma-derived factor VIII and every 4- day dosing looking the most promising, we think this looks similar to Biogen's LA compound
Biogen Idec	rFVIIIFc	LA, BDD (fusion protein)	III (to file H1 13)	2014	With a half life 50–60% longer than Advate in A-LONG, rFVIIIFc could be dosed every 3.5–5 days—shy of the once-weekly goal that could have given it a more significant benefit over Advate.
CSL Behring	CSL627 rFVIII	single chain	I/III	2015	Strong covalent bond between heavy and light protein chains could make it more stable than current options, but mostly theoretical at this point. Half-life expected to be normal, putting it at a disadvantage to next-generation versions.
Bayer	BAY94-9027, peg rFVIII	BDD, LA (pegylated)	III (data early 2014)	2015	Phase I data indicate possible 19 hr half life, 40% longer than Kogenate, looks comparable to Novo and Biogen
Baxter	BAX 855	LA (pegylated)	III (start 2013)	2015	Phase I data indicate possible 60–70% increase in half life, looks comparable to Novo and Biogen

Source: Morningstar, Company Data
BDD=B-domain deleted
FLP=full-length protein
LA=long-acting

Convenience Benefit More Apparent in Hemophilia B Pipeline

In hemophilia B, it could be easier to improve upon Pfizer's BeneFIX with long-acting technologies, but we're waiting for more data before assuming that the switch rate will be rapid.

Given their long half lives relative to Pfizer's BeneFIX, we think drug candidates from Biogen and Novo Nordisk have an opportunity to see significant convenience improvements over standard care in hemophilia B.

Biogen-Idec is also poised to market the first next-generation hemophilia B therapy. The firm's rFIXFc uses the same technology as described for rFVIIIFc. Biogen has produced Phase III data from the B-LONG study indicating that weekly dosing with rFIXFc could be a bit of a stretch; the bleed rate in this arm was almost three per year (despite dose adjustments based on a patient's factor levels), more than double that of the individualized treatment arm. We do not have specifics on the average regimen used by patients in Biogen's individualized arm, but we note that patients did achieve biweekly (twice a month) dosing during the last six months of the one-year study. We will require future data in pediatric and untreated patient populations to get a true read on safety, particularly the issue of inhibitor development. And we think initial use will also be focused largely on switching patients or adults currently using on-demand treatment, not pediatric patients new to therapy. We expect Biogen's long-acting factor IX to reach the U.S. market in 2014, and that pediatric study requirements will push back its launch in Europe and other geographies to 2016.

We think Novo Nordisk could be in a better position to achieve less frequent dosing that Biogen-Idec's rFIXFc. Novo Nordisk's N9-GP has a roughly 100-hour half life, versus the 20-hour half life of BeneFIX, which could allow for once-weekly or even twice-monthly dosing. We note that we have yet to see specific data on dosing intervals from late-stage trials of N9-GP. However, we think Novo's longer half life (Biogen's product appears to have an 82 hour half life) could make it more likely to achieve the once-weekly goal.

Long-Term Market Growth Beyond Factor Replacement

Gene therapy

Gene therapy has recently seen promising data in hemophilia B, but we think this technology is still unproven and at least a decade away from the market. In December 2011, the New England Journal of Medicine published research involving six patients with hemophilia B, all of whom were injected with the intact factor IX gene (inserted into a viral vector). Four of the six no longer needed factor IX replacement therapy following the gene therapy injection, as factor IX was being produced internally. Dr. Katherine Ponder noted that the cost of $30,000 is significantly below that of the $300,000 per year cost of continued administration of replacement factor IX. The trial has been expanded to 20 more patients, and researchers are working to find the highest dose level that will still allow the virus to remain undetected (and continue to produce factor IX). Baxter signed a collaborative agreement with Chatham Therapeutics for the next-generation of this technology, paying $25 million upfront with the potential for additional payments on development and commercialization milestones. Baxter expects to begin a Phase I trial shortly.

We note that success with gene therapy for factor IX will not necessarily translate to success for factor VIII. Factor VIII is the largest protein ever made via recombinant technology, making it more difficult to incorporate into a viral vector. We are not aware of any gene therapy programs in progress for hemophilia A in humans, but data from a study in mice was published in September.[22]

RNA Interference

Alnylam is also interested in pursuing a novel way of treating hemophilia, outside of traditional factor replacement. The firm is looking to apply its RNA interference (RNAi) technology to hemophilia by targeting protein C, and is poised to enter clinical trials in 2013 (preclinical proof of concept was achieved in July 2012, with data presented in December at the American Society of Hematology meeting). Because protein C typically reduces thrombin production, blocking the production of this protein would increase thrombin generation and blood clotting, making this a novel target for hemophilia. Alnylam's ALN-AT3 could serve as a treatment for patients with hemophilia A or B, in addition to patients with inhibitors or those with even rarer deficiencies of various factor proteins. This would also be administered subcutaneously, potentially offering a convenience advantage to current treatments. However, we note that Advate's IV administration is a five-minute IV push that is done by patients in their homes, which we think closely mirrors most subcutaneous administration methods. If Alnylam can extend time between dosing—to a once-weekly or twice-monthly dose, as hoped—this could be an appealing option for patients, but it is too early to say whether this mechanism of action will prove safe or effective in patients.

In addition, novel treatments do involve higher risks. For example, Baxter spent $30 million to acquire Archemix's hemophilia assets in 2010, based on the firm's PEGylated aptamer technology. The Phase I ARC19499 program blocked tissue factor pathway inhibitor activity and could have been a subcutane-

Source

[22] *Gene Ther. 2012 Sep 20. doi: 10.1038/gt.2012.76*

ous alternative to factor VIII and IX replacement therapies, but was discontinued in February 2012 due to safety issues. Novo Nordisk currently has a Phase I program targeting this pathway, but we do not explicitly assign any value to it in our market model.

Bayer: Pipeline and Global Reach Insulate Bayer's Hemophilia Growth Potential

Damien Conover, CFA
David Krempa

Summary
Bayer's sole marketed product in hemophilia is Kogenate, as the firm divested its plasma-derived business as Talecris in 2005 (Talecris was acquired by Grifols in 2011). We are increasing Bayer's fair value estimate to $86 per share from $84 based on increased expectations for Bayer's new hemophilia drugs. Overall, we project 7.2% five-year compound annual growth rate for Bayer's hemophilia products, ahead of our 6% market growth estimate. This is largely due to Bayer's entrenchment with Kogenate and new products BAY81-8973, BAY94-9027 and BAY86-6150 launching in the 2014–2016 time frame. We note that only a quarter of Kogenate's reported sales are in the U.S. market, which could push back the firm's biggest vulnerability to next-generation products to 2016. From a profitability standpoint, we estimate Bayer will generate 10% of total profits in 2016 from its hemophilia portfolio, up from 8% in 2011. Through 2015, we expect Kogenate will remain Bayer's most important product, but new hemophilia drug launches will be critical for Bayer to maintain its leading presence in the long run.

While Bayer's new products seem to offer benefits over existing treatments, most of these drugs have only shown minimal early-stage data. BAY81-8973 (factor VIII) is very similar to Kogenate, but is manufactured without human and animal proteins. BAY94-9027 (factor VIII) showed a 40% longer half-life as compared to Kogenate and looks on par with next-generation drugs from Novo and Biogen. BAY86-6150 has shown very little data for inhibitor treatment, but is fused to albumin, which could extend the drug's half-life.

Key Assumptions
As factor VIII is one of the most complex human proteins, we assume gross margins are the low end of biologic gross margins, or around 80%. We assume a lower margin (60%) on ingredient sales to CSL, which represent about 25% of Bayer's hemophilia sales. We use a higher R&D to sales ratio than Bayer's ratio overall due to Bayer's lower R&D businesses in agriculture and industrials. Also, we use a slightly lower SG&A ratio (15% on product sales and 5% on ingredients sales to CSL) relative to the firm's overall rate of just over 20% as the hemophilia products only need a small specialized sales team.

Moat Implications
All of the entrenched hemophilia players, including Bayer, have specialist-focused marketing teams that have established strong relationships with physicians. Many patients have been on Bayer's Kogenate for more than a decade. We think these factors give incumbents like Bayer the upper hand in treatment decisions, particularly if new products don't show meaningful benefits. About 14% of overall sales were in emerging markets in 2011, and Bayer saw 25% growth for Kogenate in these geographies. We think Bayer's global reach will help the firm penetrate these markets as newer, premium-priced products begin to slowly steal share in developed markets.

Bayer BAYRY

Fair Value $86 **Moat** Narrow **Moat Trend** Stable

	2011	2012E	2013E	2014E	2015E	2016E	CAGR
Bayer Hemophilia Portfolio (in millions of EUR)							
Kogenate	1,075	1,181	1,223	1,264	1,264	1,238	2.9%
BAY81-8673 (A)				38	57	76	
BAY94-9027 (A)					76	152	
BAY86-6150 (Inh.)						57	
Total Hemophilia	**1,075**	**1,181**	**1,223**	**1,302**	**1,397**	**1,523**	**7.2%**
Total Bayer Sales	**36,528**	**39,839**	**42,037**	**43,971**	**45,653**	**47,670**	**5.5%**
Percentage of Bayer Total Sales	**3%**	**3%**	**3%**	**3%**	**3%**	**3%**	
GM-Product Sales	80%	80%	80%	80%	80%	80%	
GM-Ingredient Sales	60%	60%	60%	60%	60%	60%	
GM-Product Sales	636	699	724	771	827	902	
GM-Ingredient Sales	168	184	191	203	218	238	
GM-Hemophilia	**74.8%**	**74.8%**	**74.8%**	**74.8%**	**74.8%**	**74.8%**	
R&D	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	
SG&A-Product Sales	15%	15%	15%	15%	15%	15%	
SG&A-Ingredient	5%	5%	5%	5%	5%	5%	
SG&A-Product Sales	119	131	136	144	155	169	
SG&A-Ingredient	14	15	16	17	18	20	
SG&A-Overall	**12.4%**	**12.4%**	**12.4%**	**12.4%**	**12.4%**	**12.4%**	
Hemophilia Operating Margin	49.9%	49.9%	49.9%	49.9%	49.9%	49.9%	
Hemophilia Operating Income	536	589	611	650	697	760	7.2%
Bayer Operating Income	6,403	6,669	7,095	7,320	7,580	7,946	4.4%
Percentage of Operating Income	**8.4%**	**8.8%**	**8.6%**	**8.9%**	**9.2%**	**9.6%**	

Sources: Morningstar Estimates, Company Data

Baxter: Despite Competition, Hemophilia to Remain a Core Piece of Profitability

Karen Andersen, CFA

Summary

Overall, we expect Baxter to see five-year average annual sales growth of 4% between 2011 and 2016 for its hemophilia portfolio, below our 6% market growth estimate. This is largely due to novel long-acting products from Bayer, Novo Nordisk, and Biogen-Idec that could slowly erode Baxter's growth potential. However, we estimate that hemophilia represents a very profitable business for Baxter, nearly a quarter of sales but almost half of operating income in 2011.

Whereas Baxter has aimed for differentiation with Advate—setting the benchmark in hemophilia A for high efficacy and low levels of inhibitor development—its late-stage pipeline more closely parallels a biosimilar strategy. Recombinant versions of factor IX and VIIa are in the works, and Baxter has openly discussed its strategy of creating products that are as close to market leaders (Pfizer's BeneFIX in factor IX, and Novo's NovoSeven in factor VIIa) as possible. If Baxter's new products reach the market on schedule in 2013 (rFIX), 2014 (recombinant von Willebrand factor), 2015 (long-acting factor VIII) and 2016 (rFVIIa), we think this will give the firm broad coverage of the hemophilia market and allow it to successfully defend its franchise, albeit at a slightly lower growth rate. Combined with the pending acquisition of dialysis firm Gambro, this reduces the impact of Baxter's hemophilia franchise from 23% of sales in 2011 to 20% in 2016.

Key Assumptions

As factor VIII is one of the most complex human proteins, we assume gross margins on recombinant products are the low end of biologic gross margins, or around 80%. We assume much lower margins on plasma-derived products due to lower prices, but we still assume slightly higher margins than for Baxter's overall business. We use a higher R&D to sales ratio than Baxter's company-wide ratio in our profit calculations (to reflect the higher costs of product development in the firm's bioscience business) but use only a 15% SG&A to sales ratio (below the firm's 20%-plus ratio), due to the relatively small, specialist-focused sales force required in hemophilia.

Moat Implications

As the only recombinant approved for prophylaxis in both kids and adults, and with a new 3-day dosing schedule, we think Advate is the best-positioned hemophilia A product on the market today, representing one of the firm's many market-leading brands. We expect Baxter could be able to translate contracts in emerging markets, such as the new Advate contract in Brazil, into broader overall penetration of the hemophilia market, lifting rates of recombinant use and prophylaxis. Because we see long-acting competition as weaker in the FVIII market than the FIX market, we think Baxter could be relatively insulated from sales erosion, and we think Baxter is poised to remain among the most innovative firms in the field of recombinant hemophilia therapies in the long run.

Baxter BAX

Fair Value $65 **Moat** Wide **Moat Trend** Stable

	2011	2012E	2013E	2014E	2015E	2016E	CAGR
Baxter Hemophilia Portfolio (in millions of USD)							
Advate	1,659	1,715	1,863	1,879	1,846	1,782	
Recombinate	553	540	520	500	480	460	
Feiba	608	641	665	720	760	800	
Hemofil M	300	296	300	300	300	300	
Immunine	100	90	90	79	82	76	
Baxter Hemophilia Late-Stage Pipeline							
rFIX (BAX326)			50	100	150	200	
rVWF (BAX111)				30	60	90	
rFVIIa (BAX817)						50	
LA rFVIII PEG (BAX855)					100	200	
Total Hemophilia Sales	**3,220**	**3,282**	**3,488**	**3,608**	**3,778**	**3,958**	**4.2%**
Total Baxter Sales	**13,893**	**14,286**	**16,186**	**17,910**	**18,885**	**19,976**	**7.5%**
Percentage of Baxter Total Sales	**23%**	**23%**	**22%**	**20%**	**20%**	**20%**	
GM-recombinant	80%	80%	80%	80%	80%	80%	
GM-Feiba	60%	60%	60%	60%	60%	60%	
GM-plasma-derived other	50%	50%	50%	50%	50%	50%	
GM-recombinant	1,770	1,804	1,947	2,007	2,109	2,225	
GM-Feiba	365	385	399	432	456	480	
GM-plasma-derived other	250	238	240	229	232	226	
GM-hemophilia	**74%**	**74%**	**74%**	**74%**	**74%**	**74%**	
R&D	14%	14%	14%	14%	14%	14%	
SG&A	15%	15%	15%	15%	15%	15%	
Hemophilia Operating Margin	45%	45%	45%	45%	45%	45%	
Hemophilia Operating Income	1,451	1,475	1,574	1,622	1,701	1,784	4.2%
Baxter Operating Income	2,946	3,250	3,537	3,940	4,391	4,844	10.5%
Percentage of Operating Income	**49%**	**45%**	**45%**	**41%**	**39%**	**37%**	

Source: Morningstar Estimates, Company Data

Biogen Idec: Expect Slow Hemophilia Sales Growth, and Small Impact Relative to MS Empire

Karen Andersen, CFA

Summary

Biogen holds rights to long-acting FVIII and FIX proteins in the U.S. and some key emerging markets like Brazil and China, and these products will likely reach the U.S. market in 2014. While we think Biogen will see peak total sales from its hemophilia products around $1 billion in 10 years, we think erosion of market share will generally be slow, and Biogen's MS franchise will keep this at a small portion of the firm's overall business (only 7% of sales and 5% of operating profits by 2016).

Key Assumptions

We have raised our assumed probability of approval for Biogen's hemophilia products from 75% to 100%, and we are therefore raising our fair value estimate from $138 per share to $142. Both have produced solid Phase III data and will be filed with regulators shortly. As part of its agreement with SOBI, Biogen records hemophilia sales in regions outside of Europe, the Middle East, Russia, and Turkey, but as we expect approvals in international markets to begin in 2016, the vast majority of sales through 2016 will be reported by Biogen directly (Biogen will pay a roughly 6% royalty to SOBI for its territories, in exchange for a 16% royalty from SOBI for its territories). We use 80% gross margins for Biogen's hemophilia products. Despite the fact that we expect a price premium to marketed products, we think Biogen will at least initially lack the scale to see improved margins over established competitors. Because the rest of Biogen's business is also focused on specialist markets and requires heavy R&D investment, we have used company-wide operating expense ratios in our analysis.

Biogen Idec does have a preclinical agreement with Amunix, which it established in 2011, for its XGEN technology. This involves the fusion of the factor protein to a long, unstructured, hydrophilic aa sequence to extend its half life. However, as this has not entered development, it does not factor into our 5-year time horizon.

Moat Implications

We think Biogen will be able to steadily build a solid foundation in hemophilia over the next several years, based on solid efficacy and a slight improvement in convenience for patients. However, we think the moat around the current hemophilia market will prevent Biogen from rapidly gaining share. For example, because Biogen and partner SOBI do not have significant experience marketing products in geographies outside of the U.S. and Europe, they could be at a distinct disadvantage reaching international hematologists versus global players like Bayer, Baxter, and Novo Nordisk. Also, the low switch rate among hemophilia patients could make it difficult to encourage current patients to move to Biogen's products without a compelling convenience benefit. Biogen's exposure to hemophilia will also likely remain small due to the massive sales and profitability of cancer drug Rituxan and the firm's growing multiple sclerosis empire.

Biogen Idec BIIB

Fair Value $142 **Moat** Wide **Moat Trend** Stable

	2011	*2012E*	*2013E*	*2014E*	*2015E*	*2016E*	CAGR
Biogen Hemophilia Late-Stage Pipeline (in millions of USD)							
rFVIIIFc	0	*0*	*0*	*100*	*250*	*375*	
rFIXFc	0	*0*	*0*	*50*	*125*	*200*	
Total Hemophilia Sales	**—**	**—**	**—**	***150***	***375***	***575***	
Total Biogen-Idec Sales	**5,049**	***5,494***	***6,113***	***7,112***	***7,775***	***8,169***	***10.1%***
Percentage of Biogen-Idec Total Sales	**0%**	***0%***	***0%***	***2%***	***5%***	***7%***	
GM	80%	*80%*	*80%*	*80%*	*80%*	*80%*	
R&D	24%	*25%*	*24%*	*24%*	*23%*	*23%*	
SG&A	21%	*23%*	*22%*	*22%*	*21%*	*20%*	
Amortization, Other Operating Expenses	12%	*9%*	*8%*	*6%*	*7%*	*6%*	
Hemophilia Operating Margin	23%	*24%*	*26%*	*29%*	*30%*	*31%*	
Hemophilia Operating Income				*43*	*112*	*181*	
Biogen Idec Operating Income	1,725	*1,890*	*2,202*	*2,749*	*3,071*	*3,310*	*13.9%*
Percentage of Operating Income	**0%**	***0%***	***0%***	***2%***	***4%***	***5%***	

Sources: Morningstar, Company Data

Novo Nordisk: NovoSeven Flattening, but Growth From Long-Acting Factor Replacements

Lauren Migliore, CFA

Summary

The bulk of Novo's hemophilia exposure stems from NovoSeven sales in the inhibitor market, and we expect the firm to enjoy steady but low-growth profits from this business. NovoSeven, the leading recombinant treatment for acute bleeds in inhibitor patients, has secured a foothold for Novo, which the firm plans to expand through a pipeline of new hemophilia A and B treatments. Novo stands to bring innovative, long-acting factor VIII and IX proteins to the market in 2014 and 2015, respectively, putting it in a position to begin to steal some of the market's growth from incumbents like Baxter, CSL, Grifols, and Bayer. Today, 10% of Novo's sales and 14% of profits stem from hemophilia, by our estimates, and we expect this contribution to remain relatively stable in the near term. The operating margins of the firm's biopharmaceuticals segment have averaged around 80% higher than the firm's core diabetes care business over the last three years. Therefore, we expect new launches from the firm's hemophilia pipeline to mostly offset the impact of the likely approval of Novo's new degludec insulin line in 2013.

Key Assumptions

We assume a 90% gross margin for NovoSeven, as we believe Novo's margins on this expensive product are slightly higher than the 89% gross margin seen in the overall biopharmaceuticals division. While NovoSeven has grown at an 11% CAGR over the past five years, we expect sales to stay relatively flat going forward as high penetration in developed markets, austerity measures in Europe, and the emergence of copycat versions in some emerging markets offset Novo's pricing power in the United States. Since the failure of Novo's inhibitor market pipeline candidates, future growth outside of NovoSeven will likely stem from long-acting versions of factor VIII and IX in late-stage development. We think Novo will be able to benefit substantially from its global NovoSeven salesforce, giving it an edge over Biogen-Idec and SOBI outside the U.S. and Europe.

Moat Implications

Novo Nordisk, long dominant in the field of diabetes care, is looking to leverage its expertise in protein therapy to establish a leadership position in other areas like hemophilia and inflammation. Though comprising just under a quarter of Novo's sales, biopharmaceuticals brought in 35% of operating profits last year. We expect new launches in this highly-profitable segment to mostly offset the impact of the likely approval of Novo's new line of insulin on the firm's profitability. Despite the fact that NovoSeven patents have expired, we think manufacturing challenges and Novo's brand will protect it from significant biosimilar competition in developed markets for the foreseeable future. In our opinion, Novo's proven ability to innovate in diabetes care, hormone therapies, and blood coagulation provides the firm with the potential for at least 20 years of excess economic profits.

Novo Nordisk NVO

Fair Value $156 **Moat** Wide **Moat Trend** Positive

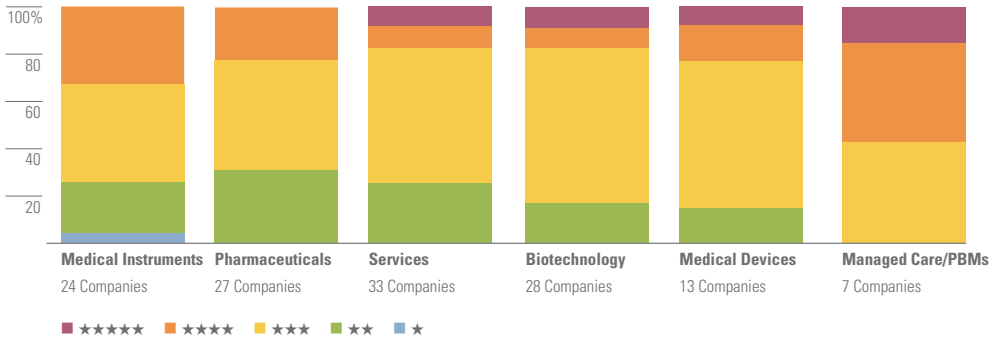
	2011	2012E	2013E	2014E	2015E	2016E	CAGR
Novo Nordisk Hemophilia Portfolio (in millions of USD)							
NovoSeven	1,214	1,226	1,239	1,251	1,263	1,200	
Novo Nordisk Hemophilia Late-Stage Pipeline							
Turoctocog alfa (rFVIII)			50	100	150	175	
N8-GP (long-acting rFVIII)				75	200	325	
N9-GP (long-acting rFIX)					100	225	
Total Hemophilia Sales	**1,214**	***1,226***	***1,289***	***1,426***	***1,713***	***1,925***	**9.66%**
Total Novo Sales	**12,387**	***13,920***	***15,180***	***16,593***	***18,216***	***20,079***	**10.14%**
Percentage of Novo Total Sales	**10%**	***9%***	***8%***	***9%***	***9%***	***10%***	
GM-biopharmaceuticals	90%	90%	90%	90%	90%	90%	
GM-biopharmaceuticals	1,093	1,104	1,160	1,283	1,542	1,733	
R&D	20%	15%	15%	15%	15%	15%	
SG&A	21%	21%	21%	21%	21%	21%	
Hemophilia Operating Margin	49%	54%	54%	54%	54%	54%	
Hemophilia Operating Income	595	662	696	770	925	1,040	11.81%
Novo Operating Income	4,177	5,191	5,798	6,436	7,120	7,857	13.47%
Percentage of Operating Income	**14%**	***13%***	***12%***	***12%***	***13%***	***13%***	—

Sources: Morningstar Estimates, Company Data

Outlook for Industries in Health Care

The ranking of industries with the highest percentage of 5-star ratings include managed care/PBMs and medical devices. The industries with the worst rankings are medical instruments and pharmaceuticals. Looking at the entire healthcare sector, the number of 5-star stocks is at a very low level with only six stocks with five-star ratings.

Ratings on Healthcare Coverage Universe



Data as of December 21, 2012

Since the August 2008 inception, our focus list has outperformed the iShares Dow Jones US Healthcare ETF Index IYH by 50% and the S&P 500 by 66%. On an absolute basis, the focus list has returned 80% since the initial launch. We measure our performance by equally weighting each holding and rebalancing at the end of each month. This month, we are removing **Roche** RHHBY (FV: $50) due to strong stock appreciation and we are adding **United-Health** UNH (FV: $65) as we feel the stock's strong competitive position is underappreciated.

Health-Care Large Cap Focus List

Company	Ticker	Moat	Uncertainty	Morningstar Rating	Price/Fair Value	Analyst
WellPoint	WLP	Narrow	Medium	★★★★★	0.68	Coffina
Express Scripts	ESRX	Wide	Medium	★★★★	0.74	Coffina
Teva	TEVA	Narrow	Medium	★★★★	0.75	Waterhouse
Covidien	COV	Narrow	Medium	★★★★	0.76	Morozov
Valeant Pharmaceuticals	VRX	Narrow	High	★★★★	0.81	Krempa
UnitedHealth	UNH	Narrow	Medium	★★★	0.85	Coffina
Medtronic	MDT	Wide	Medium	★★★★	0.86	Wang
Thermo Fisher Scientific	TMO	Narrow	Medium	★★★★	0.86	Morozov
Becton Dickinson	BDX	Narrow	Low	★★★★	0.88	Morozov
Pfizer	PFE	Wide	Medium	★★★	0.93	Conover

Data as of December 21, 2012

Outlook for Industries in Health Care

Since our recent launch at the beginning of Sept. 2010, our focus list has underperformed the iShares Dow Jones US Healthcare ETF Index IYH by 2% and outperformed the Russell Mid Cap Index by 5%. On an absolute basis, the focus list has returned 44% since the initial launch. While we are underperforming our healthcare benchmark, our investment horizon is 2–3 years, and we anticipate stronger returns over the long term. We measure our performance by equally weighting each holding and rebalancing at the end of each month. This month, we are replacing Warner **Chilcott** WCRX (FV: $10) with **Paladin Labs** PLB (FV: CAD 51) as we believe greater stock appreciation potential is present with Paladin and we recently lowered our valuation estimates for Warner due to poor new product launches.

Health-Care SMID Focus List

Company	Ticker	Moat	Uncertainty	Morningstar Rating	Price/Fair Value	Analyst
Nordion	NDZ	Narrow	High	★★★★★	0.56	Krempa
VCA Antech	WOOF	Narrow	Medium	★★★★★	0.70	Wang
Charles Rivers Labs	CRL	Narrow	Medium	★★★★	0.75	Migliore
Hospira	HSP	Narrow	High	★★★★	0.76	Waterhouse
Vanda	VNDA	None	High	★★★★	0.77	Migliore
Paladin Labs	PLB	Narrow	High	★★★★	0.80	Krempa
Myriad Genetics	MYGN	Narrow	High	★★★	0.88	Andersen
Icon PLC	ICLR	Narrow	Medium	★★★	0.88	Migliore
Smith & Nephew	SNN	Narrow	Medium	★★★	0.95	Stralow
Waters	WAT	Wide	Medium	★★★	0.95	Morozov

Data as of December 21, 2012

Coverage List

Biotechnology

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Alexion Pharmaceuticals, Inc. ALXN	Lauren Migliore	★★	18,624	95.86	78	1.23	Narrow	High	38.1
Biogen Idec Inc BIIB	Karen Andersen	★★	35,776	151.21	138	1.10	Wide	Medium	21.3
Biomarin Pharmaceutical, Inc. BMRN	Karen Andersen	★★	6,070	49.02	44	1.11	Narrow	Medium	NM
CSL Limited CSL	james cooper	★★	27,028	54.05	44	1.23	Narrow	Medium	19.5
Elan Corp PLC ELN	Karen Andersen	★★	6,222	10.51	8	1.31	None	High	NM
Regeneron Pharmaceuticals, Inc. REGN	Lauren Migliore	★★	16,690	172.84	145	1.19	None	High	53.2
Shire PLC SHP	Karen Andersen	★★	10,829	1925.00	1,568	1.23	Narrow	Medium	NM
Alnylam Pharmaceuticals, Inc. ALNY	Karen Andersen	★★★	978	18.66	18	1.04	None	Very High	NM
Amgen Inc AMGN	Karen Andersen	★★★	67,844	88.41	91	0.97	Wide	Medium	13.7
Amylin Pharmaceuticals Inc AMLN	Lauren Migliore	★★★	5,089	30.98	31	1.00	None	Very High	NM
Actelion Ltd. ATLN	Karen Andersen	★★★	5,714	45.07	49	0.92	None	High	13.9
Cubist Pharmaceuticals, Inc. CBST	David Krempa	★★★	2,780	43.16	44	0.98	None	High	24.4
Celgene Corporation CELG	Karen Andersen	★★★	33,847	80.02	84	0.95	Narrow	High	17.2
Dendreon Corp DNDN	Lauren Migliore	★★★	816	5.29	5.5	0.96	None	High	NM
Gilead Sciences Inc GILD	Karen Andersen	★★★	55,808	73.66	80	0.92	Narrow	Medium	20.8
Human Genome Sciences Inc HGSI	Lauren Migliore	★★★	2,848	14.24	14	1.02	None	Very High	NM
Incyte Corp Ltd INCY	David Krempa	★★★	2,194	16.71	15	1.11	None	Very High	NM
Lonza Group AG LONN	Charlie Miller	★★★	2,578	49.94	57	0.88	None	High	14.1
MannKind Corporation MNKD	Lauren Migliore	★★★	533	2.17	2.5	0.87	None	Very High	NM
Momenta Pharmaceuticals, Inc. MNTA	Michael Waterhouse	★★★	601	11.63	12	0.97	None	Very High	NM
Novo Nordisk A/S NVO	Lauren Migliore	★★★	93,218	160.72	156	1.03	Wide	Medium	23.6
Onyx Pharmaceuticals, Inc. ONXX	Lauren Migliore	★★★	5,302	78.96	70	1.13	None	High	NM
Parexel International Corporation PRXL	Lauren Migliore	★★★	1,808	30.73	28	1.10	Narrow	High	19.9
QLT, Inc. QLT	Michael Waterhouse	★★★	404	7.79	8.5	0.92	None	Very High	NM
Seattle Genetics, Inc. SGEN	Lauren Migliore	★★★	2,849	23.92	27	0.89	None	Very High	NM
Savient Pharmaceuticals SVNT	David Krempa	★★★	90	1.23	1.5	0.82	None	Very High	NM
ViroPharma, Inc. VPHM	Lauren Migliore	★★★	1,527	23.17	22	1.05	None	Very High	NM
Vertex Pharmaceuticals VRTX	Lauren Migliore	★★★	9,397	43.34	50	0.87	None	High	NM
Lexicon Pharmaceuticals, Inc. LXRX	Karen Andersen	★★★★	999	1.95	3	0.65	None	Very High	NM
Vanda Pharmaceuticals, Inc. VNDA	Lauren Migliore	★★★★	110	3.91	5	0.78	None	High	NM
Exelixis, Inc. EXEL	Lauren Migliore	★★★★★	861	4.69	11	0.43	None	Very High	NM
InterMune, Inc. ITMN	Lauren Migliore	★★★★★	662	10.03	25	0.40	None	Very High	NM

Coverage List

Diagnostics & Research

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Idexx Laboratories IDXX	Debbie Wang	★★	5,262	96.24	83	1.16	Narrow	Medium	27.1
Covance, Inc. CVD	Lauren Migliore	★★★	3,231	59.03	60	0.98	Narrow	Medium	22.5
Quest Diagnostics Inc DGX	Debbie Wang	★★★	9,546	60.05	65	0.92	Narrow	Medium	14.6
Gen-Probe, Inc. GPRO	Lauren Migliore	★★★	3,791	82.69	83	1.00	Narrow	Medium	31.8
Icon PLC ICLR	Lauren Migliore	★★★	1,700	28.43	32	0.89	Narrow	High	32.9
Myriad Genetics, Inc. MYGN	Karen Andersen	★★★	2,239	27.51	31	0.89	Narrow	High	20.0
Qiagen NV QIA	Charlie Miller	★★★	3,341	14.13	13	1.09	None	Medium	11.1
WuXi PharmaTech (Cayman), Inc. WX	Lauren Migliore	★★★	1,113	15.90	18	0.88	None	High	13.9
Alere Inc ALR	Debbie Wang	★★★★	1,549	19.16	26	0.74	None	High	8.9
Charles River Laboratories International Inc CRL	Lauren Migliore	★★★★	1,836	37.81	50	0.76	Narrow	Medium	18.4
Laboratory Corporation of America Holdings LH	Debbie Wang	★★★★	8,263	87.35	98	0.89	Narrow	Medium	14.2
Life Technologies Corp LIFE	Charlie Miller	★★★★	8,832	51.33	58	0.89	None	Medium	14.6
Nordion, Inc. NDZ	David Krempa	★★★★★	383	6.19	11	0.56	Narrow	High	17.5

Drug Manufacturers—Major

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Bayer AG BAYRY	Damien Conover	★★	79,164	95.73	84	1.14	Narrow	Medium	12.7
Bristol-Myers Squibb Company BMY	Damien Conover	★★	53,763	32.57	29	1.12	Wide	Medium	14.9
Eli Lilly and Company LLY	Damien Conover	★★	57,152	49.25	44	1.12	Wide	Medium	13.1
AstraZeneca PLC AZN	Damien Conover	★★★	60,096	47.75	50	0.96	Wide	Medium	8.0
Merck & Co Inc MRK	Damien Conover	★★★	128,166	42.15	46	0.92	Wide	Medium	12.2
Pfizer Inc PFE	Damien Conover	★★★	187,230	25.43	27	0.94	Wide	Medium	12.3
Roche Holding AG RHHBY	Karen Andersen	★★★	175,618	50.90	50	1.02	Wide	Medium	13.7
Sanofi SNY	Damien Conover	★★★	125,391	47.43	50	0.95	Wide	Medium	12.5
Abbott Laboratories ABT	Damien Conover	★★★★	103,613	65.55	72	0.91	Wide	Low	14.2
GlaxoSmithKline PLC GSK	Damien Conover	★★★★	111,084	44.00	49	0.90	Wide	Medium	13.6
Johnson & Johnson JNJ	Damien Conover	★★★★	196,067	70.75	77	0.92	Wide	Low	15.1
Novartis AG NVS	Damien Conover	★★★★	154,235	63.76	69	0.92	Wide	Low	13.1

Coverage List

Drug Manufacturers— Specialty & Generic

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Merck KGaA MKGAY	Damien Conover	★★	8,601	44.36	33	1.34	Narrow	Medium	10.5
Mylan Inc MYL	Michael Waterhouse	★★	11,317	27.77	22	1.26	Narrow	High	8.5
Perrigo Company PRGO	Michael Waterhouse	★★	9,730	103.64	93	1.11	Narrow	Medium	16.7
UCB SA UCB	Lauren Migliore	★★	8,044	44.21	37	1.19	None	High	21.6
Warner Chilcott PLC WCRX	David Krempa	★★	2,938	11.73	10	1.17	Narrow	High	2.7
Dr. Reddy Laboratories, Ltd. 500124	Michael Waterhouse	★★★	313,397	1845.60	1,850	1.00	Narrow	High	NM
Allergan, Inc. AGN	Michael Waterhouse	★★★	27,974	93.09	85	1.10	Wide	Medium	20.4
Dr. Reddy Laboratories, Ltd. DRREDDY	Michael Waterhouse	★★★	313,431	1845.80	1,850	1.00	Narrow	High	NM
Forest Laboratories, Inc. FRX	Damien Conover	★★★	9,478	35.63	40	0.89	Narrow	High	NM
Hikma Pharmaceuticals PLC HIK	Michael Waterhouse	★★★	1,471	751.00	725	1.04	Narrow	High	21.0
Medicis Pharmaceuticals Corporation MRX	Michael Waterhouse	★★★	2,567	43.96	44	1.00	Narrow	High	17.9
Par Pharmaceutical Companies, Inc. PRX	Michael Waterhouse	★★★	1,841	49.98	50	1.00	None	Very High	14.2
Dr. Reddy Laboratories, Ltd. RDY	Michael Waterhouse	★★★	5,780	34.04	34	1.00	Narrow	High	18.3
Watson Pharmaceuticals Inc. WPI	Michael Waterhouse	★★★	11,524	90.20	86	1.05	Narrow	High	14.9
Hospira, Inc. HSP	Michael Waterhouse	★★★★	5,337	32.30	42	0.77	Narrow	High	21.0
H.Lundbeck A/S LUN	David Krempa	★★★★	16,132	82.25	125	0.66	Narrow	High	13.0
Paladin Labs, Inc. PLB	David Krempa	★★★★	840	41.15	51	0.81	Narrow	High	24.8
Teva Pharmaceutical Industries Ltd TEVA	Michael Waterhouse	★★★★	32,984	38.00	50	0.76	Narrow	Medium	9.3
Valeant Pharmaceuticals International Inc VRX	David Krempa	★★★★	18,387	60.32	74	0.82	Narrow	High	16.6

Health Care Plans

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Amerigroup Corporation AGP	Matthew Coffina	★★★	4,704	91.87	92	1.00	None	High	23.9
Cigna Corp CI	Matthew Coffina	★★★	15,487	54.17	57	0.95	None	High	9.8
Humana HUM	Matthew Coffina	★★★	10,796	68.23	78	0.87	None	High	10.7
Aetna Inc AET	Matthew Coffina	★★★★	15,718	46.99	59	0.80	None	High	11.5
Express Scripts ESRX	Matthew Coffina	★★★★	44,609	54.64	73	0.75	Wide	Medium	19.6
UnitedHealth Group Inc UNH	Matthew Coffina	★★★★	56,652	55.46	65	0.85	Narrow	Medium	12.3
WellPoint Inc WLP	Matthew Coffina	★★★★★	18,678	61.51	91	0.68	Narrow	Medium	12.2

Long-Term Care Facilities

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Brookdale Senior Living, Inc. BKD	Damien Conover	★★	2,131	17.58	14	1.26	None	Very High	36.4
Ryman Healthcare Limited RYM	Nachi Moghe	★★	2,215	4.43	3.5	1.27	Narrow	Medium	18.0
Kindred Healthcare, Inc. KND	Michael Waterhouse	★★★	614	11.52	11	1.05	None	Very High	8.2
Skilled Healthcare Group, Inc. SKH	Michael Waterhouse	★★★	262	6.81	6	1.13	None	Very High	7.2

Coverage List

Medical Care

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Amsurg Corporation AMSG	Debbie Wang	★★	894	28.25	21	1.35	Narrow	High	NM
DaVita HealthCare Partners Inc DVA	Michael Waterhouse	★★	10,746	112.64	100	1.13	Narrow	Medium	16.3
Ramsay Health Care Limited RHC	Tim Montague-Jones	★★	5,456	27.00	22	1.23	Narrow	Medium	17.0
Tenet Healthcare Corp THC	Michael Waterhouse	★★	3,567	33.50	26	1.29	None	Very High	12.0
Fresenius Medical Care Corporation FMS	Michael Waterhouse	★★★	10,403	34.43	33	1.04	Narrow	Medium	17.8
HCA Holdings Inc HCA	Michael Waterhouse	★★★	13,761	31.17	28	1.11	None	Very High	7.6
Lincare Holdings Inc. LNCR	Damien Conover	★★★	2,128	24.64	24	1.03	None	High	10.5
Select Medical Holdings Corporation SEM	Michael Waterhouse	★★★	1,346	9.58	10	0.96	None	Very High	9.5
VCA Antech, Inc. WOOF	Debbie Wang	★★★★★	1,830	20.84	30	0.69	Narrow	Medium	21.7

Medical Devices

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Cochlear Limited COH	James Cooper	★★	4,469	78.36	62	1.26	Narrow	Medium	19.0
Thoratec Laboratories Corporation THOR	Julie Stralow	★★	2,233	38.01	31	1.23	None	High	17.1
William Demant Holding A/S WDH	Alex Morozov	★★	27,883	490.40	433	1.13	Narrow	Medium	15.8
Boston Scientific, Inc. BSX	Debbie Wang	★★★	7,977	5.81	5.5	1.06	Narrow	High	8.7
Edwards Lifesciences Corporation EW	Debbie Wang	★★★	10,652	92.30	85	1.09	Narrow	High	33.1
Given Imaging, Ltd. GIVN	Debbie Wang	★★★	550	17.74	18	0.99	Narrow	High	36.3
Medtronic, Inc. MDT	Debbie Wang	★★★	43,165	42.68	46	0.93	Wide	Medium	12.6
Smith & Nephew PLC SNN	Julie Stralow	★★★	10,587	55.66	58	0.96	Narrow	Medium	15.5
Sonova Holding AG SOON	Alex Morozov	★★★	6,867	103.00	109	0.94	Narrow	Medium	21.0
Synthes Inc. SYST	Julie Stralow	★★★	23,787	158.60	159	1.00	Wide	Medium	20.0
Waters Corporation WAT	Alex Morozov	★★★	7,768	89.33	93	0.96	Wide	Medium	18.9
Zimmer Holdings Inc ZMH	Julie Stralow	★★★	11,937	68.80	71	0.97	Wide	Medium	13.4
Abiomed, Inc. ABMD	Julie Stralow	★★★★	540	13.62	17	0.80	None	High	28.5
EnteroMedics, Inc. ETRM	Debbie Wang	★★★★	111	2.65	4.5	0.59	None	Very High	-8.5
St Jude Medical, Inc. STJ	Debbie Wang	★★★★	11,264	36.55	49	0.75	Wide	Medium	14.3
Stryker Corporation SYK	Julie Stralow	★★★★	21,508	56.57	63	0.90	Wide	Medium	15.5
Nobel Biocare Holding AG NOBN	Julie Stralow	★★★★★	970	7.84	15	0.52	Narrow	Medium	25.7

Medical Distribution

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Henry Schein, Inc. HSIC	Julie Stralow	★★	7,216	82.01	63	1.30	Narrow	Medium	14.6
Owens & Minor, Inc. OMI	Matthew Coffina	★★	1,826	28.80	27	1.07	None	Low	14.0
AmerisourceBergen Corp ABC	Matthew Coffina	★★★	10,314	43.80	47	0.93	Narrow	Medium	16.5
Cardinal Health Inc CAH	Matthew Coffina	★★★	14,376	42.31	40	1.06	Narrow	Medium	11.7
McKesson, Inc. MCK	Matthew Coffina	★★★	23,387	99.08	100	0.99	Narrow	Medium	13.8
Patterson Companies, Inc. PDCO	Julie Stralow	★★★	3,714	34.19	34	1.01	Narrow	Medium	13.4

Coverage List

Medical Instruments & Supplies

Company	Analyst	Morningstar Rating	Market Cap (USD Mil)	Stock Price (USD)	Fair Value (USD)	Price/ Fair Value	Economic Moat™	Uncertainty Rating	FV to Forward EPS
Intuitive Surgical, Inc. ISRG	Julie Stralow	★	19,417	488.31	343	1.42	Wide	Medium	22.8
Essilor International SA EI	Michael Waterhouse	★★	7,873	75.66	61	1.24	Wide	Medium	21.0
Mettler-Toledo International, Inc. MTD	Alex Morozov	★★	5,976	195.00	154	1.27	Narrow	Medium	16.6
PerkinElmer Inc PKI	Alex Morozov	★★	3,679	32.05	28	1.14	Narrow	Medium	13.7
Insulet Corporation PODD	Debbie Wang	★★	1,023	21.23	17	1.25	None	High	-17.4
ResMed Inc. RMD	james cooper	★★	6,044	42.24	35	1.21	Narrow	Medium	16.4
Baxter International Inc. BAX	Karen Andersen	★★★	37,196	67.80	65	1.04	Wide	Low	14.4
C.R. Bard, Inc. BCR	Debbie Wang	★★★	8,113	98.56	107	0.92	Narrow	Medium	16.4
CareFusion Corp CFN	Michael Waterhouse	★★★	6,447	29.05	31	0.94	Narrow	Medium	15.9
Cooper Companies COO	Michael Waterhouse	★★★	4,442	92.75	89	1.04	None	High	17.0
Illumina, Inc. ILMN	Charlie Miller	★★★	6,937	56.22	54	1.04	None	High	34.1
Varian Medical Systems, Inc. VAR	Charlie Miller	★★★	7,853	71.78	75	0.96	Narrow	Medium	19.9
DENTSPLY International, Inc. XRAY	Julie Stralow	★★★	5,734	40.40	39	1.04	Narrow	Medium	17.1
Becton Dickinson & Co BDX	Alex Morozov	★★★★	15,585	79.13	89	0.89	Narrow	Low	16.1
Covidien PLC COV	Alex Morozov	★★★★	27,447	57.98	76	0.76	Narrow	Medium	17.8
Hologic Inc HOLX	Charlie Miller	★★★★	5,447	20.42	23	0.89	Narrow	Medium	16.7
Mindray Medical International Limited MR	Charlie Miller	★★★★	4,088	34.73	42	0.83	None	High	25.0
Thermo Fisher Scientific Inc TMP	Alex Morozov	★★★★	23,468	65.15	74	0.88	Narrow	Medium	15.4
Coloplast COLO B	Debbie Wang	★★★★★	54,003	277.10	1,312	0.21	Narrow	Medium	25.0