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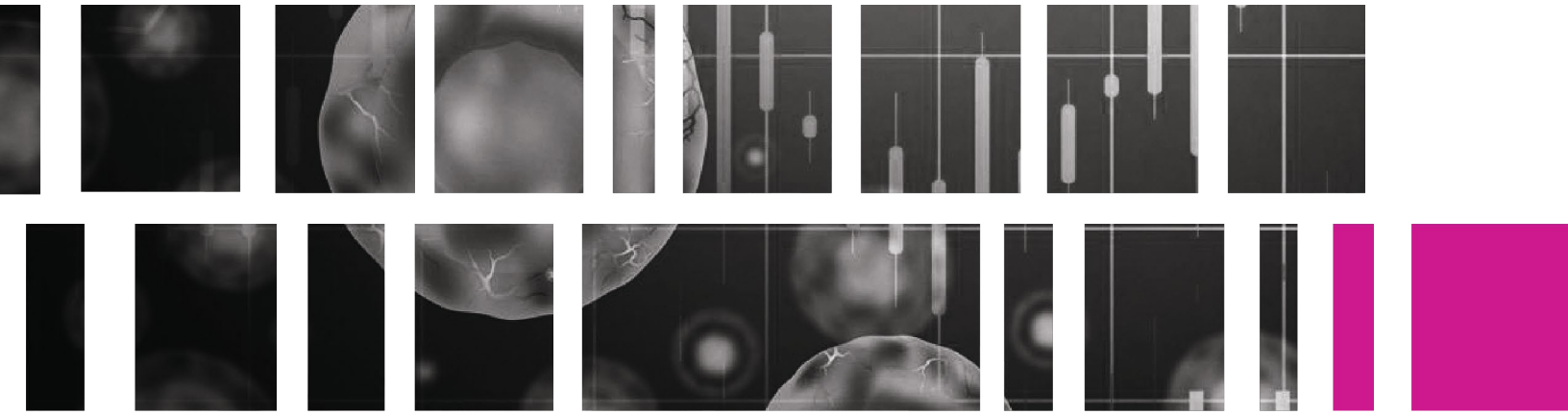

AN INDUSTRY BRIEF FROM INSTITUTE@PRECISION

Bluebird Bio: Innovation and Challenges in Cell & Gene Therapy

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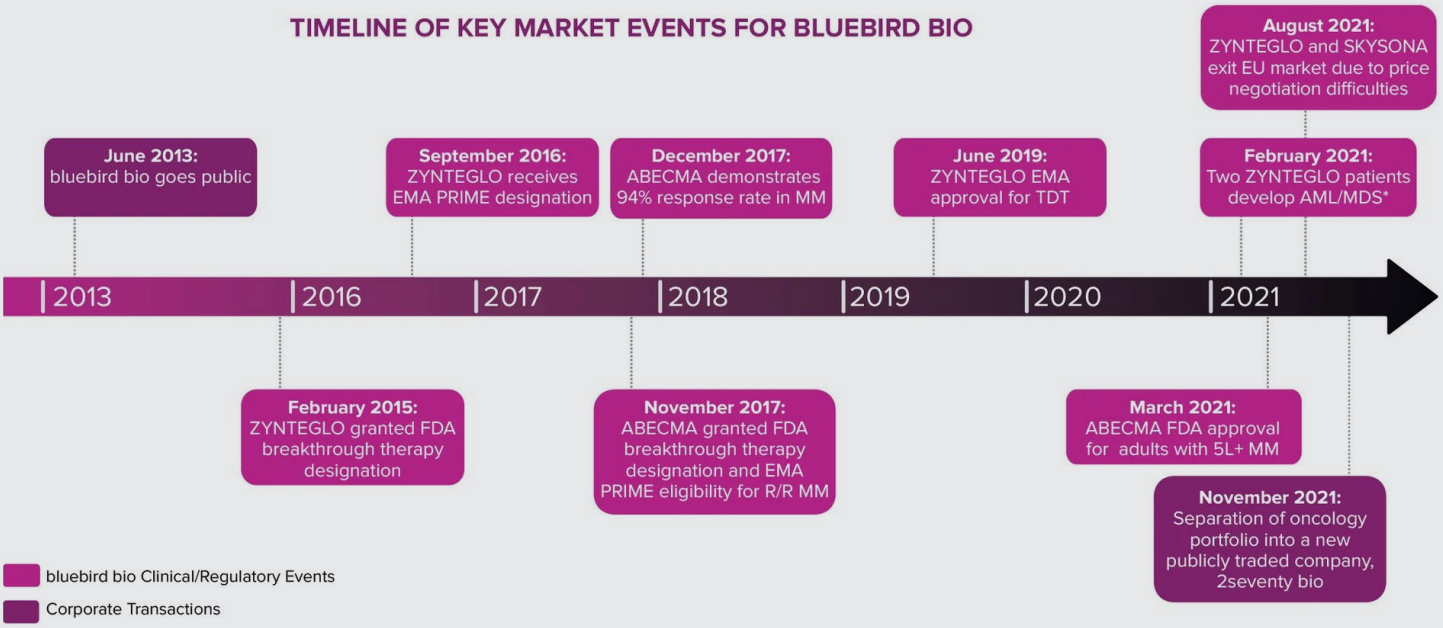
A Soaring Vision, A Quick Descent

At its peak, bluebird bio stood as a beacon of hope and a pioneer in gene therapy, with a market cap of >$10B and FDA approvals for four ex-vivo cell and gene therapies: ABECMA® (idecabtagene vicleucel) for multiple myeloma (MM), ZYNTEGLO® (betibeglogene autotemcel) for beta-thalassemia, SKYSONA® (elivaldogene autotemcel) for cerebral adrenoleukodystrophy (CALD), and LYFGENIA® (lovotibeglogene autotemcel) for sickle cell disease (SCD).

Despite these promising advancements, the company faced significant commercial and operational challenges that impeded the translation of these clinical breakthroughs into sustainable financial success.

"The market can stay irrational longer than you can stay solvent."

— John Maynard Keynes



*While EMA later announced no relation found for Zynteglo causing AML/MDS in trials, this news created significant safety concerns at the time.

Abbreviations: AML: acute myeloid leukemia; EMA: European Medicines Agency; EU: European Union; FDA: US Food and Drug Administration; MDS: myelodysplastic syndrome; MM: multiple myeloma; PRIME: Priority Medicines; R/R: relapsed/refractory; TDT: transfusion-dependent thalassemia.

In response to these difficulties, bluebird bio decided to separate its oncology portfolio, including ABECMA, into a new entity named 2seventy bio. After the split, bluebird bio focused on its core gene therapy programs but continued to face financial pressures. The company implemented several cost-cutting measures, including workforce reductions and restructuring efforts. bluebird bio also relied heavily on asset sales, such as FDA Priority Review Vouchers (PRVs), to secure essential funding. Notably, the company expected to receaive a PRV for LYFGENIA, with reports suggesting that bluebird bio had already arranged its sale to Novartis for ~$100M. The FDA, however, denied the PRV. This unexpected denial left bluebird bio without the anticipated cash inflow, exacerbating financial strains from limited uptake of its treatments.

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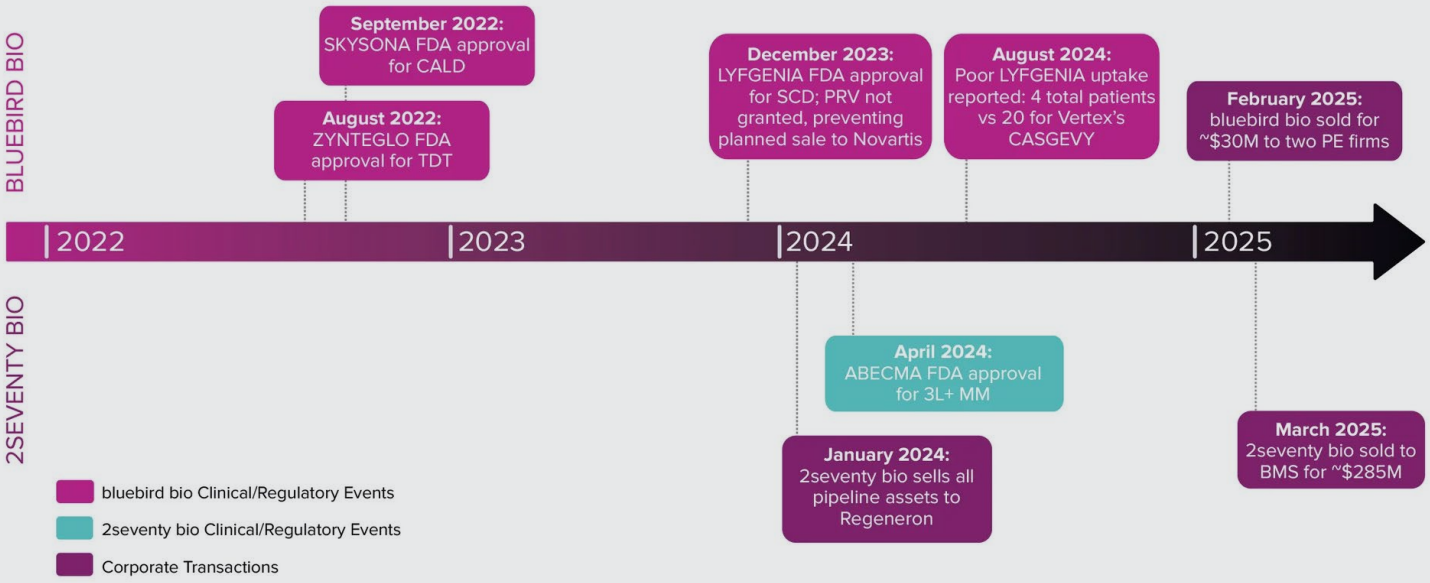
TIMELINE OF KEY MARKET EVENTS FOR BLUEBIRD BIO AND 2SEVENTY BIO



Abbreviations: CALD: cerebral adrenoleukodystrophy; FDA: US Food and Drug Administration; MM: multiple myeloma; PE: private equity; PRV: priority review voucher; SCD: sickle cell disease; TDT: transfusion-dependent thalassemia.

Despite the various cost-cutting measures and cash infusions from investors, bluebird bio ultimately experienced a dramatic collapse in value. In early 2025, bluebird bio announced an agreement to be acquired by two private equity firms for ~$30M (with contingent value rights potentially raising the total deal value to ~$95M). Just weeks after the bluebird bio acquisition, 2seventy bio announced its own agreement to be acquired by its ABECMA partner, BMS, for ~$285M. Gradually and then suddenly, bluebird bio as we knew it, was no longer.

These struggles not only highlight the challenges faced by bluebird bio but also underscore broader implications for the cell and gene therapy industry. In this article, we will analyze the key factors behind bluebird bio's decline—from inherent challenges associated with gene therapy and market dynamics to clinical setbacks and pricing concerns—to derive insights for industry stakeholders.

The Devil Was in the Details

bluebird bio faced a myriad of challenges that significantly impacted its operations and market presence. From regulatory scrutiny and safety concerns to pricing misalignments and competition, the company had to navigate a market filled with both inherent and self-imposed obstacles. These hurdles not only delayed approvals of their treatments but also strained financial resources, ultimately leading to an untenable financial position.

Safety & Regulatory Setbacks

Given historical experience, gene therapies are subject to significant safety scrutiny, and bluebird bio faced substantial regulatory and safety setbacks across both the US and EU markets that impacted their operations. One major issue involved safety concerns with SKYSONA, specifically the risk of insertional oncogenesis. Seven out of 67 pediatric patients treated in SKYSONA trials later developed hematologic cancers, leading to boxed warnings and echoing safety concerns associated with viral vectors. bluebird bio faced similar issues with LYFGENIA as well. In 2021, reports of two patients developing cancer (acute myeloid leukemia and myelodysplastic syndrome) led to FDA clinical holds, requiring additional safety data and for bluebird bio to address these risks. While later analysis suggested that these cases were not linked to the treatment itself, the reports further tarnished the image of bluebird bio's therapies and cost the company precious time and resources. These safety issues and regulatory holds significantly prolonged the approval process, delaying access to treatment for patients and much-needed revenue for bluebird bio.

Pricing Strategy & Market Response

bluebird bio priced its treatments at significant premiums compared to other alternatives, such as hematopoietic stem cell transplantation (HSCT) and clustered regularly interspaced short palindromic repeats (CRISPR)-based treatments. Despite these premium prices, the company's approved therapies secured coverage from many US payers. While payers expressed concerns about the high upfront costs of gene therapies, bluebird bio implemented flexible payment structures to help mitigate these costs. These structures included installment payments allowing payers to spread therapy costs over time, outcomes-based agreements linking payment to therapy efficacy, and risk-sharing with payers. These payment models provided payers with greater comfort regarding the high costs associated with bluebird bio therapies and likely contributed to positive access in the United States. At the same time, installment-based payment models likely contributed to cashflow problems for bluebird bio as they delayed revenue recognition for treated patients.

In Europe, however, the company faced more significant pushback on pricing and encountered challenges negotiating acceptable pricing and reimbursement terms with several national health authorities. Many European markets require clear evidence of therapeutic benefit or cost-effectiveness, and they struggled to justify the high upfront costs of bluebird bio products. In Germany, for example, bluebird bio proposed an innovative reimbursement model for ZYNTEGLO, including installment payments and a pay-for-performance scheme, similar to the structures offered in the United States. Despite these offerings, they were unable to reach an agreement on the treatment price. These issues were not isolated to Germany; similar challenges were encountered across several EU countries. Overall, negotiations for ZYNTEGLO and SKYSONA across Europe resulted in "untenable" price levels, leading bluebird bio to decide to withdraw from European markets.

Existing & Novel Competition

The gene therapy landscape has evolved rapidly, and bluebird bio has faced stiff competition from other companies in the market, with their lentiviral approach competing with next-generation gene editing. Notably, Vertex Pharmaceuticals and CRISPR Therapeutics co-developed CASGEVY® (exagamglogene autotemcel), a CRISPR-based therapy for SCD and beta-thalassemia, which launched at a price ~30% lower than that of LYFGENIA. The $2.2M price point, coupled with the lack of a boxed warning, made it a more attractive option for payers, providers, and patients, and by mid-2024, 20 patients had been treated with CASGEVY vs. only 4 patients with bluebird bio's LYFGENIA.

Beyond gene therapies, bluebird bio also competes with cheaper standard-of-care alternatives in several conditions, such as allogeneic HSCT for SCD and beta-thalassemia. HSCT remains a viable alternative, particularly for pediatric patients with a matched donor. Transplants are typically cheaper than gene therapy and are performed at many of the same specialist centers, offering trusted outcomes and proven long-term efficacy, such as high survival rates. Consequently, many payers require proof that HSCT cannot be used due to lack of a suitable donor before approving these therapies. The presence of these competitive options made it difficult for bluebird bio to attain a strong market position and further exacerbated their struggles.

Scalability & Operational Barriers

Numerous complications arose during bluebird bio's efforts to scale up their market presence. A vital aspect was the administration of bluebird bio's gene therapies, which was challenging due to the limited number of qualified treatment centers (QTCs) and the complexity of the processes involved. Initially, bluebird bio had only 15 active QTCs in the United States, creating access bottlenecks as many regions lacked centers. The company later activated around 50 more QTCs; however, more than half of these only came online following the launch of LYFGENIA in 2023. Managing and coordinating many centers adds another layer of complexity, as significant resources are needed to ensure consistent training, quality control, and patient care.

The small patient population sizes for rare diseases present additional scalability challenges. The low prevalence of these diseases, coupled with the lack of widespread testing and screening, limited the patient pool eligible for bluebird bio's therapies. Many patients remain undiagnosed or are diagnosed late, impacting the timely administration of treatments and limiting the overall market size for their therapies. This, in turn, affected the financial viability of bluebird bio's operations.

Limited Market Demand

Despite promising results from therapies like CASGEVY and LYFGENIA, which have shown significant benefits in reducing pain crises and hospitalizations, many providers and patients remain cautious about adopting these types of treatments. Several factors contribute to this hesitancy. First, the potentially significant out-of-pocket costs can be a major barrier, even with flexible payment structures in place. The high upfront costs of gene therapies make them less accessible to many patients, leading to financial concerns that may impact decision making. Second, uncertainty persists about the curative promise and long-term efficacy of these treatments. While initial results are promising, the long-term outcomes are still being studied, and this uncertainty can make patients and providers hesitant to commit to these therapies. This is especially true given the known life-threatening side effects observed in some bluebird bio clinical trials. Third, bluebird bio's ex-vivo lentiviral vector approach involves stem cell harvest, genetic modification, and reinfusion after conditioning, making the process resource-intensive and logistically demanding. This process often requires patients to travel to specialized centers multiple times or stay nearby, adding to the burden. Lastly, the intricate nature of gene therapies can be difficult for patients to fully understand, leading to uncertainty and apprehension and making patients more reluctant to pursue these options.

While bluebird bio made efforts to address these concerns through patient advocacy and support programs, the company ultimately struggled to gain widespread acceptance of their therapies. The cautious approach taken by patients and providers, combined with the logistical and financial challenges, contributed to bluebird bio's inability to sustain its market presence. This emphasizes the importance of ongoing education, support, and engagement with the patient community to build trust and confidence in gene therapies. By learning from these experiences, companies can better navigate the complexities of introducing innovative treatments and ensure that patients feel supported throughout their journey.

A Cautionary Tale, but Not the Last Word

A few weeks after the announcement of the sale of bluebird bio and just days after that of 2seventy bio, Northwell Health made their own announcement: Cohen Children's Medical Center was celebrating the "new birthday" of New York's first LYFGENIA patient. Amidst all the challenges faced by bluebird bio, the 21-year-old patient had been successfully treated with LYFGENIA, and in the ~3 months following his treatment, he had been completely free of the debilitating manifestations of sickle cell anemia that he previously endured. Despite real concerns for gene therapy manufacturers, their treatments still offer real hope for people living with devastating diseases, and we really must find ways to make them sustainable.

bluebird bio's fall from grace serves as a cautionary tale of brilliant science meeting harsh marketplace realities. For industry stakeholders, it reinforces that success in advanced therapeutics requires not only clinical efficacy but also adept navigation of regulatory hurdles, market stakeholders, competitive dynamics, and financial planning. In our next post, we will review other gene therapies on the market and explore lessons learned from other companies. By integrating these insights and balancing innovation with effective commercial strategy, companies can better position themselves for long-term success that will enable continued access to life-changing care for patients in need.