The hemophilia market could be about to undergo a wave of innovation not seen since the introduction of recombinant factor 20 years ago in response to a crisis in contaminated plasma products. Over the next three years, long-acting factor products may have an even more transformative effect on the market, reshuffling segment shares, moving patients to prophylactic use, and expanding an already substantial global market.

Long-acting (LA) products will also change the competitive landscape. Established companies like Pfizer Inc. (via its inheritance of Wyeth’s BeneFIX franchise for hemophilia B) could fade, as upstarts like Biogen Idec Inc. are expected to enter with unprecedented technology and the potential to grab substantial market share in key segments.

But dynamics are still fluid – only Biogen has reported Phase III results for two long-acting fusion proteins, rFIXFc (B-LONG trial) and rFVIIIFc (A-LONG trial) – both recombinant factors fused to the Fc region of an antibody. Although the data, released in September and October, showed improvement in dosing intervals over the standards of care – a key competitive attribute – they fell short of Phase II results, and investors punished the stock.

Biogen plans to file a BLA for rFIXFc in hemophilia B in the first quarter of 2013, and for rFVIIIFc in hemophilia A in the first half of 2013 (“Biogen Hemophilia A Product May Win Patients Who Shun Therapy” — “The Pink Sheet” DAILY, Oct. 31, 2012). Meanwhile, over the next two years, other companies competing in the hemophilia A segment, including Novo Nordisk AS and Bayer HealthCare Pharmaceuticals AG, will be reporting out Phase III data for their LA products. Novo and Bayer expect to enter the market approximately one year after Biogen.

The New Landscape: Next-Gen Players, Products, Dynamics

Established players Bayer and Novo Nordisk, as well as new entrant Biogen, have LA recombinant factors in late-stage development. Each, likely led by Biogen, is hoping to launch a LA rFVIII and/or a rFIX product over the next two to three years, Farther out, in the four to five year timeframe, Baxter Healthcare Corp. and CSL Behring, both long-standing competitors in the hemophilia market, will enter with LA rFVIII products. A LA rFVIIa product for the challenging inhibitor segment is not expected until 2017, with CSL Behring’s first-time entry into that market.

In fact, even as they protect their existing short-acting factor franchises through pricing and positioning strategies, all of the established players, with the exception of Pfizer, will enter new segments with improved short-acting and with novel LA products.

Baxter is a good example. Long dominant in the hemophilia A segment with Advate and in the inhibitor segment with FEIBA (a concentrate of plasma-derived clotting factors), Baxter will for the first time enter the hemophilia B market with a short-acting rFIX product (BAX 326; BLA submitted) and the inhibitor market with a short-acting rFVIIa product (BAX 817; will soon begin Phase III) to supplement its FEIBA franchise.

In each case, Global Hemophilia Franchise Head Brian Goff told “The Pink Sheet,” the company is going up against a single dominant player with a recombinant stake: Pfizer’s BeneFIX in the hemophilia B segment and Novo Nordisk’s NovoSeven in the inhibitor segment.

Baxter believes it has an advantage because its plan is to offer multiple options in each segment (short- and long-acting recombinant factor in hemophilia A; short-acting recombinant and plasma-derived products in hemophilia B and the inhibitor segments). Baxter feels that multiple treatment options combined with individualized pharmacokinetic dosing will allow it to tailor treatment to individual patients in each sector.

In fact, in a clean sweep of all hemophilia market segments, Baxter is also in Phase I/II development with BAX 855 (a LA recombinant FVIII) to eventually replace Advate. Phase III trials are planned for 2013.

Baxter is in some ways an anomaly in a fast-changing hemophilia market where competition turns on the ability to prolong half-life and extend dosing intervals. “The continued development of these longer-acting factors,” Goff says, “is
Hemophilia 101

Hemophilia is an orphan bleeding disorder caused by lack of or insufficient circulatory clotting factor. This makes it difficult or impossible for patients’ blood to clot. There are three distinct hemophilia patient groups, each served by a different therapeutic clotting factor: hemophilia A, B, and those patients (5-7% of the hemophilia A population at any given time) who develop immune reactions to current treatments.

Within these groups, the disease varies from mild to severe cases in which patients need to infuse frequently – as much as three times per week—and may experience debilitating or even lethal bleeds into joints or internal organs. The variable severity seen in hemophilia populations, and the wide range in propensity to generate inhibitors, points to genetic heterogeneity beyond the basic coagulation factor mutations. However, the science is at an early stage, and clinical or screening biomarkers are still far off.

1. In Hemophilia A, the largest patient segment, patients lack clotting factor VIII (FVIII). According to the National Hemophilia Foundation, approximately one in 5,000 males is born with hemophilia A. The U.S. population is approximately 13,300. Approximately 53% of the population has severe hemophilia.

2. In hemophilia B, patients lack clotting factor IX (FIX). Approximately one in 20,000 males is born with hemophilia B. The U.S. population is approximately 4,200. Approximately 35% of hemophilia B patients have severe disease.

3. At some point, up to 30% of patients with Hemophilia A develop antibodies – or inhibitors – to treatment with rFVIII or rFIX. This immune reaction may prevent the factor from working, leaving the patient vulnerable to bleeds. Most inhibitors are eliminated within one-three years. Patients with inhibitors are typically treated with recombinant FVIIa.

Because the population is already stratified by clotting factor mutation, the hemophilia market is served by a variety of products marketed by different companies. The current products are mostly short-acting recombinant factors, with plasma-derived factors still accounting for about 32% of hemophilia A sales, 44% of hemophilia B sales, and 27% of inhibitor market sales, according to Deutsche Bank.

- Hemophilia A, the largest market segment, is dominated by Baxter Healthcare Corp.’s Advate, an rFVIII product with 2011 sales of approximately $2.2 billion, and Bayer’s Kogenate ($1.1 billion). These two products currently account for about half of the FVIII market.

- Hemophilia B, the smallest market segment, is dominated by Pfizer’s BeneFIX, with 2011 sales of around $693 million. BeneFIX is currently the only recombinant factor in the FIX market. It accounts for 56% of the market, with plasma-derived products taking the rest.

- The inhibitor, or bypass, market is currently dominated by Novo Nordisk’s NovoSeven, an rFVIIa product with 2011 sales of around $693 million. BeneFIX is currently the only recombinant factor in the FIX market. It accounts for 56% of the market, with plasma-derived products taking the rest.

- The inhibitor, or bypass, market is currently dominated by Novo Nordisk’s NovoSeven, an rFVIIa product with 2011 sales of around $693 million. BeneFIX is currently the only recombinant factor in the FIX market. It accounts for 56% of the market, with plasma-derived products taking the rest.

Dominant players in each segment are likely to try to protect much of their existing share in the face of competition from the long-acting factors. In the absence of strong differentiating data, their biggest advantage will be their long safety record. The uptake of the LA factors will be determined by clinical profile, patient and physician willingness to switch, and price.

Clinical profile is a matter of safety, efficacy, and patient convenience. Safety is largely a matter of uncontaminated supply. Efficacy is measured by the ability to control bleed rates and the ability to suppress inhibitor formation. Patient convenience is a matter of reducing the number of infusions that patients must currently undergo. Advate, for instance, is dosed three-four times per week for prophylactic use. The marketers of LA factors hope to reduce dosing frequency by extending the half life of the product, and so the interval between infusions.

Patient convenience is a more powerful product attribute in hemophilia than in most other therapeutic areas. Not only will fewer infusions ease a significant burden on the patient; but they will encourage more patients to switch to a prophylactic regimen.

Prophylaxis is intended to prevent bleeding events through regular infusions of factor. The alternative is infusing “on demand” or during a bleeding event to stop the bleeding. The frequency of infusions, on average, is determined by severity of disease, with more severe patients experiencing several spontaneous bleeds per month, and so requiring more infusions to control them.

The current need under a prophylactic regimen to infuse three-four times per week using a short-acting factor discourages many hemophilia patients from trying or adhering to prophylaxis. If LA factors can reduce the number of infusions by extending the dosing interval then that would encourage more patients to try prophylaxis. But how much improvement in dosing advantage will be enough to persuade physicians and patients to switch to an LA factor?

The significance of shifting more patients to prophylaxis is twofold: it reduces patient morbidity and, from the manufacturer’s perspective, it will lead to more regular, and also greater, lifetime factor use per patient. And there is another benefit for manufacturers: as a powerful attractant to patients, longer-acting factors might also bring in the patient’s voice to weigh in on product switching decisions.
important, but in the end it’s about the bleed.” Physicians and payers will value reductions in the annual bleed rate (ABR), and they determine the uptake of drugs.

Of course, existing products already have low-single-digit ABR and inhibitor formation rates. New products won’t be able to show much improvement on those metrics. Half-life extension is the only metric where there’s room for improvement, but the jury is out on whether the new factors will achieve sufficient improvement to win over physicians.

The only LA factors with Phase III data to support them, Biogen’s rFVIIIFc and rFIXFc, disappointed in hemophilia A, not showing much improvement in dosing over the comparator Advate (3.5 days versus Advate’s 3 days), and showing robust but probably beatable half-life extension in hemophilia B. Where Biogen had been viewed as unstoppable, the unexpected Phase III results suggest that both the hemophilia A and B markets are still in play.

Ted Tuddenham, emeritus professor of hemophilia at University College London and former director of the hemophilia center at the Royal Free Hospital, doesn’t see what all the fuss is over the LA factors. The technology used to prolong half life is either Biogen’s fusion protein or direct pegylation. “Neither produces much improvement in half life, certainly not enough to make a significant difference to patient convenience and acceptability at any age,” he said.

Extending half life is a particular problem for rFVIII. Anne Prener, senior VP for the hemostasis R&D portfolio at Novo, notes that it’s more challenging to extend half life in the FVIII molecule than in FIX: “Factor VIII has more clearance pathways than factor IX. So it requires quite a lot of understanding of the clearance of FVIII in order to prolong it even further.”

Bayer, Novo, Baxter, and CSL Behring have not yet reported Phase III results for their LA pegylated factors in any of the segments. However, as noted, Biogen’s rFVIIIFc did not extend dosing intervals much beyond Advate, leaving room for

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**Selected Long-Acting Hemophilia Factors In Early and Late-Stage Development**

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Product Type</th>
<th>Stage</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Hemophilia A</strong></td>
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<tr>
<td>Biogen</td>
<td>rFVIIIFc</td>
<td>Fusion protein</td>
<td>Pre-BLA</td>
<td>Having reported Phase III data in late October, Biogen plans to submit a BLA in H1 2013. Data showed 1.5x half life advantage over Advate.</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>N8-GP (rFVIII)</td>
<td>Pegylated recombinant factor VIII</td>
<td>Phase III</td>
<td>Phase III will report out in H1 2014. Half-life extension comparable to rFVIIIFc.</td>
</tr>
<tr>
<td>Bayer</td>
<td>BAY 94-9027 (rFVIII)</td>
<td>Pegylated recombinant factor VIII</td>
<td>Phase II/III</td>
<td>Phase II/III began enrolling in July 2012. Bayer declined to say when it will read out.</td>
</tr>
<tr>
<td>Baxter</td>
<td>BAX 855 (rFVIII)</td>
<td>Pegylated recombinant factor VIII</td>
<td>Phase I/II</td>
<td>Company says Phase III will start soon.</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>CSL627</td>
<td>Single chain rFVIII</td>
<td>Phase I</td>
<td>Phase I enrolled first patient in February 2012. Half life extension is modest, approximately 1.3x in early clinical studies.</td>
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<tr>
<td><strong>Hemophilia B</strong></td>
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<tr>
<td>Biogen</td>
<td>rFIXFc</td>
<td>Fusion protein</td>
<td>Pre-BLA</td>
<td>Biogen plans to file a BLA in Q1 2013. Phase III showed half life extension of 3x.</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>N9-GP (rFIX)</td>
<td>Pegylated recombinant factor IX</td>
<td>Phase III</td>
<td>Read out is expected in Q3 2013. Half life extension in earlier trials was 5x.</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>CSL 654 (rIX-FP)</td>
<td>Recombinant Albumin fusion protein</td>
<td>Phase III</td>
<td>Initiated PIII in January 2012. May offer biweekly dosing.</td>
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<tr>
<td><strong>Inhibitor Market</strong></td>
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<tr>
<td>CSL Behring</td>
<td>CSL 689 (VIIa-FP)</td>
<td>Recombinant Albumin fusion protein</td>
<td>Phase I</td>
<td>Phase I started March 2012.</td>
</tr>
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Source: Company websites, investor presentations, interviews
others to improve. And Novo, in Phase I results for its glycopegylated hemophilia B candidate N9-GP, has shown half life extension of five times (i.e., biweekly dosing) compared to BeneFIX, making it potentially superior to Biogen's rFIXFc. N9-GP is currently in a Phase III trial, with read-out expected in the third quarter of 2013; Novo's rFVIII product, N8-GP, is also in Phase III and expected to report out in the first half of 2014.

How The Market Might Shake Out

In the absence of Phase III data, it’s impossible to predict which LA recombinant product will topple the reigning short-acting factor in each segment and capture the most share. However, it is possible to predict some aspects of the market with confidence.

Regarding hemophilia A, Marshall Urist, who heads up biotech at Morgan Stanley, said “I think there won’t be a lot of dispersion in terms of how these long-acting factors perform.”

Over time, assuming LA factors offer even modest gains in half-life extension and can bring about improved compliance with prophylaxis, they could erode the share of short-acting factors. Also, the plasma segment of the market, viewed with lingering suspicion in the hemophilia community since the HIV contamination scare of the 1980s, is shrinking.

The reshuffling of competitors in each segment will depend on the strength - product attributes, pricing, and promotion - behind the reigning product in each segment.

Hemophilia A: Baxter’s dominance of this segment will be hardest to dislodge. Although Advate rules the FVIII segment, it is surrounded by other, well-established rFVIII products such as Bayer’s Kogenate. Therefore, physicians and patients have options with well-established safety track records. Unless LA rFVIII products can show more robust half-life extension compared to Advate, players will be challenged to persuade hematologists to move patients to the next-gen LA factors for prophylactic use. So far, Biogen’s A-LONG trial demonstrated a half-life advantage of 1.5 times Advate’s circulating time, perhaps not enough to drive such a change in care.

Moreover, emerging markets offer significant market expansion opportunities for companies with hemophilia experience, portfolio options, and emerging markets infrastructure and relationships. Thus, Baxter recently entered into a 20-year alliance with Hemobras to provide recombinant Advate to Brazil’s 10,000 hemophilia A patients. According to a 2009 World Hemophilia Foundation survey, the Brazilian hemophilia market is served only by plasma-derived products. Goff says that Baxter is also conducting trials in Poland and Russia, both countries largely served by plasma-derived products.

Hemophilia B: Hemophilia B will likely be the segment that sees the most switching activity. Pfizer’s BeneFIX, the sole recombinant product in the rFIX segment, dominates this market, but it is a weak incumbent. The sponsor’s commitment to the hemophilia B market remains uncertain. Its rFVIII product, Xyntha, introduced in 2008, has failed to gain much traction. While the company has a few ongoing label expansion trials for BeneFIX, and a Phase I rFVIIa
short-acting candidate, its pipeline shows no LA factors in development for any segment of the market.

Moreover, the LA hemophilia B entrants offer the most dramatic dosing advantages. The LA factors, particularly Novo's glycopegylated N9-GP and CSL Behring's albumin fusion protein rIX-FP (CSL-654), may offer the advantage of bi-weekly dosing compared with BeneFIX which is dosed two to three times per week. BeneFIX may also be vulnerable to improvement in inhibitor formation rates.

The Inhibitor Segment: Novo Nordisk's NovoSeven is likewise the sole recombinant option in the inhibitor space. Although it has a long and excellent safety and efficacy record, it is very short-acting, and is typically administered every two-three hours for uncomplicated bleeding episodes. The annualized cost to patients is reportedly quite high. Bayer has a rFVIIa candidate in Phase II/III testing which Deutsche Bank says is long acting based on preclinical results that showed two to three times half-life extension. However, Hannojoerg Duerr, head of Bayer's global hematology unit, stressed in an interview that the company has not categorized it as long-acting.

Novo's Prener says inhibitor patients, who treat mostly "on demand," bleed more than hemophilia A or B patients, with a mean rate of around 25 incidents/year. In September, Novo Nordisk terminated vatreptacog alfa, a rFVIIa product in late-stage development that it hoped would improve on NovoSeven; neutralizing antibodies were observed in some patients. Prener's summary of Novo's takeaway from the vatreptacog failure suggests a hurdle to would-be developers: "Development of any kind of variance where you do mutations to the backbone of the [rFVIIa] molecule seems to be something that would be very difficult in this population."

The Phase III performance of the LA factors in development versus Biogen's candidates, particularly as regards prolongation of half life, will turn on the comparative merits of pegylation.

Hematologists, the primary treaters of hemophilia patients, are notoriously cautious about switching or starting patients on new therapies. This was seen in the slow migration of patients from early generation recombinant products introduced in the 1990s to the recent generation. If the LA pegylated products show even slight improvement on half-life extension compared with the standards of care - if that turns out to be the product attribute that sways physicians - then it might come down to their Comfort level with pegylation, a technology that's been proven in the market over decades, over Biogen's fusion protein technology.

Marshall Urist thinks that pegylation, despite its wide use in large-population diseases, will likely have to be validated again in hemophilia. He makes the larger point that in a market like hemophilia "where nothing has changed for a long time, many people tend to be conservative. If you do have a lot of new products it does create more liquidity in the market, which is an opportunity for new entrants." In his view, that's an opportunity for Biogen.

In fact, almost all the established players are new entrants in the sense that they're entering new segments with their recombinant LA factors. Novo hopes that its N8-GP and N9-GP will be its entrée into hemophilia A and B. Likewise, Bayer will enter the inhibitor segment. CSL Behring will compete for the first time with a recombinant product in hemophilia B and the inhibitor markets.

But unlike Biogen, each of the established players bring decades of experience in hemophilia – experience in high-touch patient care, in the molecular biology of hemophilia and the commercialization of therapies, in their long-standing relationships with key opinion leaders and the constellation of treating and supportive health care professionals that staff clinics and treatment centers. They also bring international assets in developed and emerging markets.

In the absence of markedly superior data, Biogen will face a challenge supplanting the incumbent products and competing with all the new ones. Merrill Lynch, for one, reduced its price target on Biogen from $177 to $173 post A-LONG data.

The Long View

As health economists are busy modeling the impact on the health care system of more patients on prophylactic use, Urist wonders about the system's price tolerance. Hematologists he's spoken with are expecting the LA factors to come in at a premium price, maybe 10%-20% more expensive. "How much tolerance is there for a higher price," he asks, "given the size of the dosing frequency benefit?"

The economics take a dramatically different turn in five or 10 years if gene therapy is approved for use in hemophilia B. Late last year, researchers at University College London successfully treated six patients with hemophilia B by infusing them with a corrected version of the factor IX gene delivering it with an adeno-associated virus. A commentator was quoted in the New England Journal of Medicine as saying "Treating a patient with concentrate costs $300,000 a year, with a possible lifetime cost of $20 million, but the single required injection of the new delivery virus costs just $30,000."

The factor IX gene is smaller than the factor VIII gene, making it easier to work with. So success in hemophilia B doesn't de-risk hemophilia A.

Tuddenham, who was involved in the hemophilia B trial, envisions an even more radical treatment, the ultimate cure for hemophilia and other genetic errors: "All pregnancies will be non-invasively tested for deleterious mutations which can be corrected in utero."