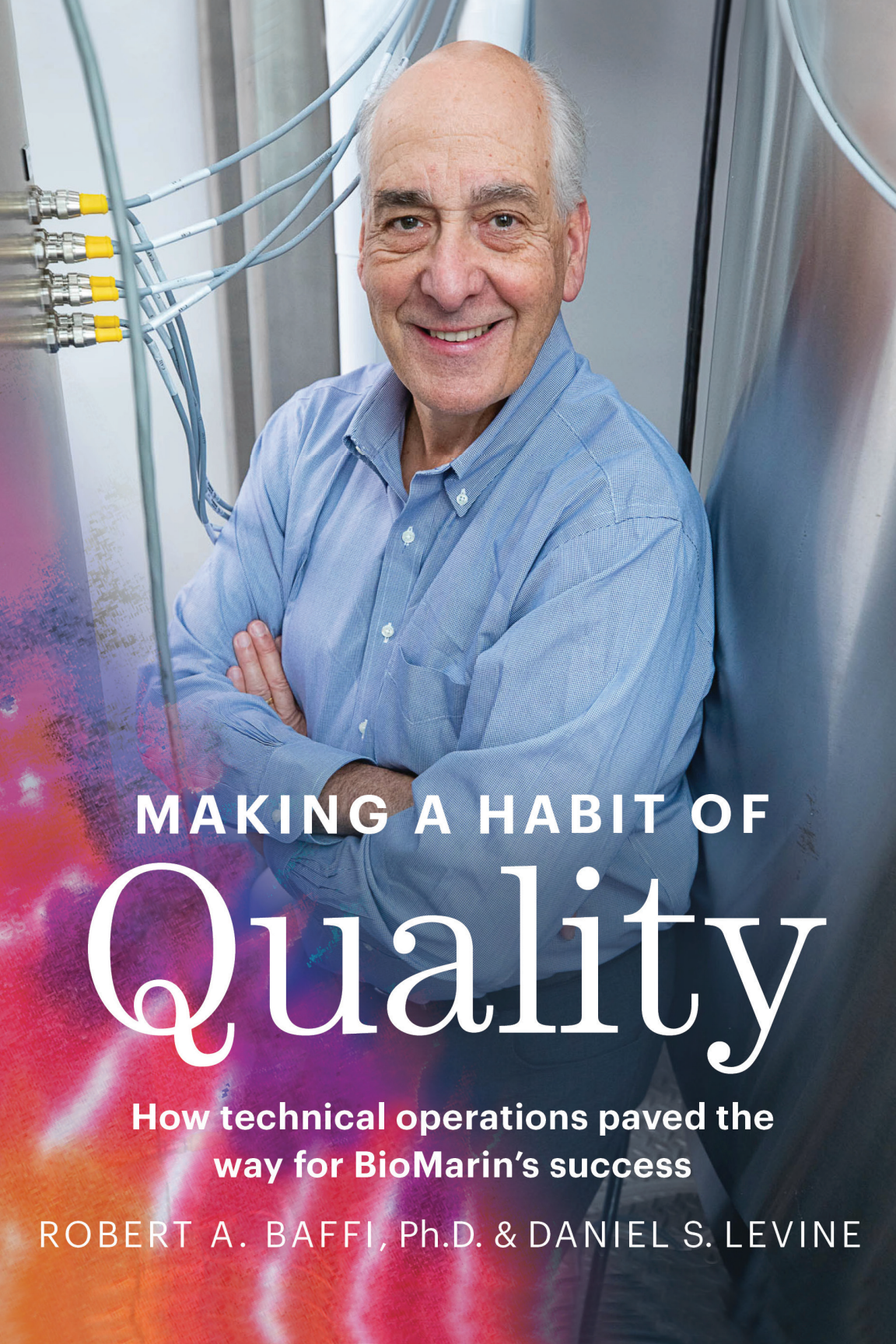

MAKING A HABIT OF Quality

How technical operations paved the way for BioMarin's success

ROBERT A. BAFFI, Ph.D. & DANIEL S. LEVINE

More than two decades of science, innovation, and perseverance.

BioMarin continues its 25-year history of developing first- or best-in-class therapies for people with rare genetic diseases. The seeds of innovation were sown initially with an enzyme replacement strategy that leveraged an emerging understanding of cellular biology and genetics that restored biological balance for patients with chronical administration of therapeutic proteins. With the approval of Roctavian to treat hemophilia A, the company stands on the precipice of a gene therapy revolution with the potential to restore biological balance for patients for long periods of time with a single administration of genetic information that enables patients to produce their own therapeutic proteins. In developing eight first- or best-in-class therapies for genetic disorders with limited-to-no treatment options the company continues to innovate by integrating biology and science within a proscribed regulatory framework to achieve clinically significant outcomes for the benefit of patients.

BIOMARIN®

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Robert A. Baffi, Ph.D., has proven leadership skills in biotechnology with a product development emphasis. During a 20-year tenure at BioMarin Pharmaceutical Inc. and as President of Global Manufacturing & Technical Operations he was responsible for overseeing manufacturing, process development, quality, logistics, engineering, and analytical chemistry. Dr. Baffi served 14 years at Genentech, Inc., primarily in the functional area of quality control. Prior to Genentech, Dr. Baffi worked for Cooper BioMedical as a Research Scientist and at the Becton Dickinson Research Center as a Post-Doctoral Fellow. Dr. Baffi has contributed to the approval and commercial success of 30 products and a dozen patents covering diverse technologies. He serves on the board of Neurogene Inc. and Mosaic ImmunoEngineering and is a venture partner with Samsara BioCapital. Dr. Baffi received a Ph.D., M. Phil., and a B.S. in biochemistry from the City University of New York and an M.B.A. from Regis University.

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This book is dedicated to:

The patients and their families who courageously participated in our drug development endeavors.

The mentors (family, friends, and colleagues) in my life whose guidance laid down the guard rails of integrity and the will to never give up.

Rosemary, who walked with me every step of the way, providing love, encouragement, support, and inspiration.

Your contribution to drug development goes deeper than you will ever know.

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"Excellence is never an accident. It is always the result
of high intention, sincere effort, and intelligent execution;
it represents the wise choice of many alternatives—
choice, not chance, determines your destiny."

—Aristotle

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FOREWORD

Sometimes We Live No Particular Way but Our Own

By Stuart E. Builder

Søren Kierkegaard wrote that "Life can only be understood backwards, but it must be lived forwards." When we look back on the life of a person or an organization, certain moments stand out as pivotal. Usually they involve decisions, forks in the road that ended up having huge and lasting consequences. Robert Baffi's account of the evolution of Technical Operations (TOPS) at BioMarin can be read as a series of stories about such decisions. The stories are entertaining, reassuring, and illuminating.

One kind of pivotal decision happens in an instant. We see such moments in sports all the time—a field goal is kicked from midfield with two seconds on the clock, or an approach shot goes in the cup on the 18th hole for an eagle and the win. It could easily have turned out differently and headed down the other fork. Such moments demand that the decision-maker be fully present, with all their wits about them, and a little luck to boot. Some of Robert's stories are like this, and it is stunning to imagine how different the outcome would have been if he hadn't been present, wits, luck, and all.

Another kind of pivotal decision is entrenched in mind-boggling complexity. It can take months to make. Case in point is the decision for a biotechnology company to build more manufacturing capacity.

It's crucial to get this right since mistakes are expensive. Too much too early, and a company can be burdened with a big empty plant it needs to maintain. Too little too late, and a company can have an approved product but unable to produce enough to meet market demand—an ultimate sin in the world of commercial biotechnology. Either of those extremes could derail a career for someone in Robert's position.

Plants take years to build and commission, a reality that forces people tasked with making decisions about building and buying manufacturing facilities to act long before they have data to understand a company's needs. Instead, they must make an educated guess. Under Robert's leadership, TOPS had an uncommon success rate with these educated guesses. At least part of that success, looking back, had to do with their skill at quantitative estimation. That didn't come about by accident. Instead, they practiced with Fermi questions.

Fermi questions are thought exercises in estimation, named for the Nobel Laureate and physicist Enrico Fermi, who was exceptionally good at making back-of-the-envelope estimates. A classic Fermi question is "How many piano tuners are there in Chicago?" On the one hand, it seems impossible to know the answer. On the other hand, with a few reasonable assumptions, it is possible to make estimates with surprising accuracy. It's a process. How many pianos are there in Chicago that get tuned? How often are they tuned? What's the capacity in number of tunings for one piano tuner? Break it down and bracket the guesses. Robert routinely challenged his team with Fermi questions, and, as a result, BioMarin was able to move deliberately and with speed well ahead of the actual data being available.

I have worked with Robert through most of his professional life, first as a colleague at Genentech, and then starting in 2003, as an advisor to him at BioMarin. For more than 15 years I visited BioMarin TOPS about once a month. I enjoyed my time with the organization he was building. It was intellectually stimulating and full of both vigorous and rigorous debate. I had the opportunity to see how Robert's and BioMarin's stories

have been marked by pivotal decisions. As the company grew to having eight commercial products plus a robust pipeline that includes gene therapies, it was Robert's responsibility to ensure BioMarin had the capacity and capability to produce its medicines in a compliant and cost-effective manner. By the time he retired, this would involve overseeing four manufacturing sites plus a large worldwide group of relationships with contractors who were not always well-behaved.

There is an African proverb that says, "If you want to go fast, go alone. If you want to go far, go together." Robert built an organization that went both fast and far by leading and insisting on a culture of rigorous scientific thought and collegiality. He proved adept at leading employees who reported to him, as well as navigating the more complex relationships of peers, bosses, board members, and interactions with health authorities while finding ways to build support for his vision for the company.

Many companies of the age and size of BioMarin would have hesitated to take on the number of different technologies and operations represented in its products and pipeline. Often the efficiency of a platform technology can influence pipeline priority. It is impressive how the company has been both brave to start and successful at finishing such a diverse set of therapeutics.

It is through stories that each generation passes on the wisdom they have gained. Read this book, hear the stories, and gain the wisdom of a great biotechnology leader.

PROLOGUE

It Costs a Lot to Win and Even More to Lose

What you do makes a difference, and you have to decide what kind of difference you want to make."

Jane Goodall

In the spring of 2000, there was a convergence of science and opportunity that played together over the next two decades to create a biotechnology company recognized for innovation leading to treatments for some of the rarest and most intractable diseases known to mankind. It was then that the Human Genome Project published an initial draft sequence of the human genome. That landmark accomplishment laid the foundation for an understanding of human biology and disease and a new era of genetic medicine. That same year, BioMarin Pharmaceutical hired me as a technical expert on the tactics for chemistry, manufacturing, and controls (CMC) for recombinant DNA products. While technical expertise would be an essential element for the success of BioMarin, no one would have imagined that leadership skills embodying authenticity, transparency, candor, engagement, perseverance, commitment, curiosity, creativity, and humor would be as important as any technical skills in my new role.

From the beginning, BioMarin has focused on developing innovative products for the treatment of rare, genetic disorders utilizing recombinant

DNA technology. In 2000, with barely 100 people at the company, we were focused on treating single gene defects with an enzyme replacement strategy that required us to be creative both from a clinical and operational perspective. Our efforts led to innovative enzyme replacement therapies to treat progressive and deadly mucopolysaccharidosis disorders (MPS I, VI, and IVA), a form of the progressive and fatal neurodegenerative condition Batten's disease known as CLN2 disease, the metabolic disorder phenylketonuria (PKU), achondroplasia, the most common form of dwarfism, and the blood clotting disorder hemophilia A.

The therapies we have developed for these disorders, including Aldurazyme® (laronidase), Naglazyme® (galsulfase), Vimizim® (elosulfase alfa), Palynziq® (pegvaliase-pqpz), Kuvan® (sapropterin dihydrochloride), Voxzogo® (vosoritide), and Roctavian™ (valoctocogene roxaparvovec) are based on our fundamental knowledge of human biology, disease, and biochemistry applied to the design of molecules that restore the normal state of physiologic balance to the body. These products are administered by intravenous infusion (directly into a vein), intraventricular infusion (directly delivered into the fluid surrounding the brain), subcutaneous injection (under the skin), or orally. These chronic therapies—given on a daily, weekly, or every other week basis—require a lifelong commitment to a rigorous regime of patient compliance and follow up. Production of these complex molecules relied on elaborate cloning techniques, and expertise in cellular biology, purification, and analytical characterization. It also necessitated massive investments in facilities designed, engineered, validated, and approved to manufacture these molecules to exacting standards of purity and compliance. Lastly, it involved the honing of comprehensive regulatory strategies to meet requirements of health authorities on a worldwide basis to assure first cycle approvals were regularly achieved.

How technical operations emerged as a focal point for success at BioMarin, enabling rapid and compliant development for one of the world's most innovative companies, provides useful insights into the critical role of process development, manufacturing, and analytical characterization in overall drug development strategies. Beyond the leveraging of science and technology, there were organizational, management, and financial challenges that needed to be navigated. In fact,

these other challenges were often more difficult to solve than the science and technology, particularly in the early days of the company.

The approval of Aldurazyme within five years from the founding of the company represents an amazing accomplishment with numerous lessons for rapid drug development. Beyond the scientific, engineering, and regulatory successes, we built a sustainable and open culture focused on scientific rigor and risk-based decision-making where everyone was encouraged and expected to contribute. Creating the right culture in a financially and managerially challenging environment of a start-up company was essential then, and perhaps even more important today as BioMarin balances competing requirements of a rapidly growing company, evolving technology, and growing scientific understanding of human biology and disease.

We continue to leverage scientific rigor and risk-based decision-making, and have pivoted our efforts to place a strong focus on developing gene therapies. The promise of gene therapy is that rather than replacing a missing protein by chronic administration, we could instead deliver the human gene coding for that missing protein once to specific cells and enable patients to produce their own proteins consistently with the potential of restoring the normal state of physiologic balance within the body. Our first gene therapy effort to treat hemophilia A, a hereditary bleeding disorder caused by a lack of clotting factor VIII, won approval from the European Commission in August 2022. Most patients treated have been able to reduce or eliminate their requirements for factor VIII infusions while drastically lowering or eliminating bleeding events for multiple years. The scientific advancement and understanding that comes with new technology inevitably creates scientific, regulatory, compliance, manufacturing, and leadership challenges. This book focuses on how we overcame those challenges while leveraging our collective experience and capabilities honed during the development of our enzyme replacement therapies and then applied the learnings to the development of our gene therapy products.

While business deals and clinical results garnered headlines for BioMarin in the financial press, we developed a strategic strength and core capability that was essential to the success of the company and that

is often overlooked and undervalued. One element that is too often taken for granted within the biotechnology industry is technical operations (TOPS). TOPS at BioMarin has evolved to include all aspects of process development, engineering, manufacturing, quality, and supply chain operations for a wide range of products. Today, the TOPS organization encompasses about 1,500 people, four manufacturing facilities, and a dozen or more strategically chosen contractors who produce BioMarin products that are presented to patients as tablets, sachets, vials, or prefilled syringes in more than 70 countries around the world to treat some of the rarest and most debilitating diseases known to mankind.

Daniel Maher's book *A Rare Breed* captured the history of the company over its first 20 years. This book tells the story of the strategic plans that were devised, adapted, and reframed to meet the challenges that the company overcame. As the leader of the TOPS organization for more than 20 years and the longest tenured member of the senior management team, I had a different perspective and insight into the planning and implementation of our corporate goals and the leadership philosophy that emerged. Paramount to our success was the development of core competencies in process development, manufacturing, quality, and logistics that allowed us to navigate the development and regulatory requirements needed to bring life-saving therapies rapidly and compliantly to patients in critical need around the world.

We also developed an esprit de corps that served the company well in both good times and bad. Building a cohesive team has been critical to our success in evolving our capabilities from manufacturing proteins in bioreactors to our ability to make and deliver genes to patients so that they may make their own proteins. Throughout our growth from the very beginning, and especially within TOPS, we continually asked ourselves what-if questions so that we could arrive at why-not solutions. The lessons learned and refined over time provide a strategic process development framework for how to meld scientific, technical, organizational, and business decision-making in the development and implementation of corporate goals to meet regulatory expectations while remaining true to science, compliance, and company culture.

INTRODUCTION

You Who Choose to Lead Must Follow

If I have seen farther than others,
it is because I was standing on the shoulders of giants.

Sir Isaac Newton

Over the course of nearly 40 years and multiple reporting relationships, my leadership style has evolved to encompass an innate curiosity that is science-driven and patient-focused. Underlying that approach has been a positive outlook that viewed problems as opportunities to develop creative solutions. And BioMarin afforded many opportunities for creative solutions.

Working in a highly regulated industry where peoples' lives depended on the decisions made and our ability to execute against them, we have strived to ensure our actions not only complied with regulations but were also conducted with integrity and scientific rigor. Essential to our success was a commitment from the leadership team to encourage and empower people throughout the company to rely on their training, skills, and experience to manage risks with scientific and business practices focused on attaining goals. This approach was both flexible and effective for achieving scientific and business outcomes and led to the rapid approval of innovative products so that patients around the world could benefit. Although the leadership team provided the vision and strategic

direction, the ideas, tactics, execution, and accomplishments were possible due to a group effort from determined, talented, and passionate people throughout the company.

The effort that extended across technical operations and the rest of the company in bringing these products to patients was gratifying for all involved. The journey described within this book outlines the strategic process development tactics and decision-making techniques employed to resolve challenges in the approval of some of the world's most innovative products in treating some of the most devasting genetic disorders.

Within technical operations we implemented a simple yet effective strategic process development approach that helped pave the way for the company's success by enabling the approval of products in half the average time for the industry. That garnered BioMarin recognition as one of the most innovative companies in the world. The lessons learned in the development of our protein therapeutics were leveraged extensively and accelerated our gene therapy development efforts.

What made this even more remarkable was that we developed drugs that represented many industry firsts. For example, Brineura, our enzyme replacement therapy for a form of the deadly neurodegenerative condition Batten's disease, was the first protein therapy that required chronic intracerebroventricular administration. Palynziq, our therapy for the metabolic condition phenylketonuria (PKU), was the first chronically administered bacterial enzyme and required cloaking to avoid immunological neutralization of the product. These accomplishments were even more compelling when considering that the mix of products that we were developing—small molecules, peptides, enzymes, and gene therapy products—did not lend themselves to a platform approach to manufacturing. As a result, they created contractor, facility, scientific, analytical, and compliance complexity that required an integrated approach to solving a confluence of engineering, process, manufacturing, quality, logistical, and regulatory challenges.

In retrospect, the lack of a platform approach to the various product modalities we were developing honed our skills to think creatively. It was this need for unconventional thinking that would serve us well when we were presented with numerous gene therapy challenges starting in 2013.

Crafting the strategy to develop innovative products and processes that met the clinical and regulatory requirements within the budget and timeline constraints required a science-driven, decision-making approach in which the right questions were asked sufficiently early in our drug development efforts to assure that assumptions and constraints were valid. Once valid assumptions and constraints were identified, we challenged ourselves to develop workarounds to assure that we moved quickly to meet company objectives.

In 2015, the investment bank JPMorgan Chase hosted a dinner for BioMarin for about 40 analysts the night before it kicked off its annual healthcare conference in San Francisco. Our CEO suggested I join him at the dinner as our first gene therapy product was about to enter clinical studies. As we discussed our foray into gene therapy, I outlined our technical operations approach to developing a new technology at the company. After dinner, one of the analysts began chatting with me and asked how long I had been at the company. I responded, "it has been 15 years."

He was surprised and asked, "How come I don't know you?"

"Because," I said, "we don't have manufacturing problems."

Even to the most sophisticated industry observers, the role of technical operations is often overlooked, undervalued, or misunderstood. In many biopharmaceutical companies, process development, manufacturing, and quality often remain invisible. These activities only come into view during times of product shortages or when lack of regulatory compliance becomes public. This book offers an account of the critical role that technical operations have played in the success of BioMarin. By shining a light on this part of the organization, we hope the hard-fought lessons learned will continue to be applied and provide an understanding of what it takes to develop safe and effective medicines for patients whose lives depend on them and match the urgency they feel.

1.

The First Days Are the Hardest Days

The scientist is not the person who gives the right answers,
but the person who asks the right questions.

Claude Levi-Strauss

Bill Anderson had an imposing presence. He had the build of a prize fighter. He stood 6'3" and weighed 230 pounds, but he was a sweetheart of a guy and never used his size as a tool for intimidation. Anderson graduated from West Point and served in Vietnam, but now he was the chief financial officer (CFO) of BioMarin Pharmaceutical, a biotechnology company focused on rare, genetic-based disorders that was getting ready to advance its first therapeutic candidate to late-stage clinical testing. It was my first day on the job at BioMarin and Anderson was my boss, a fact that would have confused anyone who looked at an organizational chart.

When I joined BioMarin as vice president of quality in 2000, I knew there was a lot of work ahead. The fact that I was reporting to the CFO was already a sign that there was much that needed fixing. Anderson in our brief first meeting informed me that the California Department of Food and Agriculture (CDFA) would be inspecting our manufacturing operations in 17 days.

BioMarin was headquartered in Novato, California, about 30 miles north of San Francisco in Marin County. The executive offices sat inside

a two-story building dubbed "The Pink Palace" because of its garish, two-tone paint job. Even though it was May 9, 2000, caricatures like Cyra McFadden's book from the 1970s, *The Serial: A Year in the Life of Marin County,* still shaped perceptions of Marin County. Say "Marin County" and people think of hot tubs, yuppies, and people searching for self-actualization. It was not, at the time, known as a place for cutting-edge biotechnology.

Of course, as the saying goes, art imitates life. Leaving Anderson's office I thought it would be best to get a sense of the size of the task before me, and headed to the company's manufacturing facility known as "Galli," because it was located at 46 Galli Drive. The Galli facility, in a previous life, had been used to make the iconic hippie sandals Birkenstocks, something that does just scream Marin County.

Like any biotechnology company, BioMarin had to comply with the requirements outlined in the Code of Federal Regulations (CFR) and other guidance documents and regulations from around the world. Because we were located in California, we were also under the jurisdiction of the CDFA, which had the authority to regulate any drug manufacturing facility in the state. Its purview is to make sure that the production of medicines conforms to all regulations. It was not the only agency that regulated us, but it was one of the many that had the capability of impacting the clinical development of our programs if it determined we were not in compliance with regulations. The plant was already running its third batch of what would become Aldurazyme. At the time, Aldurazyme was an experimental recombinant enzyme replacement therapy to treat people with the rare lysosomal storage disorder mucopolysaccharidosis I (MPS I). People with the condition are unable to produce adequate amounts of an enzyme, alpha-L-iduronidase, needed to clear metabolic waste from the cells in their body.

With no treatments available at the time, children with the condition faced a grim prognosis. MPS I is a progressive and fatal genetic disorder. Only about 40 children a year born in the United States are afflicted with MPS I. As the disorder advances, it causes joints to stiffen, organs to swell and harden, and pain to become a way of life. In the absence of treatment, children with the condition become blind, deaf, and require

the use of a wheelchair. Prior to Aldurazyme, children with MPS I were not expected to live past the age of 12.

While the first task was to make sure that we passed the inspection with the CFDA, Anderson also indicated that my greater charge would be to get the manufacturing and quality groups to stop working at cross purposes. It is not unusual to find dynamic tension between these groups in any biotechnology organization, but the friction between these teams at BioMarin was getting in the way of addressing problems that needed to be fixed. Eliminating the friction so we could make progress was an essential goal we would have to collectively achieve if we were to be successful.

The dynamic tension between manufacturing and quality was a problem because it became an obstacle to fixing technical problems that complicated our regulatory strategy. BioMarin needed to improve the quality of the materials it was producing at the time for them to be considered commercial grade. The quality and regulatory teams insisted that making any changes to the process at this point would trigger unwanted regulatory scrutiny that would derail the company's timelines and cause costly delays. In reality, this so-called conservative approach to limiting improvements to the manufacturing process to enhance robustness and improve quality was creating greater risks because the current process was not producing product of suitable quality, a sure way to get health authorities to come calling.

Surveying the landscape

On that first day on the job at BioMarin, I walked around and introduced myself to people and began asking questions as I tried to avoid sounding like an inspector conducting an audit. It was good to see that the standard operating procedures (SOPs)—the sets of step-by-step instructions to carry out the operations—were sound and well drafted. The facility had its quirks and limitations but was well designed. It was capable of making our first commercial product if the manufacturing and quality groups could learn to work together as a team.

While walking through the loading dock of Galli, I was puzzled to see red and green tape on the floor. I asked about the significance of the tape. It turned out it was used to demarcate where quarantined and

released raw materials were stored. The green tape signified the storage area for released raw materials while the red tape signified the storage for quarantined raw materials. I sought clarification. As I asked more questions, it became clear that when raw materials arrived, they were released on variance, meaning that manufacturing got access to them before the quality control and quality assurance teams completed their testing and review of the materials. If that wasn't shocking enough, the entire raw material release on variance procedure was codified in an SOP.

When raw materials come into a biotechnology manufacturing facility, they need to be quarantined, sampled, and tested before they can be released to the manufacturing team. Not doing so would create a red flag for regulators, because if the raw materials are somehow inadequate, the end product will not be useable. Theoretically, you can inform health authorities that if the raw materials fail in testing, you are going to throw out that batch that is in production, but health authorities are skeptical that companies will do that. Instead, it is mandated that raw materials are tested before the manufacturing team is allowed to get its hands on them.

In addition to the ongoing Galli production facility, BioMarin was also manufacturing inside the Pink Palace on the second floor. The company had set up an area to make a second experimental enzyme replacement therapy there. This would eventually become known as Naglazyme, an enzyme replacement therapy for mucopolysaccharidosis VI (MPS VI). MPS VI is an inherited lysosomal storage disorder that involves the deficiency of an enzyme, N-acetylgalactosamine-4-sulfatase, which is needed to break down and clear metabolic waste from the cells of the body. The company had created a production area to produce the first batches of Naglazyme for an early-stage clinical trial. This facility was much smaller than the Galli facility and was only capable of producing enough material for a small phase 1/2 study. The Galli facility on the other hand was a purpose-built renovation intended for producing commercial quantities of product.

I returned to Anderson's office in the afternoon and made the first of many requests for a capital improvement project, albeit a modest one. Over the next week, we erected a chain link fence to segregate quarantined and released raw materials. While the cost of the project was

minimal, the significance was immense. We were now on a journey to define for ourselves a science driven, risk-based, quality philosophy for compliance that would be proudly on display in the one hundred plus successful inspections we would host over the ensuing 20 years. Of course, before that could happen, we had to pass our first inspection by the CFDA in 17 days.

The next order of duty was to meet with the people who reported to me. Following introductions about our experiences and backgrounds, we moved quickly to my concerns about the way the team was releasing raw materials to manufacturing without first testing them. It is an exercise in futility to try to solve a problem before first understanding it. I asked questions and listened to answers until it became clear why this was being done. Problem solving requires a thorough understanding of the assumptions, causes, and constraints that led to the problem in the first place. Getting to the root cause of any issue required asking questions until the correct assumptions were being applied and reasonable solutions could be developed.

When asked why we were doing this, the team explained the challenges with limited space for storage of the raw materials, the time it took to get testing performed by outside laboratories, the long lead time needed for raw material orders, and the demands of the manufacturing schedule. Though they may have seemed like reasonable arguments, none of them were compelling for continuing to release raw materials on variance. With the problem defined, our discussion morphed into creative problem solving.

It was clear that we needed to separate quarantined and released raw materials and acquire additional space for storage. We also needed to increase our inventory to allow for longer lead times. And, instead of outsourcing testing, we needed to bring testing in-house to control scheduling. The segregation issue was the easiest to address with the chain link fence that Anderson approved. Increasing storage capacity and inventory while bringing testing in-house were more expensive and required long-term planning to tackle, but it became readily apparent that while quality reporting to the CFO was certainly unorthodox it did have its advantages.

It was now time to catch up with John Jost, BioMarin's vice president of manufacturing. I knew Jost well from our days at Genentech. Jost had led the manufacturing, science, and technology group that supported operations. Walking into his office with a copy of the SOP that described the release of raw materials on variance in my hand we discussed how to address the issue. As we talked, it became apparent that we could not change this practice immediately and we instead laid out a strategy to increase storage capacity, order raw materials earlier, and bring testing in-house. We would be ordering raw materials for the Aldurazyme process performance qualification (PPQ) campaign within three months. Health authorities would scrutinize this campaign, including the raw material purchase and release, during the pre-approval inspection. We knew that raw material release on variance could not continue. With this new clarity and commitment, we coordinated activities across manufacturing, quality, facilities, purchasing, and finance to implement the plan we had discussed to order, sample, test, and disposition all raw materials for the PPQ campaign before release to manufacture and retired the SOP for the release of raw materials on variance.

With the start of the Aldurazyme late-stage clinical trial at stake, we took every opportunity to prepare for the CFDA inspection. Many companies use war game analogies when being inspected. We decided to use baseball metaphors to clarify roles, have a little fun, and avoid a confrontational mindset. We established a dugout where all the inspectors' questions would be tracked and triaged. The next person to speak to the inspectors was in the on-deck circle. Resident technology experts were standing by to be called on from the bullpen if needed. Each presenter sat between the inspector and a coach.

We began by making a presentation to the inspectors in a conference room. Not only did this allow us to introduce them to the company and the team, but it was a way to create a rapport with the inspectors and establish trust. Talking about the company and the important work we do, providing an overview of the organization's structure, and explaining our science and compliance philosophy laid the groundwork for how we would engage with them throughout the inspection. The examples may have varied from presentation to presentation, but the mantra was always

the same. We're knowledgeable about the regulations. We understand the critical control points of the manufacturing process. We do the right thing. That is the mantra that comes in that opening presentation. From the very beginning the message we gave them spoke to the core of what they wanted to hear. And during the inspection, we backed it up. That led one inspector to state toward the tail end of an inspection, "I knew in the first hour this was going to go well."

As the inspection unfolded, we had staff acting as scribes to track questions, document requests, and file updates on the action as it occurred so that everyone involved would be kept informed and up to date. The inspection preparation activities were cross-functional with people from process development, manufacturing, regulatory, program management, and quality all chipping in to fill out the roster. What we lacked in experience with each other's style, approach, and knowledge we made up for with commitment and enthusiasm. The fact that I barely knew the names of the team members, or the full spectrum of issues that might be discussed during the inspection, did not interfere with our preparation activities.

A crash course

There is nothing better than an inspection to illuminate your strengths, weaknesses, and your opportunities for improvement. On the 17th day of my tenure as a BioMarin employee, three inspectors from the CDFA arrived to evaluate the compliance of our manufacturing facilities. As it turns out, these same inspectors the previous week toured Genentech's brand-new Vacaville facility, a stainless-steel Taj Mahal of biomanufacturing. Now they were here to have a detailed look at our converted sandal factory with its single-use disposal bag technology that supported our perfusion mode of manufacturing. We presented the requested documentation in an organized and knowledgeable fashion. There was a well-written SOP to describe all the pertinent operations in both manufacturing and quality and the data we presented was scientifically sound and compliant. Four days of questions and answers had not raised any areas of specific concerns and both facilities were approved to produce clinical grade material. The inspection was a success, and we celebrated

our efforts in the Galli courtyard the afternoon it ended. Being able to manufacture clinical grade material out of both facilities was an important and critical corporate milestone. It also provided me with a crash course on the capabilities and limitations of the facilities, procedures, systems, and people in the company that may have taken me months to otherwise gauge. The good news was that there was plenty of passion and pride exhibited by everyone and it turned out to be a bonding experience for all involved. Resolving all the friction between manufacturing and quality would take more focused efforts. The shared success with the inspection, perhaps for the first time, showed the benefits of working together towards a common goal.

Orchestrating inspections was always gratifying because it provided an opportunity to showcase the diligent work that goes on at the company, but it is the musicians who make the music. That week the team made some beautiful music and I appreciated the hard work that had been performed by quality, manufacturing, and process development. While much more needed to be done, we had overcome the first of many critical hurdles. We did it as a team with helping hands coming from people throughout the company, a theme that would be repeated over and over again as we developed.

Is it good enough

While we passed the inspection, we still had significant challenges with the manufacture of Aldurazyme. The manufacturing process needed improvement to address significant overall robustness and purity concerns and the standoff amongst the manufacturing, quality, and regulatory teams was allowing risks to fester that required mitigation.

We used hamster ovary cells to produce Aldurazyme. When you make a recombinant protein, there is not only the protein that you want, but also DNA, lipids, and proteins from the hamster cells that come along for the ride. These are considered process-related impurities that derive from the manufacturing process itself. The goal is to remove as many process-related impurities during purification as possible. It is critical to keep measuring these process-related impurities during production. And it is important to do that with good analytical methods that can

characterize and track the removal of them. The more sensitive and selective the methods, the better able you are to understand what happens to the purity levels when you make changes to the process. Without that data, you cannot perform good quality control. Some people have a misconception that at the end of the process, we test the product and it either meets the specifications or not. That is the worst way to build a quality system. If you wait until the end to do testing, you're going to have a high percentage of batches fail. You need eyes (good methods) and understanding (good data) early on and throughout process development so that when you get that product at the end and you test it, 99 out of 100 lots pass. You might find that something happened during the process and that one lot failed, but if you are just testing at the end to find out if the lot is good, you're going to have many unpleasant surprises.

Chris Starr, co-founder and chief science officer agreed with me that the quality team did not have enough analytical capabilities to monitor the process appropriately. He offered to help. He gave me carte blanche to utilize people from within his research and process development groups to address process and analytical questions we needed answered. Working with research and process development allowed us to understand vital control points during the manufacturing process and then implement effective corrective actions and selective limits to assure acceptable product quality. This joint exercise between all the technical experts in the company was enlightening as it enhanced our depth of understanding of the manufacturing process, as well as the gaps that existed in our process knowledge. Some people in the quality and regulatory teams argued that altering the process would trigger a regulatory review of the manufacturing process that would delay the phase 3 clinical trial. While that was a distinct possibility, it was evident that making improvements to the process to enhance product quality and robustness would be less risky than submitting an amendment to our filings with health authorities that had not addressed these critical regulatory and compliance concerns. Not fixing these issues before the start of the phase 3 study would create greater risks than making process changes that would increase the robustness of the process and purity of the product. Convincing the quality and regulatory teams that we could chart a path

forward to not only improve the manufacturing process but lower regulatory exposure at the same time required trust in me that was being earned day by day. They simply had never come across that problem, issue, or solution previously. With a bit of cajoling, we implemented several process and procedural improvements, continuing our maturation as a technical operations group focused on making science-based risk/benefit decisions consistent with regulatory expectations.

When you manufacture a recombinant product, you start with a vile of cells that have been engineered to produce a desired protein. Those cells are placed in small flasks and allowed to grow and expand. That is known as the seed train. After about 14 days, there are enough cells in the seed train to move them to a bioreactor, a much larger container to grow the cells and produce the desired protein. A review of the seed train growth performance data indicated that cell growth was stalling out at 10 or 12 days, and we were not readily attaining the required cell density to move on to the next step of the production process. The cells should have been in an exponential phase of growth, but they barely limped on into the bioreactor. The media we were using for the seed train was minimal and did not have all the nutrients to sustain growth of the cells throughout the 14-day period. The cells were starving by the end of their time in the seed train. The bioreactor had a richer media, and once there, the cells were healthier, happier, and more productive as they returned to their expected exponential growth. We decided to try using the richer bioreactor media to grow the seed train. While we did not have data to prove that the cells would grow better, the intuitiveness of this suggestion was rather straight forward. The cells are going to grow better in a richer media, and we were already using the richer media in the process where we had plenty of data that showed that the cells recovered their exponential growth rates while producing the expected product. From a regulatory perspective this seemed like a no-brainer. The cells indeed grew better, and we resolved the issues we were having with seed train expansion.

What was not fully appreciated was the regulatory implication of having your seed train stall before it gets to the bioreactor was much worse than changing the media to improve seed train robustness. Health

authorities generally do not object to making changes when informed of the rationale and projected benefit for more robust and consistent cell growth, especially when backed up with data. The agency allowed changing the seed train media with the appropriate amount of data. That was an example of the regulatory and quality teams thinking they were acting conservatively when in fact they were actually taking big risks. When we changed that media, the cells grew more consistently, and the process performed better. That was the first of many science driven modifications to our process.

Another challenge was the presence of a specific host cell protein impurity. We determined that most of this specific host cell protein impurity eluted with the desired product in the first two column volumes during the first chromatography purification step. We showed this by testing each fraction from that step of the purification process. Rather than trying to change the process to separate this host cell protein impurity, we simply discarded the first two column volumes during collection. This was a time saving decision that reduced the content for this impurity to undetectable levels and had only a minimal impact on overall yields. Everyone agreed that the tradeoff of improved purity for a slight reduction in process yields while leaving the purification process unchanged was worthwhile. We also discovered that the product contained DNA at levels that were too high. Studies demonstrating that a DNA removal filter added prior to final formulation effectively removed DNA to an undetectable level were expeditiously conducted to keep us on the timeline.

Overall, we made four changes that improved our chances of technical and regulatory success significantly. One was procedural, with the discontinuation of release of raw materials on variance. The other three changes were more technically based. They included changing the seed train media, discarding the first two column volumes during the first chromatography purification step, and adding a DNA removal filter to the process. By implementing these improvements, we made the process more robust and increased the purity of the product to greater than 99 percent. The improvement to the process allow us to have a successful PPQ campaign as we were establishing for ourselves a science-dominated and

data-driven methodology to decision-making that defined our approach to process development directly targeted at regulatory compliance.

Bigger problems

In June of 1998, BioMarin entered into a letter of intent with Genzyme for a 50-50 joint venture to develop and commercialize Aldurazyme. Genzyme seemed like a logical partner. It was a trailblazer in creating the business model for rare disease drug development and had already brought to market Ceredase, the first tissue-derived enzyme replacement therapy to treat Gaucher disease. Gaucher disease, like MPS I, is a lysosomal storage disorder caused by a genetic mutation that results in an enzyme deficiency.

The deal provided BioMarin with immediate and potential future funding and the benefit of Genzyme's experience in navigating the approval process and commercializing a rare disorder therapy. Genzyme made an $8 million equity investment in BioMarin and agreed to purchase an additional $10 million of BioMarin stock in a private placement concurrent with BioMarin's initial public offering at the public offering price. In addition, it agreed to pay BioMarin a $12 million milestone payment when the United States Food and Drug Administration (FDA) granted approval to Aldurazyme. For Genzyme, it provided a way to leverage its existing commercial organization and generate additional revenue with a product that paired well with its pipeline.

My first meeting with Genzyme executives occurred in July 2000, just two months after joining the company. Before a planned dinner between representatives from both companies, two Genzyme executives sat down with me in a conference room. I assumed this would be a meet-and-greet opportunity to get-acquainted. Instead they led off by dropping a bombshell.

2.

If You Plant Ice, You're Gonna Harvest Wind

Above all, don't fear difficult moments.
The best comes from them.

Rita Levi-Montalcini

I first learned about Project Brewster when a group of executives from Genzyme came to BioMarin headquarters in Novato, California in July 2000 for a get-acquainted dinner and a day of meetings. Before the dinner, senior vice presidents of manufacturing and regulatory affairs for Genzyme had scheduled a meeting with me. It made sense that they would want to introduce themselves since I was new to BioMarin. As our partners on the development and commercialization of Aldurazyme, our enzyme replacement therapy for MPS I, they would want to talk about how we would be working together going forward.

As one of the most successful biotechnology companies in our industry, Genzyme brought credibility to BioMarin when the partnership was signed in 1998. The agreement defined the responsibilities of each company. BioMarin would be responsible for manufacturing Aldurazyme and would file the biologics license application (BLA) with the FDA for marketing approval, and Genzyme would be responsible for commercialization and regulatory filings outside the United States. The roles were clear, but the intentions were a bit more complicated. While I

was still getting my bearings at the company, having been on the job for just two months, whenever discussions turned to Genzyme the BioMarin management team grew embittered. The two companies consummated their deal during the phase 1 study for Aldurazyme, which used material manufactured at the Harbor-UCLA Medical Center and BioMarin's Torrance, California facilities. Both parties understood that the Torrance facility could not support phase 3 or projected commercial demand of Aldurazyme and BioMarin made the decision to build the Galli facility in Novato. This first meeting with these Genzyme executives was my opportunity to build some rapport. By the time the meeting was over, I would be soured on our partners and the future of manufacturing at BioMarin would be my responsibility to defend.

The meeting was important as there were many outstanding issues to be resolved before starting the process performance qualification (PPQ) campaign. But before any questions about the PPQ campaign were raised, the manufacturing executive began speaking in a matter-of-fact way about a change Genzyme was going to make. "I just want to let you know the plan going forward," he said. "We are going to take over manufacturing of Aldurazyme and move it to Cambridge, Massachusetts."

I was caught off guard and asked them to clarify what they had in mind. They offered some of the details of what Genzyme was calling "Project Brewster." It might have been that our partners did not have confidence in our ability to deliver on our manufacturing responsibilities, or it might have been Genzyme's plan from the very beginning to take over manufacturing since they had completed construction on a new manufacturing facility in Cambridge, Massachusetts in 1997 and had available capacity. Not being familiar with the details of the agreement between Genzyme and BioMarin, it was assumed Genzyme had the authority to do this, or enough leeway in the language of the agreements to justify doing so. Nevertheless, it was a bad idea for Genzyme, and a disastrous one for BioMarin if it ever hoped to become a fully integrated biotechnology company. If BioMarin lost responsibility for manufacturing, the company would be relegated to discovery and early development.

As discussions continued it was clear that the ramifications of this decision and the consequences it would have on the development of

Aldurazyme had not been fully vetted. There were many technical and regulatory implications that needed to be considered. The decision, if enacted, would impose significant delays on the phase 3 study and push revenues from the therapy off for several years. There was no sense getting into an impromptu debate with my Genzyme colleagues at this point. It would not serve any purpose. This plan might have been feasible had they implemented it before phase 3 materials were being produced. My BioMarin colleagues understood the gravity and implications of Project Brewster even though it was not apparent to them how to fend Genzyme off from its aggressive attempt to strip BioMarin of its manufacturing responsibilities. Notwithstanding being the newest member of the management team, it was now time for me to carry the load.

Just one more thing

In early August, Genzyme invited me to tour its new manufacturing facility in Cambridge, Massachusetts and meet with the tech transfer team there. I was the only one from BioMarin invited and it seemed like an intentional effort to outnumber me in any meeting. The purpose of the visit was to acquaint me with the company's manufacturing facility at Allston Landing and to meet with the manufacturing, quality, and validation teams to discuss how BioMarin would go about handing off the manufacturing of Aldurazyme to Genzyme.

The Allston Landing plant was a showcase facility. It had earned its nickname "The Cathedral" because the structure from the outside looked as if it had a transept and nave. On the tour, we moved from incoming raw materials to cell culture to purification. It was a brand-new facility that was stunning and had plenty of available capacity.

As I toured the facility, it was apparent that Allston Landing had the capacity and capability of handling Aldurazyme manufacturing. While walking through the large structure it became clear why Genzyme was interested in transferring Aldurazyme production. The facility had unused capacity, and Genzyme had developed plans to scale manufacturing by 10-fold. Transferring Aldurazyme production to Allston Landing would not only relieve Genzyme of its share of the manufacturing cost associated with the Galli facility, as required by the agreement with

BioMarin, but it would also lower the cost of goods for manufacturing of Cerezyme, Genzyme's recombinant enzyme replacement treatment for Gaucher disease that was already being produced there. Moving the production of Aldurazyme would elevate Genzyme to full control of production and commercialization for the program and would relegate BioMarin to a subordinate role.

It was not hard to imagine Genzyme's thinking about the case for moving manufacturing of Aldurazyme. Under the agreement with BioMarin, it was responsible for covering half of all the manufacturing cost related to Aldurazyme. That meant it was paying to build BioMarin's manufacturing capabilities while it had available capacity in its own plant. No doubt, Genzyme could have also had reservations about BioMarin's ability to do world class manufacturing. Our ability to operate an FDA approved manufacturing facility and produce high-quality biologics remained nascent and unproven.

After touring the facility, a meeting was convened in a conference room with about 20 Genzyme employees. People from manufacturing, validation, quality and regulatory affairs were in the room. The purpose of the meeting was to work out the details for the tech transfer from BioMarin to Genzyme. It was clear that this visit and tour was intended to win my support of the plan, or at least gain my cooperation in initiating the transfer of Aldurazyme production from BioMarin to Genzyme. As we settled into the conference room it was my goal to put an end to any discussion about moving Aldurazyme production. The devastating impact this decision would have on the future of BioMarin was concerning. The risks it posed to the timing and ultimate approval of Aldurazyme were significant and perhaps not fully appreciated by Genzyme.

The challenge was how to accomplish this while maintaining a reasonable working relationship with a corporate partner vital to the development of the program and our company. Drawing on my knowledge of regulatory expectations, having helped develop nearly a dozen therapeutics and from my role in building the foundation of Genentech's alliance management program, the essence of a counterattack emerged. We went around the room and everyone introduced themselves. It seemed that the Genzyme personnel were already of the mindset that

moving production was a done deal and they were eager to start the tech transfer discussion. Rather than challenge the wisdom of Project Brewster, I channeled Lieutenant Columbo, the television detective played by Peter Falk, and innocently posed the first of three questions. "How long does it take to transfer the process of making Aldurazyme?" This led to a lively discussion on the information necessary to facilitate a comprehensive and effective transfer. After about 15 minutes of discussion a preliminary list of requirements was being generated on the whiteboard. As we returned to the question of timing, it became evident that this would require about nine months of sustained effort. We were all in agreement. My next question focused on what is known in the industry as a process performance qualification campaign or PPQ and how long it would take. This is the validation process that health authorities require, and it includes such things as the manufacturing conditions necessary to make the product, the types of data that need to be collected during the process, testing that needed to be performed throughout each step of the process, how data would be analyzed and decisions made, what the normal operation parameters were, how deviations to the manufacturing process would be handled, and the establishment of product specifications. These would need to be written up and provided to health authorities for an in-depth review as part of the product approval process.

The requirements for conducting a PPQ campaign are detailed by a variety of worldwide health authorities' regulations. They are scientifically rigorous and linked directly to the quality of the tech transfer that was the basis of my first question. They are time consuming, especially for the perfusion process established for Aldurazyme production. The actual time in the plant would be at least six months or longer if all went well. PPQ campaigns are expensive and can cost tens of millions of dollars to conduct when you consider the purchase of raw materials and equipment, plant time (including depreciation), testing requirements (including long-term stability), and the expertise to coalescence all the information into a coherent and persuasive set of reports to demonstrate validation to multiple health authorities. With that backdrop, I asked my second question. "How long does it take to validate the process of

making Aldurazyme?" Once again, my question set off a lively discussion on the requirements and timing of activities. After about fifteen minutes of back-and-forth, there was consensus in the room that this work would take at least a year. We were all in agreement.

The plan to transfer production from BioMarin to Genzyme was going to take nine months with an additional year to fulfill PPQ requirements just to file with worldwide health authorities. Keep in mind that all this work was to be ongoing while BioMarin conducted identical and simultaneous PPQ activities to support the phase 3 study and registration of Aldurazyme for the initial approval. While Genzyme might have had the resources to address all these activities, BioMarin at the time had less than 125 employees. We were in no position to conduct our own PPQ campaign while supporting a tech transfer to Genzyme.

The first two questions were meant to ensure that both companies were aware of the cost and timing of moving manufacturing. It also provided me with some cover. Rather than attacking the concept of Project Brewster, my intent was to let it sink under its own weight. Genzyme senior management had already calculated the benefits of moving Aldurazyme production to Allston Landing. Aldurazyme would utilize available plant capacity, further reinforce Genzyme's leadership in treating orphan disorders with enzymatic therapies, and relieve Genzyme of paying its share of our ongoing manufacturing costs. There was one more question that I needed to pose that would torpedo Project Brewster.

As eagerness was building within the room to further detail the tech transfer plan, the final question was asked. "What kind of data would you need to convince health authorities that the products produced at BioMarin and Genzyme are comparable so that you do not need to repeat the phase 3 clinical study?" This question was one that had not been addressed in any of Genzyme's presentations. Even if the tech transfer and PPQ campaigns were successful, would health authorities approve the transfer and scale-up of production of Aldurazyme based on analytical or animal testing, or would they compel BioMarin and Genzyme to conduct a second phase 3 study to demonstrate comparability? We were having this discussion six years before the European Medicines Agency (EMA) had approved its first biosimilar product, and 14 years

before the FDA had approved one. In fact, just a month before at a United States Pharmacopeia meeting, the FDA had advocated that the hurdle for biosimilarity would be quite high from an analytical characterization perspective and would require clinical evaluation as well.

The discussion in the room was lively and continued for 40 minutes. This was the Achilles heel that Genzyme senior management and technical experts had failed to think through adequately. As I sat quietly in the room, they worked through the requirements and how difficult a hurdle moving manufacturing would be. As the technical experts debated the regulatory challenges of the plan, the view of the benefits drifted into the distance. The cost, timing, and risks of such an undertaking were unveiled for both companies to see. Three questions and a little more than one hour into the meeting, Project Brewster was sunk. While a decision was not made that day, Project Brewster never came up during future joint venture meetings.

The outcome from this meeting was not lost on me. It would be necessary at times to develop and drive important strategies through to completion while maintaining good rapport with partners, regulators, and colleagues along the way. While it was critical to maintain control of Aldurazyme production, it was also necessary to maintain a good working relationship with our Genzyme counterparts. Even though the case to leave Aldurazyme production with BioMarin had been made, it had been done in a way that allowed Genzyme senior management to withdraw the proposal gracefully. This one-day meeting was one of the most important days in the success story that is BioMarin. Had manufacturing of Aldurazyme moved to Allston Landing, the negative impact on BioMarin would have been substantial and long lasting. Our abilities to bring other products through to approval would have been limited. This interaction now put the manufacturing responsibilities squarely on our shoulders and would both illuminate the capabilities and exposed the limitations of BioMarin's technical operations, procedures, and quality systems. The upside was we got to continue the manufacturing of Aldurazyme. The challenge was that the chemistry, manufacturing, and controls (CMC) that go into the making of a medicinal product were now to come under tremendous scrutiny from both our partner and health authorities. Our

approach to drug development would need to be on a solid footing to gain approval of Aldurazyme. Ironically, Project Brewster was intended to tilt the field drastically into Genzyme's favor. Instead, the playing field had been leveled by asking three simple questions. As we gathered back in Novato, planning for the PPQ campaign started in earnest.

Takes all you got just to stay on the beat

We survived the inspection by the CFDA. We survived Genzyme's ill-planned flirtation with Project Brewster to take over manufacturing. But there were plenty of other things to worry about. We still needed to make enough material to conduct and support all the phase 3 studies. If we failed to make the phase 3 material, Project Brewster would immediately be back on the table. My first three months at BioMarin had been many things, but boring was not one of them. The combination of having a facility inspection, overcoming challenges in releasing supply for the upcoming phase 3 study, fending off Genzyme's attempt to move manufacturing, and planting the seeds for a science-focused data-driven approach to compliance were all victories that cleared the way for the upcoming Aldurazyme PPQ campaign. With five months before the campaign was to start, we were just beginning to get a handle on our level of preparation, or in some cases our lack of it.

3.

Think This Through with Me, Let Me Know Your Mind

> The practice of medicine is an art, not a trade;
> a calling, not a business; a calling in which your heart
> will be exercised equally with your head.
>
> **William Osler**

The comprehensive scientific improvements we put into place prior to the start of the Aldurazyme phase 3 study paid dividends during the process performance qualification (PPQ) campaign and subsequent inspections. We won approval of Aldurazyme in the United States and Europe in 2003. The approval gave credence to our growing manufacturing prowess and converted hope into a therapeutic option for MPS I patients. It also put us in a strong position to develop our next therapy, Naglazyme, an enzyme replacement therapy for mucopolysaccharidosis type VI (MPS VI), also known as Maroteaux-Lamy syndrome. Like MPS I, MPS VI is a rare and fatal lysosomal storage disorder. Naglazyme was advancing in clinical trials, and we needed to plan for expanding our manufacturing capacity.

At the end of 2003, I was appointed head of technical operations, a newly created position that would oversee manufacturing, quality, engineering, and process development. That put me in charge of three groups: manufacturing, process development, and engineering, which I had never managed previously. My responsibilities extended across

half the people in the company as other functions, such as logistics and purchasing, got folded in as well. As BioMarin advanced Naglazyme, the company faced a growing existential crisis as clinical failures, strategic missteps, and growing friction between investors and management pushed the company to the brink. For readers who are interested, the events are recounted in detail in the book *A Rare Breed*.

Technical operations, in the face of growing financial pressure on the company, not only had to solve the manufacturing logistics for Naglazyme, but also figure out how to keep everything running as employees grew concerned about the future prospects of BioMarin. An ongoing exodus of talent throughout the company characterized the first six weeks of 2004. Numerous organizational and technical challenges demanded attention. I needed an objective sounding board for ideas to chart the path forward and asked Stuart Builder, a former Genentech colleague and trusted confidant, to join BioMarin as an advisor. For me he was a consigliere who provided guidance on a wide range of tactical and strategic decisions needing to be made.

My initial discussions with Builder focused on the structure of the technical operations organization as numerous senior people in quality, purchasing, and manufacturing were leaving the company. It would take nearly 18 months, until mid-2005, to get a team in place that would provide stability on the technical operations side of the business. That would coincide with the appointment of Jean-Jacques Bienaimé as BioMarin's CEO. While numerous personnel changes were ongoing during that time, we also had to contend with the worldwide launch of Aldurazyme and the regulatory filings for Naglazyme as it advanced in the clinic.

We made the material for the Naglazyme phase 1/2 clinical trial in the Pink Palace, but we needed to find a place to produce material for the late-stage clinical trial and commercial product. It was not too soon to be thinking about long range planning to accommodate growth. As it turned out, facility planning would consume a greater and greater portion of my time once I became head of technical operations. As my responsibilities grew, the demand on my time increased. Long-range planning needed to be made, construction projects overseen, contractors managed, and a team needed to be built. That came in addition to

the technical, science, business, and regulatory issues that demanded my attention.

Our previous CEO, Fred Price, proposed leasing a facility in Palo Alto, California that Yamanouchi Pharmaceutical owned. It was a beautiful building that looked like an Italian villa right down to the grape vines that grew on the nearby hillside. The problem was that the building had been built to manufacture tablets, not biologics. It had the wrong equipment and all the wrong air handling configurations. As we put the plan together to convert a tableting facility into a biologics facility it eventually became too expensive. When the price tag for converting the facility passed $20 million other alternatives were evaluated.

We explored outsourcing manufacturing and evaluated several contactors. Unfortunately, both the timing and the cost quickly removed that option from consideration. Another alternative, and the one we implemented, was to make Naglazyme in the Galli West facility in the same place where we had been making Aldurazyme. Turning Galli into a multiproduct production facility made a lot of sense, but it was controversial as some of the quality and regulatory team members expressed concern as to whether regulators would allow such a plan. In reality, others in the industry had already been doing multi-product manufacturing for many years. The challenge was to develop the procedural controls for multi-product production. In fact, the regulatory groundwork had already been laid. When we filed for Aldurazyme approval we included the concept in our application to market the therapy and had in-depth discussions with the U.S. Food and Drug Adminstration (FDA) about our approach. Of course, we had to generate the data and procedural controls to demonstrate we could operate the plant as a multi-product facility.

BioMarin had already begun a series of facility expansion projects. We moved out of the Pink Palace in 2004 to new headquarters at nearby 105 Digital Drive in Novato, California. At the same time, we built out 95 Digital Drive to house our research and process development labs. The buildout allowed us to free up space for development of Galli East. Within 7,000 square feet of space on the east side of Galli, we housed our orginial research and process development modular labs. A clear Lucite enclosure walled off the labs and earned them the moniker of "the fishbowl."

As we built the capacity of Galli West, our cell culture capabilities grew to six bioreactors from two. That created the need to increase the capacity to produce our own media and buffer for growing the cells that produced our drugs and purifying them required significant expansion to our purified water for injection systems.

What multi-product production meant was that we would produce Aldurazyme for six months a year, then implement an extensive changeover procedure (including cleaning and testing) to then produce Naglazyme for six months. It was an efficient way to run a plant. Producing both products in one facility had multiple benefits. We were still a small company with about 200 employees. Splitting operations across multiple facilities would have also meant shipping people and materials back and forth and would have been counterproductive to our efforts in building a sustainable company culture. It also was the most cost efficient of all the alternatives we evaluated. As it turned out, that would be a critical factor in our survival as a financial storm was brewing for the company in late 2004 and the first half of 2005. The decision allowed us to create a manufacturing nucleus for the company out of which both our culture and technological prowess could blossom.

With the decision made, the technology transfer of Naglazyme commenced in 2003 with the production of phase 3 material to support the pivotal trial. A cornerstone of our drug development strategy was to develop the to-be-commercial process in the to-be-commercial facility prior to the commencement of phase 3 studies to avoid inevitable scrutiny from regulators that would come with changes made to the manufacturing process after conducting pivotal clinical studies. In late 2004, after a successful phase 3 study and PPQ campaign in Galli West, we submitted the biologics licensing application to the FDA and the market authorization application to the European Medicines Agency (EMA) for Naglazyme. The FDA approved Naglazyme in the first half of 2005 and the EMA approval was granted in early 2006.

Clinical continuity and partnership

It had taken just seven years from the founding of the company to get our first two biological products (Aldurazyme and Naglazyme) approved.

That is an enviable accomplishment for any biotechnology company. Over the next 17 years, we would win approval for six other products (Kuvan, Vimizim, Brineura, Palynziq, Voxzogo, and Roctavian). During that period, a manufacturing metamorphosis would be required including a multi-pronged expansion of the Galli facility and the acquisition of the Shanbally facility. While the Galli and Shanbally facilities were intended to support our growing biologics aspirations it would not be long before the company would be adding a new modality, gene therapy, into the mix. This would create the need to develop dedicated manufacturing and analytical capabilities that would create unique challenges for technical operations.

In some cases, we followed the lead of the clinical team while establishing requirements to assure that the quality, potency, and safety of our products would not waiver from our commitment to patients. Conveying those ideals throughout the company and living up to them was one of our most important accomplishments.

The partnership between clinical and technical operations allowed for the development of manufacturing processes that were focused on producing products with defined critical quality attributes that were inextricably linked to desirable clinical outcomes. The finish line was product approval, and it was essential that we both fulfilled our responsibilities to arrive at the finish line together.

Throughout the development of our products, we established rigorous criteria for product quality and continually developed more sensitive and selective analytical methods to better understand the relationship between the structure of a molecule and its function. We created a feedback loop to ensure that when analytical information pertinent to critical quality attributes was gained it informed process knowledge and development. Linking process development to facility design required a flexible approach so that increases in scale or productivity could be implemented as process understanding evolved.

Well everybody's dancin' in a ring around the sun

Our process development, facility design, and analytical characterization approach was shared with health authorities in real time through formal meetings, conferences, and health authority-sponsored workshops.

The back-and-forth communications with health authorities provided valuable insight for the development and validation of processes, facilities, and assays. We explained our intentions to health authorities as we integrated the framework for our clinical studies with plans for process development, facility design, and analytical characterization into a comprehensive approach for our drug development efforts with the goal of gaining alignment and agreement.

One of the benefits that arose out of the approvals of Aldurazyme and Naglazyme was that we were building a strong reputation with health authorities with our focus on strategic process development. This provided opportunities to interact with health authorities in a more general and collegial framework through professional society meetings and FDA sponsored workshops. Shortly after approval of Aldurazyme, we had an opportunity to share our approach with the industry through an FDA sponsored workshop for monitoring protein particulates, an area of persitent health authority focus. During the latter days leading up to the approval of Naglazyme, questions arose about the substrate used in the potency assay utilized for release testing. Our response to health authorities during the approval process resulted in an elaborate evaluation of multiple biomemetic substrates leading to not only approval but an invitation to contribute a chapter on enzyme kinetics and the design of biomemetic potency assays to a book on the topic, *Comprehensive Biotechnology*, that the FDA was editing.

As health authorities grappled with developing and evolving guidance documents for the emerging field of gene therapy, we were forthright in sharing our approach with them. In formal meetings with health authorities, we laid out our plans in detail and challenged ourselves to be as thorough in our development and validation efforts for gene therapy products as we had been with our recombinant DNA products. We developed highly sensitive and selective analytical methods for characterization of these complex gene therapy products. We delineated the critical process parameters leading to the desirable critical product attributes we were controlling for during production. We codified all of this work in rigorous validation documentation with prospectively defined acceptance criteria.

As we built out our manufacturing infrastructure to support the

largest phase 3 gene therapy study ever performed, we were one of the pioneers in addressing and solving challenges associated with scaling up the technology. We participated in multiple symposiums where industry and health authority representatives were brought together to present, debate, and clarify both health authorities' expectations and industry approaches to manufacturing and testing of gene therapy products. These symposiums would play a critical role in the formation of guidance documents health authorities would publish in 2015 providing needed clarity for the development of gene therapies. As we gained experience in analytical characterization of these products we were invited to an FDA sponsored workshop to share our approach for measuring vector genome levels to faciltate industry adaption of best practices. The collborative interactions we were having with health authorities harken back to my days at Genentech where similar collboration led to the establishment of "the rules of the road" for the development of recombinant DNA products that were codified in the International Conference on Harmonization guidance documents. The clinical success of our hemophilia A gene therapy program was driving us to rapidly develop facility, manufacturing, and analytical testing capabilities that were creatively addressing the evolving expectations of health authorities. Industry and health authority information and thinking was being shared publicly to faciltate discussions on developing solutions to challenges with the manufacture and control of these products.

Motivated by patients

A shared goal of addressing the unmet need of patients drove the close interactions and collaboration with health authorizties. Working in the biotechnology industry involves developing medicines that make a big difference in the lives of our patients. Work on enough products and occasionally you will find a friend or relative that has benefited directly from treatment. At BioMarin, which developed medicines for small patient populations, the opportunity to get to know patients is a far more immediate experience. Clinical studies are small and often conducted locally. Oakland's Children's Hospital ran the phase 1/2 clinical studies for Naglazyme, which involved 16 participants. The proximity of the

clinical trial site allowed many people in the company an opportunity to meet all the patients who participated in the study. Twenty years later the participants in those studies continue to visit, inspire, and motivate us.

There have been hundreds of opportunities to meet with patients. At times we gowned up patients and their families and gave them tours through the facility and laboratories where we made and tested the medicines they were taking. Other times we had the chance to meet with patients and their families as we prepared for interactions with health authorities. The patient voice is critical to health authorities as they work with us in evaluating the clinical outcomes of the studies we have performed. The patients who have participated in our clinical studies are biomedical pioneers. Their willingness and bravery to participate in long and often invasive studies provides the data necessary for approval. Even those patients and families who have not qualified for participation in our clinical studies have supported our efforts as advocates and ambassadors knowing that they are helping families whose children are also afflicted and could benefit from treatment. Every one of those patient interactions has been powerfully motivating for many in the company and has propelled us to do everything in our power to bring these therapeutic options through to approval.

While the role of technical operations might have ended with the delivery of a vial to the patient's bedside, it extended well beyond manufacturing and distribution. We were a full partner in tactics and strategy as we brought to the table technical capabilities that were interwoven with clinical and commercial plans and shared with health authorities to expedite the development of our products. Of course, if you didn't have the capacity to produce what patients needed, they weren't going to get the medicines they required. Ensuring BioMarin had the manufacturing capacity, not only to address current demand, but for its growing pipeline, would be an ongoing challenge that would occupy the technical operations team throughout the rest of my time with the company.

4.

The More That You Give, The More It Will Take

Measure what is measurable,
and make measurable what is not so.

Galileo Galilei

Even though BioMarin had three commercial products (Aldurazyme, Naglazyme and Kuvan) on the market by 2007, scientific and regulatory success did not translate into financial stability. We were still not profitable as we created the commercial and operational infrastructure to complete our transformation into a fully integrated pharmaceutical company. The pipeline needed replenishing after label extension studies for Kuvan failed. The Galli West facility was churning out both Aldurazyme and Naglazyme, and it was becoming clear that we would exhaust the production capacity of the facility within the next year or two. It was time for a manufacturing reboot that was comprehensive, strategic, and affordable.

From the fencing we installed in the Galli facility during my first week at BioMarin in 2000 to segregate quarantined and released raw materials, one ongoing job over the next decade would be to configure and reconfigure BioMarin's manufacturing footprint in Novato, expand it, and find ways to respond to the evolving and unknown makeup of the next wave of clinical products. Prior to 2007, most of the efforts in

technical operations were geared toward maximizing the output of Galli West. Aldurazyme and Naglazyme approvals consumed nearly all of our technical capabilities. Even before we secured approval of Aldurazyme we had implemented operational enhancements to increase both media and buffer preparation production capacity to support the increase in the number of bioreactors and doubled the purification output. These improvements were critical to not only meet the projected commercial requirements for Aldurazyme but also to allow for Naglazyme production to transfer from its manufacturing set up in the Pink Palace. By the time we gained approval for Naglazyme, we had configured the Galli West portion to maximize output from the facility. Due to the unpredictable nature of product launches, it was unclear how long that capacity would support commercial demand. In addition, it was unclear where we would make future clinical products. Capital investments in building the company's infrastructure during those first ten years were significant. The build out of the Galli West facility and assorted quality control, process development, and research laboratories, along with administrative support needs, were approaching $200 million. As we started to plan for the next 10 years of growth, similar or greater capital expenditures could easily be envisaged. This would involve overseeing not just renovation projects, but major construction projects as we expanded from the 11,000 square-foot Galli West facility to improvements that would give us 7,000 square feet of manufacturing space on the top floor of Galli North, and eventually the more ambitious 21,000 square-foot expansion in Galli East. It takes years to develop a biotechnology product. Even the most promising products can be derailed on their path to an approval because of regulatory issues, competitive threats, financial constraints, and biology. What looks hopeful in an early-stage clinical trial can fail to demonstrate safety or efficacy in a pivotal study. The challenge for us was to ensure that needed product was available for clinical studies and that capacity existed to produce a commercial product should we gain regulatory approval. To do that requires extensive planning and large capital commitments long before a regulatory authority grants clearance to market a therapy. Along the way, that may mean building in anticipation for a product that requires one type of manufacturing process and

being able to pivot to repurpose a facility for a different product that demands an alternative manufacturing technology.

Biotechnology manufacturing facilities are complex and expensive. It can take years to design, commission, and validate one. Because companies must design and construct a facility today for a product that is years in the future and support a pipeline that is subject to change, it is essential to build flexibility into facilities. Our manufacturing facilities in many ways are similar to a Swiss Army knife. Designing the facilities to be versatile represented a philosophic approach that we undertook from the start. We were one of the first companies to utilize single use technology exclusively throughout production. In some cases, our products did not encounter any stainless steel until they were pumped through the filling needles into the vials of the drug product itself. From bioreactors to product hold vessels, single-use technology reduced capital expenditures, eliminated the need for cleaning validation studies and provided us with flexibility that was essential for building facilities long before we could be certain what processes and products would be manufactured in those facilities. We incorporated ballroom design concepts where possible to allow for different sizes and types of equipment to be moved into rooms as needs demanded. Many companies produce products of a single or similar type. We produced very different types of products so it was vital to have flexible facilities capable of manufacturing a wide range of products utilizing different technologies.

A drive to maximize

Before we ever thought about expanding our manufacturing footprint, our initial focus was on maximizing Galli West output, where we had continuously produced Aldurazyme and Naglazyme commercially. We made modifications to the facility so that we could make as much product as possible in the space that we had. This was an effort we referred to as "GalliMax." We increased the number of bioreactors to six from two in Galli West to expand our cell culture capabilities and increased our production and storage capacity for media, and buffers. We doubled the size of the columns to purify the bounty coming from the six bioreactors. And, with all of that, we transformed Galli West into a multi-product

facility by alternating the production of Aldurazyme and Naglazyme there. We continually challenged assumptions and removed constraints until the limiting factor for total output was dependent, not on the number of bioreactors or size of the columns, but on how much water for injection we could generate in-house. We took health authorities on the journey with us, keeping them informed of our plans and providing them the data to demonstrate successful implementation. We were counting on first-cycle approvals of our modifications to the facility and manufacturing process improvements as regulatory delays would have carried consequences for our ability to meet inventory demands. The numerous improvements to the facility and the manufacture processes were all accomplishments based on the merits of analytical comparability testing and rigorous validation studies and did not require supportive animal or human testing that would have delayed their implementation significantly.

By 2008, our production demand was approaching the predicted maximum output for Galli West. We were running the manufacturing facility 24 hours a day, seven days a week, employing multiple shifts. We utilized the graveyard shifts for making media and buffers to limit the types of activities that might occur when the least amount of supervision was available. The quality control laboratories were also run 12 hours a day, seven days a week. The plant was humming, making one product or another for eleven months of the year with a scheduled one-month shut down for maintenance. Our partner Genzyme and our commercial organization had no complaints as product was always available when ordered. Our CEO, board of directors, and finance group were also pleased as the cost of goods consistently beat expectations due to the nearly continuous and efficient operation of the facility. What was less evident to these groups was that we were running the plant at near capacity.

At one of our CEO's leadership meetings, each group head was asked to state as simply as possible a philosophical statement that was easy to understand and drove our functional goals. My response was both humorous and serious. "If I have too much inventory, I get yelled at," I said. "If I do not have enough inventory, I get fired." It reflected the need to ensure that we never stocked out of product for our patients, but also that we maintained a high degree of flexibility in case we had changes

in plans, or if the only manufacturing plant we had to produce commercial product was shut down for any reason. It was a lighthearted way to express to management and to others throughout the organization the importance of assuring a continuous supply of product for our patients.

With supply of product in mind, the production planning and manufacturing groups were tasked to over-produce both products at every opportunity. If we were scheduled to make ten batches during a campaign, we reworked the schedule continuously to see if an 11th or 12th batch could be produced. Both products had excellent stability. That stability gave us the luxury to build inventories stored as either bulk or drug product up to 24 months or more in advance. While this was tying up vital capital in the form of inventory, the inventory provided an insurance policy against increased demand or manufacturing being shut down for an extended period for any number of reasons. The logistics group within technical operations was planning for commercial needs two to three years beyond current forecasts. We used the commercial forecasts as guideposts knowing that they were subject to a lot of variation. Naglazyme sales exceeded commercial forecast by more than 30 percent in each of its first three years on the market. Had we limited our production to the commercial forecasts, we almost certainly would have stocked out of product.

Building out Galli

While building a facility is expensive, thinking about doing so didn't cost much and was a lot of fun. Knowing that we were nearing capacity in Galli West, the team was tasked to design a facility on the east side of the building. This area, known as Galli East, consisted of a 7,000 square area where the original research and process development laboratories had recently been vacated. Those labs had been known as "the fishbowl" because they were encased in clear Lucite walls. There wasn't a budget for this buildout, and it would be nearly three more years before board approval was secured.

After the approval of Kuvan our research efforts once again turned to enzyme replacement therapies. Recruiting talented people to the company was always a priority for me. Gordon Vehar was a staff scientist at

Genentech when we met one day while dropping our sons off at the company's day care center in 1991. Vehar's group had cloned the factor VIII gene in 1981. That gene sequence would later be used in BioMarin's first gene therapy product valoctocogene roxaparvovec (Roctavian). To this day, it is the largest gene ever to be cloned. He joined BioMarin in the beginning of 2008. Not only did we now have a renowned scientist leading our research efforts, but I now had a carpool buddy as Vehar lived nearby.

Spending two plus hours a day in the car together gave us the chance to discuss our enzyme replacement strategy for MPS IVA disease and the research being conducting on the enzyme replacement therapy that would eventually be marketed under the trade name Vimizim. This project advanced from preclinical to clinical testing in 2009 and presented several manufacturing challenges.

The enzyme N-acetylgalactosamine-6-sulfatase shares some common features with our Naglazyme product as both are sulfates and require a post-translational modification at the active site of the enzyme in which the amino acid cysteine gets converted to formylglycine. It is only the formylglycine version of the enzyme that is potent. For Naglazyme, we performed extensive screening to find a cell line that produced the activated form of the molecule. We found many cell lines that produced the enzyme in its inactive form at high titers, but active forms were produced at much lower titers. We selected one of the lower titer cell lines for Naglazyme production.

The number of potential MPS IVA patients that could benefit from Vimizim was much larger than the MPS VI market for Naglazyme. We were also planning to explore higher doses than we had for Naglazyme. Vimizim won approval at a dose that was twice the dose used for Naglazyme. In addition to doing exhaustive screening to find a cell line that produced high titers of the active form of the product, we also produced a double cloned cell line that included both the gene of interest coding for N-acetylgalactosamine-6-sulfatase and also the gene for the enzyme sulfatase-modifying factor 1 (SUMF1), which facilitated the conversion to the active form of the enzyme. We were successful in producing the double cloned version of the cell line that provided adequate titers and predominately produced the active form of the enzyme. The SUMF1 enzyme was

patented by another company and our business development and legal groups were able to negotiate a license under favorable terms. The good news was that we had identified our next clinical candidate. The challenge, once again, was determining where we were going to manufacture this product.

There was no capacity left in Galli West to add a third perfusion product. In fact, the Galli West facility was running at full capacity by 2008 producing Aldurazyme and Naglazyme. The Galli East facility only existed on the back of an envelope and could not possibly be ready to produce the initial clinical supplies of Vimizim. In one of our facility meetings, we considered whether we could build a small manufacturing area on the north side of Galli. The third floor on the north side of the facility had been the previous home for research and process development offices when their laboratories were located in the fishbowl on the east side of the building. There was only about 7,000 square feet of space to work with. The team was enthusiastic yet quickly identified obstacles that would make this approach challenging. Over the course of 2008 we worked through all the challenges and by year-end started construction on what would become known as Galli North.

The bioreactor we used for Aldurazyme and Naglazyme had working volumes of 100 liters. We decided to use bioreactors that were twice that size for Vimizim production. This established the requirement to make up media in 2,000-liter batches, which was sufficient to run the bioreactor for two days. Of course, we needed to store enough harvested cell culture fluid at refrigerated temperatures, up to 4,000 liters, before initiating the purification steps of the production process. While the technical requirements were straight forward and could fit into the limited space, we became aware of a structural obstacle. The floor could not hold the weight associated with the equipment and the more than 6,000 liters of liquid that would be necessary to run the process. We needed to reinforce the floor. We had to craft a solution that employed a 60-foot-long, 12-inch by 12-inch piece of timber. We used wood because steel was in short supply in the days leading up to the Great Recession due to the boom in construction activities in China. We cleared the building over the Labor Day weekend to insert the enormous wooden beam. In

addition, the roof covering the north side of the building was removed so a crane could lower in the 2,000-liter media preparation tank. With the floor reinforced and the roof back in place, the rest of the buildout and commissioning proved to be uneventful. In 2009, we produced the phase 1/2 material needed for the clinical studies. We knew that we would not be able to make the larger amounts of Vimizim in Galli North that would be needed for the late-stage study or commercialization. Once again, we found ourselves racing the clock to find another manufacturing solution.

With our previous clinical timelines for Aldurazyme and Naglazyme as guideposts we estimated that we had about 30 months to further refine the manufacturing process and to find a home for the production and release of phase 3 material to conduct a pivotal clinical study utilizing a commercial-ready process and facility. This meant that we would need to be producing phase 3 material by early 2011 to have the material we would need to start the phase 3 studies in late 2011.

As initial results from the phase 1/2 studies came in, our Chief Medical Officer Hank Fuchs decided to double the dose to 2 mg/kg of body weight. This represented a four-fold increase over Aldurazyme dosing and a twofold increase over Naglazyme dosing. In conjunction with the increase in dosing, our Chief Commercial Officer Jeff Ajer was estimating that there could be up to 3,000 patients who could benefit from Vimizim worldwide. We were being challenged as we had never been before. The charge was to build a facility with six to eight times the capacity of Galli West and have it operational within 18 months.

The team was working on possible scenarios for the build out of the Galli East facility. The first set of plans involved a single-story design on the 7,000 square-feet of available space. We rejected the proposed $30 million plan because it fell far short of the production capacity that would be needed to support a commercial launch. We next evaluated a two-story buildout and were pleased with the increased production capacity that came with a second story. The addition of a second story added $20 million to the cost of the facility. Someone joked that if we added a third story, it would come for free. The team went back to work redefining layouts and plans and came up with a three-story design. It did not quite come for free, but only increased the costs by an additional

$10 million. We now had a plan that could be presented to the board that would support three commercial products (Aldurazyme, Naglazyme, and Vimizim) for the foreseeable future. The facility would have separate production areas on the third floor for media and buffer make-up and storage, cell culture and harvest hold on the second floor and purification capabilities on the first floor. The functional design capitalized on gravity flow of liquids from the third floor to the first and allowed multiple bioreactors to run simultaneously. While Galli East was less than twice the square footage of Galli West, it was eight times more productive thanks to improved titers from the SUMF1 cloned cell lines and the design and operation improvements. Not only did we use the facility to make Vimizim to support phase 3 studies, but we also moved Naglazyme production from Galli West to Galli East, scaling the process two-fold. The movement of Naglazyme from Galli West to East would pave the way for the approval of Brineura several years later.

On November 23, 2011, the enormity of the challenge we had overcome was delineated to BioMarin employees in an email when we secured approval to commence commercial production of Naglazyme and clinical production of Vimizim in the Galli East facility:

> It was at the September 2007 Board of Directors meeting that the green light was given to build the Galli East facility. With two growing enzyme products on the market and one in development, it was time to plan for adding more capacity. The fact of the matter was that many discussions and planning sessions had been underway since as early as 2003 about where the next expansion of our manufacturing capacity would occur. In fact, some of you old-timers will recall that we nearly leased a facility in Palo Alto to manufacture Naglazyme but decided instead on running the Galli West facility in a multi-product mode.
>
> One of the most enjoyable aspects of this project was that this was never a technical operations project as much as it was a corporate initiative. This project required the talents, skills, and creativity of people throughout the company. Nearly every functional group in the company pitched in, including Research, Toxicology, Product Development, Human Resources, Regulatory, Corporate Compliance,

Corporate Communications, Legal, Finance, Information Technology and Medical Affairs. It was reassuring to know that Clinical Operations was poised to roll up their sleeves and pitch in if needed but this facility was approved based on the merits of analytical comparability testing without requiring clinical evaluation.

The scope of this project encompassed more than expansion of the existing facility. The scale of production at the cell culture stage was doubled, the scale of production at the UF/DF concentration stage was tripled, numerous technology and automation control enhancements were implemented to enhance manufacturing flexibility in accordance with good manufacturing practices, and High Temperature Short Time (HTST) technology for pre-treatment of media was implemented lowering the risk for potential viral contamination. The ability to gain rapid first cycle approval of this state-of-the-art manufacturing facility and associated process improvements are paramount to assuring our patients of uninterrupted supply of high-quality product and a testament to our sustained focus in meeting this strategic corporate goal.

Again, "flexibility" was our watchword with regards to manufacturing. When we moved Vimizim production to Galli East, this allowed us to free up Galli North to begin production of Palynziq, our bacterial enzyme therapy for the metabolic condition phenylketonuria, or PKU. To accomplish that, we converted Galli North from a cell culture suite used to make the phase 1/2 material for the Vimizim program to a fermentation suite for making Palynziq. PKU is a rare inherited disorder that causes an amino acid called phenylalanine to build up in the body. PKU is caused by a change in the phenylalanine hydroxylase (PAH) gene. This gene helps create the enzyme needed to break down phenylalanine. Without the enzyme necessary to break down phenylalanine, a dangerous buildup of phenylalanine can develop when a person with PKU eats foods that contain protein. This can eventually lead to serious neurological health problems.

Banking on a bacterial enzyme

The making of Palynziq would require a process that involved the use of a centrifuge, an extremely heavy piece of equipment. Because of its weight, we needed to construct additional support for the floor, and

even then, there were only certain places strong enough to support its placement. But while structural issues and matters of physical layout represented ongoing challenges, they were the least of the problems we faced with Palynziq production. BioMarin had established a history for moving from first-in-human studies to approval of a therapy in less than five years. It took close to ten years of clinical and manufacturing efforts to bring Palynziq to market because of the many technical challenges of developing a bacterial enzyme to be delivered on a chronic basis by subcutaneous administration. The level of scientific creativity needed to be successful with Palynziq required a high degree of collaboration among technical operations, pharmacology, research, and clinical operations and illustrates the deep cross-functional interactions that are at the heart of our drug development efforts. Ultimately, it was our ability to develop methods to characterize molecules and innovate our process development efforts that allowed us to advance Palynziq to the market.

A triumph of process

On the manufacturing side, we still needed to increase capacity for producing Palynziq to meet clinical and projected commercial demand in the rigidly defined footprint of Galli North. In addition to the column and filtration steps we performed with our other products, the process for making Palynziq initially included two centrifuge steps that were complicated and time consuming but were important for purifying the product. Stuart Builder helped us to reduce this to a single step, which represented a significant improvement.

Serendipity also played a role in our purification development efforts. Over a long holiday break, samples of Palynziq were inadvertently left on the benchtop for more than a week. Many proteins when stored at room temperatures for that period degrade and lose potency. When these samples were tested, though, they had maintained full potency. As Louis Pasteur said, "chance favors the prepared mind." When we discovered this, our scientists conducted stability studies and determined we could heat Palynziq for an hour at 65 degrees Celsius (149 degrees Fahrenheit) and it would maintain full potency. Most proteins are not that stable to heat and readily precipitate when heated even for the shortest periods

of time. That meant we could heat the harvested cell culture fluid for an hour at 65 degrees Celsius precipitating non-product proteins prior to performing the centrifuge step. The combination of the one hour of heating and the centrifuge step gave us 85 percent purification before we moved on to the column purification steps of the process. Overall, these improvements to the purification process resulted in a three-fold improvement in productivity.

The other thing we were able to do was to modify the way we performed the PEGylation, a critical element in allowing for chronic dosing of this product. The polyethylene glycol (PEG) was expensive. At any one time we had $1 million worth of PEG in the tank. We took a design of experiments (DOE) approach and discovered that if we made the PEGylation components more concentrated, changed the way we added reagents together, and controlled a handful of additional operational parameters, we could reduce the quantity of PEG and the volume of buffers used during this step of the process by two-thirds, further improving process robustness and productivity.

In 2019 Palynziq was approved. It was manufactured in the Galli North facility originally designed not for bacterial fermentation of Palynziq but for perfusion cell culture of Vimizim. The craftiness involved in the initial design of Galli North as a cell culture perfusion facility eventually converted to a bacterial fermentation facility is a testament to the creativity and technical prowess of our scientists and engineers. Doing all this work, consistent with the goals and timelines established by our colleagues in clinical and commercial operations and in compliance with health authorities' requirements, helped propel the company to success.

Pedal to the metal

While Palynziq took longer to develop than any other product BioMarin has brought to market, Brineura set the pace for the fastest therapy we were able to develop as it took us just three-and-a-half years to go from first-in-human studies to approval. Moving at that speed presents its own challenges, but as an enzyme therapy that is delivered directly and regularly into the brain, Brinuera had a unique set of challenges we needed to solve. Brineura is an enzyme replacement therapy for CLN2 (late infantile

neuronal ceroid lipofuscinosis type 2) disorder, a form of the lysosomal storage disorder known as Batten disease. CLN2 is an ultra-rare and rapidly progressing pediatric brain disorder. While people with PKU had medical options while they waited for Palynziq to reach market, children with CLN2 had no such alternatives. It is a progressive and devastating disease that generally results in death by age 12.

Children with CLN2 have a deficiency of the enzyme tripeptidyl peptidase 1 (TPP1). Without enough of this enzyme, children are unable to properly dispose of metabolic waste and it accumulates in the lysosomes of cells in organs, particularly in the brain and retina. As the disease progresses, children lose the ability to speak, walk, and see. The prognosis for CLN2 patients without treatment is grim. Seizures start at three years of age and the cognitive decline progresses rapidly.

The development of Brineura had additional and lasting significance for BioMarin because it was our first therapeutic to be manufactured through the more efficient fed-batch, rather than perfusion, process. Within technical operations, we had been working on moving away from the perfusion-based production system used for Aldurazyme, Naglazyme, and Vimizim production. All our future protein and gene therapy products are expected to be produced using a fed batch process.

Brineura posed both clinical and manufacturing challenges that we had to overcome. The enzyme needed to be delivered into the brain by intracerebroventricular (IVC) infusion. This requires implanting a port in the skull that makes use of a complex pumping system that directly delivers Brineura into the cerebrospinal fluid in cerebral ventricles. The proposed concentration of 300 mg fixed dosing administered bi-weekly was 40-times higher than the dose requirements for Aldurazyme. We had no existing game plan to follow for what we were trying to do. No therapeutic enzyme had ever been chronically delivered directly into the brain. And we were seeking to do this in children as young as two years of age.

Beyond the technical obstacles, there were commercial realities that caused us to question whether we would be able to identify patients early enough in the progression of the condition to provide benefit to them. That's always important for the types of genetic disorders that we worked

on, but even more so in CLN2 given the rapid and irreversible cognitive damage caused by the disease. Estimates indicated that there were 300 people in the world with CLN2 disease, and not all of them would be candidates for treatment. The combination of clinical, manufacturing, and commercial challenges led us to question ourselves for more than a year about whether we should pursue Brineura. Eventually compelling, non-clinical data convinced us that the treatment had the potential for significant benefit to children with the condition, even though commercial viability of the program remained uncertain.

We also had to figure out where we would make the product and at what scale. At the time, Galli East was busy with the approval of Naglazyme and Vimizim on a worldwide basis. We did not have capacity to accommodate a third product in Galli East. We were able to squeeze in a single manufacturing campaign of Brineura in Galli North before moving it, first to a redesigned Galli West facility once Naglazyme was moved to Galli East, and then ultimately to our Shanbally facility in Ireland. The nimbleness employed to manufacture Brineura speaks to the creative effort put forth across technical operations to bring this therapy to patients as quickly as possible.

With Naglazyme production now exclusively occurring in Galli East, we challenged the Galli West team to ramp up Aldurazyme production to build up enough inventory to allow manufacture of Brineura for the ongoing clinical studies. To add to the challenge, we were using a new, single-use bioreactor technology that we had never used before for GMP production.

We were following the plan that had worked well for Vimizim. We would produce enough material to support phase 1/2 studies out of Galli West and then later transfer the process to our new facility in Ireland for phase 3 and commercial supplies. The clinical plan, however, was in flux. There were ongoing negotiations with the clinical investigators, FDA and the EMA. An aggressive plan to conduct a single phase 1/2/3 study using a natural history control was developed and initiated. That decision had tremendous ramifications for technical operations and set in concrete requirements for where we could make the product.

Complications grew when Brineura was designated as a combination drug-device product because of the pump and syringe we used in

its delivery. These two items had been approved for delivering drugs through the lumbar region of the spine but not to the brain directly. This nearly derailed the program and sent our team scrambling to make deals with the manufacturers of the pump and syringes to secure the necessary data we needed for the FDA submission.

In all, Brineura was produced in three different facilities (Galli North, Galli West. and Shanbally) and filled into drug product both in the United States and Germany over a three-year period. The activities to support the regulatory approvals in such a short period of time relied on our experience and thorough contingency planning, working hand-in hand with health authorities, contractors, and clinicians in both the United States and Europe.

The three-and-a-half-year journey from first-in-human to product approval was intense for all involved but well worth the effort. The devasting nature of this disorder and the strong clinical data were the common denominators that had health authorities, contractors, clinicians, and the full commitment of BioMarin rallying for children and families that were holding out hope for Brineura. The extraordinary effort by technical operations was met with equal determination from clinical operations in setting up and conducting the study and in answering hundreds of queries from health authorities. The commercial group was equally challenged and successful in developing early detection testing that identified afflicted patients while there was still time for them to benefit from treatment. Administrative functions in legal, finance, and information management engaged as well. Given more time we could have proceeded more deliberately, but at what cost to patients? The system worked as intended with scientists, clinicians, contractors, suppliers, and health authorities working together to ensure product quality standards were not compromised, and that rigorous science was applied and diligently reviewed. As drained as we felt at the time of that approval, the emotional and professional satisfaction was palpable as we celebrated the most rapid development project in company history.

With all of the manufacturing challenges resolved with both FDA and EMA, we were well into the planning cycle for the transition of the bulk manufacturing process to our plant in Ireland. The challenge was less

about technology and more related to scale-up, logistics, and defining the schedule. It was a complicated validation as we scaled the cell culture process 15-fold. Now one bioreactor produced more material than could be purified in a single purification cycle. Decisions pertaining to the number of purification cycles were made and a diligent effort was put forth between the process development team in California and the Manufacturing Science and Technology team in Ireland. The validation effort went well, and we submitted applications to the FDA and EMA within a few months of the initial approval. We received first-cycle approval in both regions. We never had to manufacture Brineura bulk product in the Galli West suite again as we now do that in Ireland exclusively. But how we came to manufacturing product in Ireland is another story.

5.

One Man Gathers What Another Man Spills

Science is bound by the everlasting vow of honor
to face fearlessly every problem which can be fairly presented to it.

Lord Kelvin

The Galli East buildout was still months away from completion, but the wheels were being put in motion for adding more manufacturing capacity before the concrete had barely set. While Galli East would more than quadruple our capacity, it did not alleviate the concern that we were manufacturing two commercial products and all four of our clinical products essentially in a single building with no redundancy. We had planned to begin manufacturing in Galli East in April 2010, but the team was having difficulty validating some of the equipment, balancing the airflow in the facility to meet prospectively defined requirements, and generating the environmental data needed to complete the commissioning requirements to begin production.

We would need to start production in this new facility within the next few months to support the anticipated start of the Vimizim phase 3 study. The time to begin production was well established and we were rapidly running out of runway. It was essential to be successful out the gate. The team was given an additional two months to complete the commissioning.

Game of chance

In early 2010, with Galli East work in full swing, discussions began with the team about what our long-term manufacturing requirements would be. We would need additional capacity beyond Galli East to produce commercial quantities of Vimizim once it won approval. We also wanted to expand our manufacturing network outside of the Bay Area to enhance business continuity. We focused on building a presence in Europe as we had significant fill-finish activities and generated a good portion of our commercial revenues there.

Chief Legal Officer Eric Davis and I were tasked with finding the location for our next bulk manufacturing plant. In June 2010, we headed to Switzerland to begin our search. Representatives from the various Swiss cantons, the member states of the Swiss Federation, showed us about a half dozen different plants that were for sale. Unfortunately, they did not have the right type of plant in mind for us.

We started in a metallurgy facility before moving on to a newspaper printing facility, and then on to a cheese factory. We toured a half dozen plants, none of which were designed to produce biopharmaceutical products. When we further explained our needs and why these facilities would not satisfy them, they took us into the countryside and showed us field after field in the middle of nowhere. They were pretty settings and would have been great if we were shooting a sequel for *The Sound of Music*, but they were disconnected from any existing biopharmaceutical industry presence. While Switzerland is home to some of the largest drug companies in the world, we were being shown property that would not only saddle us with the cost of building from scratch, but where there was no adjacent talent pool from which we could draw staff. We saw nothing that made sense and we returned home.

In early July 2010, the two of us set off on our next reconnaissance trip. We were headed to Dublin where the Irish Development Authority (IDA) was coordinating our visit. IDA is focused on attracting direct foreign investment into the country. We already had a toehold in Ireland as we had established a small, two-person contract manufacturing office in Dublin a year earlier. The two-person staff there oversaw our

fill-finish activities in Germany, as well as our manufacturing activities in Switzerland and France. Since we had already decided to set up an office in Dublin as a base from which we would manage our contract manufacturing relationships in Europe, it made sense to look for manufacturing facilities in the same country. It was a difficult time for Ireland as the Great Recession had taken a toll on the country. It had been more than two years since any companies had made a direct foreign investment in the country. In 2007, Ireland was viewed as the Celtic Tiger. By 2010, though, the tiger was on the run as the global economic downturn took its toll.

IDA was welcoming and gave us an expansive tour of the country. The IDA team introduced us to academics at Trinity University and University College Dublin to demonstrate the deep knowledge of biotechnology within the country and the fact that the next generation of students were being trained to enter the industry. They took us through Athlone where they showed us a fill-finish plant. It was not the right fit for us, even if we were in the market for a fill-finish facility. We were beginning to worry once again that we would not find a suitable property to meet our manufacturing growth. At least the IDA was taking us to biotech facilities rather than cheese factories. Prior to dinner with the IDA folks, we took a call from a consultant with whom we had been working to identify potential locations. He told us that Pfizer was about to put a new plant in Shanbally on the market. Shanbally was a town in the southern part of Ireland in County Cork.

The IDA team said nothing about the Pfizer facility. As dinner wore on, we finally broached the subject. We told our hosts that we had heard that the Pfizer plant was available and that we would like to tour it. They reacted oddly. They did not want to discuss it. They said it's not for sale yet and that we would not be able to get in there. As the dinner progressed, we continued to press the matter without getting much of a response. "We've travelled 6,000 miles to invest in your country and you are telling us something is coming for sale, and you are not going to show it to us?" I finally said with exasperation. " Why don't you see if we can get into the plant tomorrow."

The next day in the afternoon we toured the Pfizer Grange Castle facility that the company had obtained when it acquired Wyeth in 2009. This was a huge facility that had cost more than $1.5 billion dollars to build. In fact, it was the acquisition of this facility that made the Shanbally facility redundant capacity in Pfizer's manufacturing network. We kept pressing our IDA hosts the next day and they finally agreed to get us in to see the plant towards the end of the afternoon, but we were given strict instructions for how we would tour the facility. We were told to use only our first names and that we should offer no business cards while there. The sensitivity had to do with the fact that Pfizer had not yet announced its intention to sell the plant.

The Pfizer plant in Shanbally was a $200 million gem of a facility. It was the fourth biotechnology plant the company had developed, and they had gotten everything right this time. It was love at first sight. When we left the plant, I turned to Davis and said, "We have got to figure out how to buy this facility." After Pfizer announced in 2009 that it would acquire the pharmaceutical company Wyeth for $68 billion, it needed to eliminate redundancies between the two companies. It developed a plan to reconfigure its global manufacturing plant network. Pfizer slated a total of eight plants for sale including the new one in Shanbally.

When we returned home from Ireland, it was time to review progress the team had made in completing the commissioning of the Galli East plant. Much progress has been made over the past two months. The facility had passed all requirements and we were prepared for the start of operations in compliance with Good Manufacturing Practices (GMP). We set August 1 as the date to crack open the vial of working bank cells (biotech slang for starting GMP production). There were two reasons to start GMP operations on August 1. Doing so established a timeframe for production that would align with the clinical team's plans to start the phase 3 study for Vimizim. The other reason was that our next board meeting was scheduled for August 1 and it was important to be able to tell the board that we had begun GMP operations in the Galli East facility so that we could pivot the discussion to our next potential manufacturing investment.

In approaching Bienaimé about buying the Shanbally plant it was apparent that additional spending on a new facility would be challenging. Though he laughed at first when I broached the subject, he remained open to making a modest, non-binding offer to ensure we were in the game when Pfizer put the facility on the market. At the meeting, the board was happy to learn the good news that Galli East was GMP operational. I praised the team for the great job all had done to reach this significant corporate milestone and reassured the board that we were on track to support the phase 3 Vimizim study. "Thank you for your support," I said. "Now let me show you the next plant we need to buy" as slides of the Pfizer Shanbally facility were being projected onto the boardroom screen.

The paint was barely dry on the $60 million Galli East buildout, so the boldness of the proposal drew a few chuckles from board members. Nevertheless, Bienaimé and the board approved a nonbinding bid for the Shanbally plant, and in September we offered Pfizer a placeholder amount for the plant. Over the ensuing 10 months we successfully acquired the plant for $48.5 million and committed to hire 150 people to bring the plant into operation.

Building a team

Daniel Patrick Maher is an Irishman, born on St. Patrick's Day, an avid fisherman, and was senior vice president of product development at BioMarin. He was with me in Ireland on the day we acquired the Shanbally facility on June 23, 2011. We were there to talk with the hundred or so employees who had many questions about who BioMarin was and what our plans for the facility were. A mixture of emotions was sweeping over me as Maher led off the meeting with introductions. Co-leading the business development negotiations with Davis to acquire the facility had taken ten arduous months and was tremendously gratifying. Our plans were to slow walk starting operations at the facility and we were to hire only ten of the people crammed into the canteen to meet us that day. There were many unknowns about the costs and the need to acquire this facility. Awaiting my turn to speak that day, one thing was certain:

success was going to be a daunting task. Like the skilled fisherman he is, Maher's poignant opening words set the hook for the people in the room. It also centered me and encapsulated the reason BioMarin exists. "If you remember nothing else I say today, remember this," he said. "We are the company that helps sick children get better."

Before we were ever going to be able to employ large numbers of people and put the plant into production, we had to first shut it down. The factor driving when we would begin full production of Vimizim depended on if and when the FDA granted us approval to market it. The fact was we had bought this facility nearly eighteen months before we would have the clinical data to support approval of Vimizim. It would take another eighteen months to gain approval once we had that data in hand. At the time, the Galli East capacity was just revving up. We were making this investment five years before we would need the capacity, assuming the clinical data for Vimizim warranted approval. That meant we would initially need a skeleton crew to maintain the plant once Pfizer went through an orderly shutdown. We worked closely with Pfizer to assure they put into place a rigorous process for shutting down operations so that we would be able to show health authorities that all of this was done in a deliberate and proscribed manner. While we were five years away from presenting the shutdown plan to health authorities during an inspection, the strategy for the opening presentation was being formulated and it would start with how we handled the transfer and shutdown. Pfizer impressed me with its approach to transferring the facility and the diligence that its staff put into the planning and execution of the plan, especially as most of them knew that they would not be continuing to work at the plant.

The plan was to hire only 10 people to maintain the plant. We interviewed more than 125 people over a period of a few weeks. We whittled down our list to 20 candidates and broke them into groups, assigned them problems to solve, and then asked them to present their solutions. They did such a good job that it did not help us whittle down the group by much. We finally hired 12 people and one temporary employee.

A year after we purchased the Shanbally facility we held a Rare

Disease Day event to introduce BioMarin to the community. We invited elected officials, dignitaries, site heads of nearby biotech facilities, and the press. About a hundred people in total were invited to tour the facility. The highlight of the day was a presentation from Chris Hendrix, the lead investigator for our ongoing phase 3 program for Vimizim, and one of his phase 2 patients who had been on the drug for several years. Hendrix laid out the biochemistry, clinical manifestations, and difficulties in conducting clinical studies for MPS IVA. Our patient stole the show. Elevated in a motorized wheelchair, she described the challenges of living with MPS IVA before treatment and the profound improvements in her quality of life resulting from the therapy. She talked about her plans to become an author and how she looked forward to life knowing that a treatment that was made available to her through the clinical program might soon be available to all patients who suffer from MPS IVA. As we got ready to start the tour of the facility, one of the other site heads came up to me and said that he had been in the industry for 15 years, but this was the first time he had gotten to meet a patient.

Over the years BioMarin has honored the patients who have put forth the time and effort to be part of our clinical studies. You can feel the lift everyone on the site experiences when patients and their families who benefit from our medicines visit our facilities and they put into words the tangible outcomes of our work. We take pride in providing tours to patients and their families through our facilities where we make the products. Our employees have described a deeply felt humility and the powerful charge of motivation that emanate from these interactions with patients. It makes our work that much more meaningful.

Newspaper and radio coverage following the event at the Shanbally plant described our patient-focused commitment to science and the development of treatments for rare genetic disorders. We decided to follow up that Rare Disease Day event with a Biotech Career Day event in September thinking it would be a good opportunity to meet the talent pool in the area because we would need to begin staffing up as we moved to restart operations at the plant. The event got little attention in the press, but there was good word of mouth in the community.

As the event neared, we were astounded to learn that more than 700 people had registered. It was not just former employees from the Pfizer plant but many other employees from the greater biotech community. It also attracted the attention of people who had never worked within the industry. We made multiple presentations throughout the day. We met with everyone who showed up and gave them all at least a five-minute interview. We then followed up afterwards and we did hire people who showed up that day. It was my first real sense of what our direct investment in Ireland, the first such investment since the start of the Great Recession, meant to the community. As BioMarin grew its presence in Ireland, we would strive to become part of the community beyond just creating jobs.

We planned to keep the manufacturing side of the Shanbally plant shut down for two years. In the meantime, we devised a plan to bring online the quality control laboratories sooner to facilitate our European in-country testing requirements. The plan was to wait until November 2012 when we expected to have positive phase 3 results for Vimizim to make sure the data warranted an approval before we would make substantial additional investments. When the clinical trial results proved positive, Bienaimé asked me whether we had enough capacity in Galli East to delay staffing up Shanbally and put off the associated $50 million in spending, construction, and process performance qualification expenses that would be needed to get the plant licensed for commercial production. His concern reflected the fact that despite the positive results, there was still much work to do with health authorities to assure they recognized the clinical benefit of Vimizim. We reviewed our capacity and planning assumptions and informed Bienaimé that we could delay the buildout for a year.

We now had thirty people in Shanbally in November 2012 and had the need to inform them and the IDA that we were going to wait another year before making the plant operational. The team was disappointed, but readily took up the challenge to rethink our plans. The resiliency of the team struck me. They dug right into the planning assumptions that had been made to see whether they were still valid. At dinner that

night I told our site head Michael O'Donnell how impressive it was to see the willingness of the team to move past the disappointment of the delay and get to the task at hand. He told me that the forthright discussion about the reason for the delay sat well with the team and that they respected the transparency in how both good and bad news was being communicated in an open fashion. During the next three months, the team drilled down on the assumptions to determine what the rate-limiting factor was for the facility in terms of capacity and throughput. They used many of the processes we had developed in our "GalliMax" efforts to figure out how to maximize productivity. In fact, they even took on the moniker of "ShallyMax." They determined that the second floor was not strong enough to support the weight of the buffer needed to purify the output of more than three bioreactors. As had been the case in our Galli North build-out, reinforcement of the floor to hold additional liquid weight was part of the solution in increasing production capacity. Investing $150,000 in steel to reinforce the floor while storing buffer in double high containers doubled the capacity of the plant. The decision to wait a year for the buildout was paying unforeseen dividends beyond delayed spending. The extra time afforded us the opportunity to rethink our assumptions and come up with a revised plan to double the perfusion capacity of Shanbally to six bioreactors with little incremental facility costs beyond the additional equipment. What seemed like a drastic delay of a year gave us the time to devise an even better plan and added tremendous value to the company.

One of the things we did before putting the plant into production was to bring the Shanbally leadership team out to California. We had them go through an orientation and meet the board of directors. We established a best practices forum and were able to improve operations at both facilities. There were some powerful learnings that came out of the best practices forum. For example, in Ireland they had a clever way of recycling wastewater. We were not doing that in the Galli facility, and we implemented some of that to cut down on our water usage substantially. Cross fertilization continued to take place across the board in analytics, bioprocessing, and quality systems.

We spent about a year sending people back and forth from Ireland to California. We embedded our Irish employees in manufacturing campaigns in Galli. We would have people from Ireland come and work in process development or manufacturing for three months during Vimizim campaigns. This helped expose them to BioMarin's culture and our way of doing things. Likewise, we sent people from California to Ireland to help them understand the capabilities we had in Shanbally and to tailor processes that could be readily transferred.

It takes a village

Our CFO Dan Spiegelman once stated that "buying a facility is a gateway drug to more spending." It was an acknowledgement that the purchase price is just the start of the spending. We still had to hire people, build labs, and make facility modifications. He was correct that our acquisition of this facility would lead to more spending.

When we purchased the plant, Pfizer had not completed the entire buildout. Pfizer did enough work to get it to a point where they could sell it as a fully integrated plant that was ready to go, but it had a lot of empty space that we were able to repurpose without destroying what was already there.

Shanbally was built as a fed-batch facility that was designed to make monoclonal antibodies. When we first saw the plant we were not working on Brineura, our first fed-batch product. We wanted to produce Vimizim there through a perfusion process, so we needed to buy equipment to do that. Before acquiring the plant, it was envisaged we might have to destroy some or all of the fed-batch capabilities of the facility to accommodate a perfusion process. Once we acquired the plant and got the Novato process people together with the Shanbally staff, we began to evaluate the many good ideas that emerged. We brainstormed on ways we might be able to run a perfusion process product there while leaving the fed-batch capabilities intact. There was clean room space that was being utilized for cubicles within the facility so that was easily reclaimed for manufacturing production.

One of the things that struck me upon seeing the facility was the 20-foot-wide corridors, some of which were 100-feet long. I joked at the time to the Pfizer folks that if they had come to our plant in Novato, they would realize they could set up the entire perfusion process in the corridor. People rolled their eyeballs at that comment. When we did put in the perfusion process, we created the room to do so by extending the wall of the clean room into the corridor by five feet to create enough space to accommodate the cell culture, harvest hold, and the ultrafiltration/diafiltration processing areas.

One consequence of moving the wall was that the existing lighting in the corridor was no longer centered. The movement of the wall had created more than 500 square feet of critical manufacturing space. O'Donnell asked if we should recenter the lights in the corridor. When informed it would cost $65,000, my response was "leave the lights as they are and if you hire anyone who says something about the lights, let them know how we used the hallway to maximize manufacturing space." To this day the lights in that one corridor are not centered.

The transfer of Vimizim was filled with the types of challenges and successes associated with any facility start up. Establishing how to perform scale down runs in the manufacturing science and technology lab required a major plumbing renovation. Transfer of the cell-based bioassay required the buildout of a new laboratory. Vimizim did go on to become BioMarin's biggest product and production in both the Galli East and Shanbally facilities was needed to meet commercial demand. The bet had paid off big time.

It was fortuitous that we were able to devise a plan for Vimizim perfusion manufacturing that left the fed-batch capabilities of the facility completely intact. As Brineura became a part of the pipeline and we won approval for it, we were able to make use of the fed-batch equipment originally installed in the facility. We now also produce Brineura in Shanbally. In addition to reinforcing the floors to expand our capacity, there were other investments we made. We added redundancy to the utilities to support the perfusion process.

We had to disconnect ourselves from the adjacent Pfizer facility that was supporting our power and wastewater treatment requirements. We also created the company's first packaging line and brought in the label and package operations that were being performed through a web of contractors. We also later built a three-story office area to accommodate all the employees we have there today. We added an analytical lab dedicated to the testing of cell-based and gene therapy products. Over time we would spend more than four times the initial purchase price to build out the facility, but we now have two commercial products in production there, analytical testing capabilities for small molecules, proteins, and gene therapy product, and label and packaging capabilities that allow us to distribute our products with exquisite control.

At the start of 2014, BioMarin initiated construction, validation, and the start of manufacturing operations at Shanbally. We were gearing up to begin making Vimizim there. We had about 50 employees at the plant at the time and then we announced plans to double that. In addition, we employed 65 construction workers during the expansion. By the end of 2016, the headcount at the facility would be approaching 300, and today we have about 400—far beyond the commitment we made to the IDA.

To expand the Shanbally plant and bring the facility online as a commercial production site required a company-wide effort. It came in conjunction with bringing new products online for commercial production at the company's facility in Novato, California. It also overlapped with the construction of state-of-the-art research facilities in our expanding headquarters in San Rafael, California and the buildout of our gene therapy capabilities in Novato. In an explosion of growth from 2008 to 2016 we were investing $100 to $150 million of capital a year into the infrastructure of the company as we more than doubled in size. To do this involved not only those within the operations of the plant, but virtually in all aspects of the organization.

In a four-month period in early 2016, BioMarin faced unprecedented, worldwide regulatory scrutiny as inspectors from the United

States, Japan, Brazil, Turkey, and Ireland reviewed the company's compliance with good manufacturing practices in Shanbally, as well as in Novato, California, and at several sites of contractors used by the company. A dozen inspectors collectively spent 30 days on-site conducting inspections while reviewing 2,500 documents covering all aspects of BioMarin's business. The successful inspections cleared the way for the company to start distributing product made in Shanbally in 2017.

Being in the conference room during inspections is just the tip of the iceberg. Under the surface there is tremendous support from groups throughout the company. No one would be surprised to find out that regulatory affairs and compliance provided tremendous support prior to, during, and after inspections. But so many other groups participated as well.

In an email to executives and the Shanbally staff following successful completion of inspections in 2016, I took the opportunity to recognize the company-wide effort behind the success. Technical operations relied on research, pre-clinical, and clinical data provided by development sciences to establish specifications and testing strategies. The information technology group established and maintained the infrastructure that assured the computer systems used to manufacture product and track data were reliable, robust, and compliant. The legal and commercial teams negotiated and assured that agreements—which specify how technical operations interfaces with its raw materials and equipment suppliers, contractors, and distributors—were in place and ready during inspections. And then there was the indirect but critical support provided by groups including human resources, finance, product development, business development, and others. All these group interactions required orchestration and organization against a well thought out plan. The functional heads across the company were supporting the efforts in a synchronized and coordinated fashion. It was not unlike musicians jamming together to create something that did not exist before. We were improvising on several different fronts simultaneously. It was a group effort to accomplish our patient-focused

goals. It does take a village to get a plant approved.

Shanbally would not be the last plant to be built out on my watch. There was one more project ahead for technical operations and that would squarely put BioMarin on the leading edge of biotechnology.

6.

Till Things We've Never Seen Seem Familiar

"In science novelty emerges only with difficulty, manifested by resistance, against a background provided by expectation."

Thomas Kuhn

In 2013, BioMarin CEO Jean-Jacques Bienaimé asked for my thoughts about the company licensing a gene therapy program for the treatment of hemophilia A. Gene therapies have the potential to radically change the landscape for monogenic rare disorders. Gene therapy products harness the natural capability of a viral vector to carry DNA into human cells while stripping the vector of any pathogenic properties. Using vectors as the delivery mechanisms to carry a gene needed to produce a protein that a person with a rare condition is unable to make naturally because of a genetic mutation offers the potential to restore biologic balance for long periods of time from a single administration. Though gene therapies had long been pursued, the activity around them gained momentum over the past decade as science advanced and their commercial viability became clearer. "For 30 years the goal has been to keep viruses out of the process," I said in response to Bienaimé's question. "Now you tell me it is the product. This will take some getting used to."

The idea of pursuing gene therapies was not new at BioMarin. In the first half of 2000, we conducted a few gene therapy experiments. But

in the ensuing years, the field of gene therapy advanced slowly and it would take another decade before industry embraced the therapeutic potential of gene therapies as the field matured. While my response to Bienaimé was intended to be humorous, it was also meant to convey the fact that we were going to have to be thoughtful about how we were going to manufacture a gene therapy product and consider carefully the challenges inherent in doing so.

BioMarin had been looking for an entry point into gene therapy and our due diligence efforts led us to the work of Amit Nathwani at the University College London's Cancer Institute. In February 2013, the company licensed the hemophilia A program from the University College London (UCL) and St. Jude Children's Research Hospital.

Patients with hemophilia A have a genetic mutation that prevents them from producing needed quantities of the protein factor VIII, which is essential for blood coagulation or clotting. Many patients with hemophilia A suffer from spontaneous bleeding events. Hemophilia A patients with a severe form of the disorder use a prophylactic regimen of recombinant factor VIII infusions as often as three times a week. Even with this treatment, many patients have multiple spontaneous bleeding events annually and suffer from progressive and debilitating joint damage.

Though hemophilia A is a rare condition, the market is substantially larger than the rare disorders for which BioMarin had previously developed products. While BioMarin had been targeting populations of a few thousand patients with its enzyme replacement therapies, hemophilia A affects about 90,000 people in the markets in which BioMarin does business. This represented an outsized opportunity, inherent with technical challenges, compared to any indications for which we had previously developed products.

BioMarin moved to bolster its in-house expertise in gene therapy. In 2013, it hired Barrie Carter to serve as vice president of vector biology. He had conducted basic research pertaining to vector biology and published one of the first examples of the use of vectors for gene transmission. There were many scientific challenges that needed to be addressed. Among those was how to deliver the gene needed to produce factor VIII. The factor VIII gene is so large that it approaches the storage

capacity of the vector. To get it to fit inside the vector, we used a cleverly designed codon-optimized version of the gene.

But it fell to technical operations to figure out where and how we were going to produce a gene therapy product while meeting the timelines and product demands of the clinical and commercial teams and the evolving technical and compliance requirements being developed by health authorities. There were few if any people in the company who had experience working on manufacturing gene therapy products. When Bienaimé asked how long it would take and how much it would cost to generate clinical material, the team was at a loss. Nevertheless, we did our best, based on our recombinant DNA experience, to calculate a rough estimate and projected that it would take 18 months and $12 million. Although the time and cost estimates turned out to be accurate, we did not know that at the time, but figured it gave the team the time and resources to determine the right answer while making progress.

At the crossroads

Though our first staff meeting after licensing the hemophilia A program was filled with enthusiasm from people who wanted to be involved in developing a gene therapy product, the reality was there was not a lot of direct experience with this new modality in the room. As we gained more information about the product, the timelines, and the expectations, we came to realize that there was nothing about our approach to process development utilized for our recombinant proteins that could not be applied to gene therapy. We leveraged our understanding of manufacturing biotechnology products and used our well-established approach to strategic process development.

Instead of creating a new organization structure that would segregate gene therapy process development from protein development, we decided to integrate activities into upstream and downstream operations. There was significant overlap for the types of processes that would be developed. This allowed us to leverage the experience gained from developing protein processes while maintaining continuity in terms of the technical development organization structure. It also eliminated any notion that only certain groups could work on the gene therapy products.

Rather than establishing an elite gene therapy group, we were able to use the desire for career development that employees had to serve as an enticement. Working with BioMarin's research team, we developed methods and processes that not only resulted in consistent manufacturing of this new therapeutic modality, but also elucidated the mechanism for how the product was metabolized within cells to generate durable expression of the gene of interest. Patients in the phase 1/2 studies have demonstrated therapeutically relevant levels of factor VIII expression for six years and counting from a single administration of the product, and have had drastic reduction in factor VIII usage (98 percent) and annualized bleeding events (85 percent) as compared to standard of care. A phase 3 study has substantially confirmed these results. The UCL team had used a process for producing the gene therapy product in human cell lines that would be challenging to scale up for commercial production. The scientists had used what is known as a "hyperstack," a series of plates stacked upon each other that are placed into an incubator to grow the vectors in human embryonic kidney (HEK) cells. This may have been the state of manufacturing in 2013, but this was a manual process that required scraping cells from the plates and was ill-suited for expansion to a commercial scale.

The team was also troubled by the thought of using human cells to grow the vector because it increased the risk of other unwanted human viruses getting into the mix and contaminating the product or the potential for the transmission of oncogenes. One reason Chinese hamster ovary (CHO) cells are widely used to produce recombinant DNA products is that human viruses do not readily propagate in them, and the risk associated with oncogenes is virtually nonexistent. Even though HEK cells were being used to produce vectors, we challenged ourselves to evaluate other production systems.

Through discussions with Carter, we identified an insect cell line from moths as a potential alternative. We utilized a contract manufacturer and had it produce material in both insect and HEK cell lines so we could conduct a head-to-head study. When the insect and HEK preparations were tested in a mouse model we found there was no statistical difference between the factor VIII expression levels.

There was a distinct manufacturing advantage to using insect cells for production. If we used human cells, we would need to use a process of transient transfection each time to introduce the genetic material into the cells, which was prone to variability, enhanced regulatory scrutiny, and created capacity concerns for producing large quantities of expensive starting materials. The process with insect cells was more streamlined and much more akin to producing a recombinant protein. Vector titers were also substantially higher—40-fold or more—and the whole operation was scalable to large tank fermentation. The combination of higher titers and scalability to larger tanks offered the promise of substantially greater overall productivity and ease of operation.

A buy-or-build dilemma

After we licensed the gene therapy program, we began working with several contractors to produce material. The contractor that made the material comparing the HEK and insect cell production systems could only produce a small amount of research grade material. We contracted with another company to help develop our production process. As we thought about producing an experimental gene therapy for the first human clinical trial, Carter introduced me to Richard Snyder, director of biotherapeutic programs at the University of Florida, at a gene therapy conference we attended.

Our discussion morphed into a lengthy conversation about the manufacturing challenges and the merits and drawbacks of one system over another. We soon arranged to see his operation in Florida. It was what you would expect from a university operation. There were good technical people working in a facility that was grappling with the challenges of conforming to good manufacturing practices (GMP) in the emerging field of gene therapy. We worked with Snyder and his team to produce not only the initial material for the phase 1/2 clinical trial, but to facilitate operational improvements to enhance compliance. As it turned out we could only manufacture enough material to treat 15 patients. In essence, that set the limit for the number of patients recruited to participate in the study. It harkened back to our initial clinical studies for Naglazyme when

the number of patients enrolled into the phase 1/2 study was also limited by manufacturing capabilities. Over the course of our relationship, the university was in the process of spinning out their contract development and manufacturing organization called Florida Biologix.

We had modest ambitions at the outset of clinical studies about the level of factor VIII expression the gene therapy product would produce. We were waiting to see the six-month data and hoping to have expression levels of at least 5 percent of normal, but we saw levels approaching 70 percent of normal. As the level continued to increase, there were even concerns that we could see numbers well exceeding the normal range, but that wasn't the case. The factor VIII levels have plateaued over time but have been maintained in a clinically therapeutic range. In 2015, Fuchs began designing the largest phase 3 gene therapy study ever conceived. The scale of the study, 135 patients, dwarfed the capabilities of the contractor we had used to make the phase 1/2 material.

It was important to conduct the phase 3 study with materials made with the same process, scale, and facility we would use for commercial production. We were concerned that changing to commercial scale production after the phase 3 study would be challenging from a comparability perspective and might require performing multiple process validation studies and perhaps additional clinical studies.

After the 2015 spinout, Florida Biologix had been growing and was now a private company with backing from a private equity firm that specialized in biomedical services. In doing our due diligence we found that the private equity firm generally holds its investments for about five years and then sells them. While we were assured that with this investment everything would remain the same, our previous experience with contactors had taught us when new owners acquire the business, it can often result in disruptive changes that create problems. The assurances were typical of what other contract development and manufacturer organizations had told us only to see those companies later sold. Within a year of the private equity investment, Florida Biologix was rebranded Brammer Bio and was eventually acquired by Thermo Fisher almost four years to the day from the initial investment. It maintained the Florida operation for phase 1/2 clinical production and planned to expand into

Massachusetts for phase 3 and commercial production. In 2016, we began discussing having Brammer Bio produce our phase 3 and commercial gene therapy product.

The plan for Brammer Bio was to continue to use the Florida facility to make early-stage clinical material. It had purchased a building in Lexington, Massachusetts and suggested converting that into a gene therapy production facility with BioMarin as its first client. This facility would require an extensive buildout to accommodate our production requirements. In essence, Brammer Bio was saying, "Help us build the facility and we'll make your product." We didn't have many alternatives. There wasn't existing capacity within our facilities or well-established capacity to turn to other contract manufacturers.

While working with Snyder and Brammer Bio had a lot of appeal, the rising cost became concerning. By the second quarter of 2016, concerns about going the contract manufacturing route were becoming more evident. The cost was going to continue to rise as we moved to validate the facility and produce commercial volumes. The facilities team was tasked to evaluate what it would take for us to do our own manufacturing. A few years earlier, we had purchased a building across from the Galli facility on Leveroni Drive in Novato, California when we needed additional office and warehouse space. We began to explore the feasibility of converting the Leveroni building into a gene therapy manufacturing plant.

We now had two alternatives under consideration, both of which were risky and expensive. The first was to support our contractor and its ambitions to build a larger facility that would support our product demands. When Brammer Bio shared its plans to build out the Lexington building, there was uncertainty on the cost projections, timelines, or that the process could be scaled to meet the projected product demand.

The second alternative was to build the facility ourselves. While we knew we could convert the Leveroni building into a vector production facility, we would need to find a place to store equipment and house the 100 people who worked there. This created additional questions about when we needed to be in production, what process we were going to use to manufacture the product, and how much all of this would cost. The Leveroni facility was basically an office building with a high bay warehouse

area. It was not an ideal choice. It didn't have the requisite utilities, wastewater treatments, or loading dock. We put together a high-level plan to build our own facility and have material ready for the phase 3 study.

Building a platform

In June 2016, a presentation to the BioMarin board laid out the alternatives. Brammer Bio had an empty building they were willing to build out with our financial support. The timelines and cost were moving targets. On the other hand, we had a building we could use to construct our own facility. It could be used to make other vector products if needed. We could build a facility that could support up to 1,000 patients annually at a cost of $42 million. Our team had estimated building and commissioning the facility would take 14 months to enable production of GMP material to support the phase 3 study. The good news was the board agreed to fund our plan. The bad news was that the plan was not fully baked, and we immediately revised our assumptions.

The first order of business was to lease two buildings to relocate the people who we would need to move out of Leveroni and find a place to store all the equipment and materials in the warehouse portion of the building. It took until the fourth quarter of 2016 to resolve these issues, empty the building, and begin construction of the gene therapy facility. In the meantime, we discussed the design and scope of the facility. We found ourselves stuck between the budget and the process requirements. If we stayed within the approved budget, we would build an operationally constrained facility that would add millions of dollars to our annual operating expenses in the future. Exceeding the budget would increase the cost but would reduce operational expenses going forward. It also had the potential to increase the overall production capability of the facility.

Throughout 2016, the process development group refined the commercial process for producing our product. It ran experiments in a scaled down mode early in the year. By mid-year, we had locked down the scale of the cell culture activities. We settled on 2,000-liter bioreactors. The increased scale and duration of the cell culture process set in motion a detailed modelling exercise for what the downstream requirements needed to be in terms of column sizing and other aspects necessary for purification.

Defining the process requirements allowed us to drill down to plant scheduling and the number of operators that would be required to staff the plant for multi-shift operations. We found ourselves applying for permits while continuing to modify the scope of the project. This was different than the approaches we had taken for other construction projects. The board approved the Galli East expansion in late 2008, but we had been having what-if facility design meetings as early as 2005 for what that facility could look like when and if we built it. BioMarin acquired the Shanbally facility in 2011 and modifications to the facility underwent multiple revisions, eventually doubling the expected capacity when implemented in 2014.

For the gene therapy facility, we compressed the what-if phase from three years (for both Galli East and Shanbally) to three months. This was challenging as this facility introduced a number of firsts for the company. It would be the first vector facility we had built. It would be the first Biosafety Level 2+ facility we had built. It would be the first negative pressure facility we had built. It was the first buildout of a fill finish facility in company history.

It also coincided with the build out of the 85,000 square-foot BioMarin Research Center in San Rafael, our new headquarters, which represented the largest capital expenditure in company history, and the commissioning of the Shanbally facility. There was a lot going on for the engineering group. More than 10 percent of the people in the company—nearly 300— were focusing their efforts on the buildout of our vector facility and development of the commercial process and control system. Our collective experience from the multi-phase buildout of the Galli and Shanbally facilities helped to shape and focus our thinking relating to facility design. We had 15 years of facility design, construction, commissioning, validation, and manufacturing history to draw on and we needed every bit of it as the race against time hung over the project at every stage of planning and execution.

We decided to put the budget aside for a moment and to design the facility to maximize operational efficiency, capacity, and throughput. While the clinical studies to treat hemophilia A would be for our first gene therapy product, we were working on developing gene therapy products for other indications in research. We knew that we would be designing this facility for platform manufacturing where the process for one product

would be similar to another. We also anticipated that like our other facilities, it would likely be run as a multi-product facility where we would produce different products on a campaign basis one after the other.

We debated the constraints from a facility design, footprint, and scheduling perspective and challenged ourselves to find ways to maximize our output. We soon developed a design that doubled the initial capacity of the facility so it could produce enough product to support 2,000 patients per year. It was straightforward to project production outputs, but we still had to calculate how much additional cost this would require. As the team worked, it became apparent that any estimate on facility output and costs were just estimates as we had never run the process at this scale. As we moved closer to locking down the facility design, we conferred with the clinical and commercial groups to understand what other projects would be advancing toward clinical studies and what the potential commercial demand might be for these products. Once again, we were trying to get a clear view of a distant future to inform decisions that needed to be made in the present. Unfortunately, the crystal balls in the research and commercial groups were just as hazy as our own. It was too early to make definitive calls about future demand. It was up to our team to justify additional spending beyond the approved budget to achieve additional capacity and operational efficiency.

During the last three months in 2016, we evaluated the tradeoff for increased capital spending against increased capacity and greater efficiency. At the time, we had limited clinical data for our hemophilia A gene therapy program and there was a long clinical development road ahead, rife with risks and uncertainties. We took an incremental approach as new information came in on process improvements and facility design concepts. It was hard to know if all this information, once vetted, would stand up to scrutiny.

Our revised estimate was that the facility would be able to support up to 4,000 patients annually when fully equipped. Of course, there was no need to fully equip the facility from the start. Additional equipment could be brought into the facility as demand warranted. The critical point that management needed to understand was that we had to build out the facility now to accommodate more equipment later.

We received authorization for an additional $10 million of spending. What started off as a $42 million estimate to build a facility capable of producing enough vector to treat 1,000 patients annually grew to a $52 million facility capable of producing enough vector to treat 4,000 patients annually. At the next project team meeting, we were able, for the first time, to set concrete goals for time, scope, budget, and deliverables while also letting the team know that we had rubbed the lamp for the last time. No additional wishes were to be granted and no additional funding would be approved. With clear direction, the team went to work.

Box of rain

With an empty building and a finalized design, we began construction in January 2017 with a goal of starting the first GMP production run that August. Winters in the Bay Area can be mild, especially during relatively dry years. The winter of 2016/2017 was the third wettest on record. In nearby Lake Tahoe, the skiing was great as the locales referred to it as a "snowmaggeddon" winter with snowfall totals of 120 feet at the higher elevations. In Novato, rainfall totals reached 95 inches—more than twice the normal level. During the first three months of 2017, there were more than 10 days where more than two inches of rain fell per day with half of those days being greater than three inches per day.

Our construction site was flooded for days at a time and conditions on many of those days were too dangerous to work. Nonetheless, we maintained a perfect safety record with no injuries during nearly 300,000 man-hours of construction. The weather, at times, put a damper on the work, but our enthusiasm managed to hold up. The construction crew and our project team rescheduled activities over and over, based on the weather forecast. We added a second shift to make up for lost time and kept the project on track.

While construction was ongoing, the process development team worked with procurement to order the equipment to outfit the facility. The heart of the facility was going to be the cell culture suite where we would grow cells in a 2,000-liter bioreactor similar to the 200-liter bioreactors that were being piloted for the production of the initial clinical batches of Brineura. We would be using a relatively new technology,

certainly at this scale. Instead of using stainless steel bioreactors, our plan called for single-use bioreactors. The cells would be grown inside massive plastic bags suspended inside a metal housing. We were certain that we were the first company to produce a vector at the 2,000-liter scale. On the other hand, many unknowns remained, and the entire team got good at holding our breath. While we had some experience with this technology, it was at a much smaller scale. When the 2,000-liter housing was delivered, the entire team felt a jolt of excitement. In short order, we were going to get the answers to our scientific questions.

Since the facility was not ready for the housing to be installed, we set up the bioreactor in the process development area of the Digital Drive labs. The first development run at 2,000-liters provided some answers along with more questions. The performance and control system scaled beautifully to 2,000-liters from 200-liters. The productivity of the cells surprised us when they produced 50 percent more vector than we anticipated. This created several issues for the downstream purification team as they hadn't scaled it for such a high level of productivity. Fortunately, we were able to cycle the downstream purification so we could process all the bounty that was coming from the bioreactors. These results created the possibility of producing up to 6,000 patients a year worth of material from the facility.

Just a step at a time

Historically, BioMarin had relied on contract manufacturers to conduct all fill-finish operations. There was little to no capacity for filling of vectors in the contract world and we were debating how to proceed with fill-finish operations. This is a technically challenging area of pharmaceutical manufacturing that requires heightened attention to aseptic control. The state-of-the-art approach to fill-finish is to perform this ultimate step in the manufacturing process in specifically designed isolator systems. If we were going to build our own fill-finish operation, it was going to include state-of-the-art technology. The only problem was that we would need two of these isolator systems and they were special order items that required lead times of nearly two years.

Jack Regan, who previously ran Genentech's fill-finish operations, was now in charge of contract manufacturing at BioMarin. Regan was

attending a vendor show in Germany in early 2017 and while there called me to say one of the vendors who made isolators was hawking its wares at the meeting and had a floor model for sale. He was standing next to the isolator in a huge conference center when he called. As we discussed whether we should snap it up, I asked a few important questions. Was this vendor reliable? What type of fill-finish equipment was compatible with this isolator? Did they have a second one available? When asked what we should do, Regan was thoughtful and then put his stake in the ground. "Both time and opportunity are not on our side," he said. "We should go for it." With that, we started the purchase process. We bought the floor model and ordered a second isolator. That turned out to be a bit of good fortune and a $2 million decision made on the fly that was instrumental to keeping us on our timeline.

Our fill-finish challenges were far from complete. Not only did we have to get the isolator shipped, installed, and validated, but we had to purchase filling equipment and all the components that would be necessary for startup. Since we could only get one isolator, there would be a portion of the process, vial capping, that we would initially need to perform in a biosafety cabinet until the second isolator became available. To assure we maintained aseptic control, we placed the biosafety cabinet near the isolator and performed the capping of the vials as quickly after filling as possible. After searching the globe for isolators and setting up the company's first fill-finish facility, we anxiously waited for more than a month as we put the system through its paces and conducted three successful media fills.

As winter gave way to spring and the weather improved, we added a weekend shift as well. Equipment was coming in and installed on schedule. The last big hurdle we needed to clear was getting our utility company to lay a new line to power our facility. The facility was fully equipped, powered, and ready for commissioning, but we were still a bit behind schedule. The team worked out a plan where we could commence development runs with the newly installed equipment while simultaneously commissioning the facility. To comply with GMP regulations, we drafted, reviewed, and approved nearly 900 documents for the facility. Many of these documents could not be drafted until the equipment was

installed and validated. By the middle of August, we were ready to crack the vial, to produce GMP material for the upcoming phase 3 study.

The next challenge was to assure that we had approximately 75 knowledgeable manufacturing operators to run the facility. One of the benefits of building the vector facility adjacent to Galli was that we had 500 trained people working in Galli, albeit on recombinant protein products. When we issued a call for staff who might be interested in moving across the street to help start and run the new gene therapy facility, we got an enthusiastic response. In all, we transferred more than 50 employees to the gene therapy facility and hired 25 additional people with unique skills in vector production or fill-finish operations.

Gotta make it somehow on the dreams you still believe

We were now ready to manufacture the first vials. On December 17, 2017, we filled the first vials intended to be used in the phase 3 clinical study. It would take until March 2018 before we would submit all the documentation and required test data to gain U.S. Food and Drug Administration (FDA) authorization to distribute clinical material made in the Leveroni facility at what was then the largest scale for vector production ever performed.

Going from board approval to FDA authorization took 21 months. In total, we made five production batches during that campaign and produced all the material, and then some, to conduct the phase 3 study. In addition to the material itself, we gained valuable experience and garnered important process and product knowledge that was built upon to perform the process performance qualification that was to follow in 2018 and led to the submission of marketing applications in the United States and Europe in 2019, just four years from the time we had dosed our first patient in 2015 and six years from the license of the program from UCL in 2013.

The facility also won the prestigious International Society for Pharmaceutical Engineering award for Facility of the Year in the project execution category and gained GMP certification after an inspection by the European Union. The project encapsulated 20 years of TOPS experience and tapped the strategy we had devised and refined for designing, building, and commissioning complex biological production facilities. Our approach to the development of gene therapy technology is a

testament to the tenacity of BioMarin's creativity, ingenuity, and spirit. With the experience in hand of running the facility at scale, we revised our estimate for production to 10,000 treatments annually.

I don't trust to nothin', but I know it comes out right

At the end of 2019, BioMarin submitted a Biologic License Application to the FDA for approval to market Roctavian, our hemophilia A gene therapy. The submission was based on interim analysis of the ongoing phase 3 study and three-year data from the phase 1/2 study. The European Medicines Agency validated the company's Marketing Authorization Application for the gene therapy on the same day.

In August 2020, the FDA notified BioMarin that it would not approve the gene therapy based on the existing interim clinical data. Instead, the agency wanted to see greater evidence that the gene therapy produced a durable effect and asked for the complete two years of data from the company's ongoing phase 3 study to reassess approvability.

The agency recommended that BioMarin complete the phase 3 study and submit two-year follow-up safety and efficacy data on all study participants. BioMarin completed enrollment of the phase 3 study in November 2019, and the last patient completed two years of follow up in November 2021.

The company had previously withdrawn its application from the European Medicines Agency after it was determined that it would not be able to provide data the Committee for Advanced Therapies (CAT) sought relating to the results of clinical studies within the current procedure.

At the start of 2022, BioMarin reported results from the phase 3 GENER8-1 study for Roctavian. Two-year phase 3 results showed a consistent clinical benefit as measured both by Annualized Bleeding Rates (ABR) and reduction in the need for factor VIII treatments. Phase 3 and phase 1/2 studies with Roctavian found significant reduction in ABR by 85 percent from baseline. The gene therapy treatment also reduced the mean annualized factor VIII infusion rate in the rollover population by 98 percent from baseline.

Throughout the development of Roctavian we worked closely with clinical operations, research, and regulatory affairs groups to supply

clinical material for the studies, develop assays to unravel the molecular biology of vector metabolism, and to address hundreds of questions posed by health authorities. While the learning curve was steep, we relied on our collective experiences in building facilities, developing processes, creating analytical controls systems, and conducting comprehensive characterization studies in answering vexing questions and removing concern as we developed our gene therapy treatment for hemophilia A.

The European Medicines Agency validated BioMarin's resubmission of the Marketing Authorization Application, and a Committee for Medicinal Products for Human Use (CHMP) and Committee for Advanced Therapies (CAT) had rendered a positive opinion recommending approval of the product in June 2022. On August 24, 2022, the European Commission approved Roctavian for adults with severe hemophilia A. The one-time infusion is the first approved gene therapy for hemophilia A and works by delivering a functional gene that is designed to enable the body to produce factor VIII on its own without the need for continued hemophilia prophylaxis, thus relieving patients of their treatment burden relative to currently available therapies. The approval of Roctavian and the Leveroni facility for commercial production represent a breakthrough in science, a milestone in medicine, and a capstone accomplishmen for BioMarin. The challenges met and overcome within technical operations relied on a streamlined approach to strategic process development and an organized systematic approach to decision-making along with a relentless commitment throughout the company to persevere for the benefit of patients afflicted with hemophilia A.

7.
Well, I Ain't Always Right, But I've Never Been Wrong

It is through science that we prove,
but through intuition that we discover.

Jules Henri Poincaré

Einstein referred to intuition as a "gift" in contrast to the rational mind, which he called the "faithful servant." Some people think of intuition as an instinct, perception, or sixth sense. It can come to your mind in a flash as a hunch, insight, inkling, or suspicion. All of us are blessed with the gift of intuition. But much like a muscle, we can strengthen it. We can strengthen our intuitive muscles by asking questions that limit uncertainty, validate assumptions, and resolve constraints. Through repetitive exercise, the skill of intuition can be developed and is an important component of effective decision-making. Intuition is a critical part of success in biotechnology. We develop our intuition by taking today's circumstances and comparing them to our individual or shared experiences. Things that have worked for us in the past will likely work again in the future, even if we lack the data to prove it. Sometimes, though, challenges arise that require creative solutions that result in the need to flex our intuitive decision-making muscle. To be successful, though, it is essential to strike a balance between the use of intuition

and the rational mind. Therein lies the secret to good decision-making.

The complex information that a biotechnology company must process to come to good decisions should, as often as possible, be based on sound data. The data must not only be scrutinized internally for scientific validity, but should then be viewed through the prism of regulatory and business criteria to assure that solutions can meet general and specific expectations.

In reality, data sets are sometimes incomplete because the needed information cannot always be known at the time that a decision must be made, or we do not know how to generate the data we need. We would all prefer to take the time to collect more data and delay decisions to rely on the faithful servant rather than the gift. But often, time is a resource we lack. Waiting for complete data to be collected is not always an option and delays can result in additional costs and lost opportunities. Decisions in biotechnology companies, at times, must be made before all the ideal information can be known. In those situations where there are multiple options to choose from and limitations on the time to decide, intuition can be a valuable tool to apply for setting a course. The challenge is to determine how much information is needed to make a good decision that is likely to be correct and that optimizes time, cost, quality, and compliance while minimizing risk.

Most of the operational decisions that have been critical to BioMarin's success have been made using the rational mind rather than relying on intuition. Much of the data-driven decision-making occurs in the background with diligent people using their expertise to generate, analyze, and organize both scientific and business data that, to the untrained eye, blurs the line between data-driven decision-making and intuition.

Consider BioMarin's 2011 acquisition of Pfizer's Shanbally, Ireland facility. At first take, acquiring a new facility for a fraction of the cost of building it in a business-friendly country where people speak English would seem like a straightforward decision. Upon closer inspection, though, the complexity of that decision and the interplay between rational thinking and intuition were critical in convincing management that this was a prudent acquisition. At the time, BioMarin was completing a $60 million expansion of Galli East, the largest capital expenditure in

its history. The Galli East facility at that point was still 18 months away from its first of many health authority approvals. While two of our enzyme replacement therapies, Vimizim and Brineura, are produced in Shanbally today, the company was just starting to enroll patients into the phase 3 study in support of Vimizim approval and Brineura was a preclinical program at the time the Shanbally acquisition was first presented to the board. It would take the better part of a year to gain board approval and negotiate the deal. It would take five years from the board presentation to the production of the first Vimizim bulk drug substance batch at Shanbally.

Rationalizing the acquisition relied on envisioning the needs of the company several years in the future, which we couldn't know with certainty at the time we acquired the plant. Nevertheless, having this facility would be integral to solving those future needs. While the purchase price of the facility may have been a bargain, the ongoing costs to alter it and bring it online were substantial. We had to be thoughtful about how we maximized the facility and the investments we made to do that, but those costs could not be accurately determined at the time we acquired the facility.

Often, what looked like intuitive decisions were, in fact, data-driven decisions based on perspectives from experts and input from stakeholders across the company. One of the keys to good decision-making is to determine early on what decisions need to be made and by when so that the team could drill down on the issues and provide approaches in a timely fashion. As part of that process, it is critical to test any assumptions to ensure that they are valid and represent actual constraints. We applied this iterative process to not only facility acquisitions or expansion, but also to process development and validation activities that ultimately defined our chemistry, manufacturing, and controls regulatory strategies. All this work was underpinned by fastidious modelling and an unwavering commitment to developing sensitive analytical methods to ask important scientific questions with the hope of unraveling the structure, function, and relationship between the molecules we were manufacturing and their desired biological properties. At times, data sets

were incomplete when time constraints forced us to make a decision. It is at those times that intuition comes into play. While we could not be sure what activities would be appropriate to move to Shanbally, it was evident that the utility of having that facility was greater than the uncertainty about what products we would produce there. Even though many uncertainties remained, BioMarin moved forward to acquire the plant.

Fundamental to this decision-making process was what BioMarin advisor Stuart Builder referred to as "thought experiments." Thought experiments were a process we used often to ask what-if questions. In many team meetings, we discussed what would be the benefit if something was experimentally true. Only if the benefit was sufficiently large—or removed some significant constraint in terms of time, cost, quality, or capacity—would we expend the resources to generate the data to validate the concept and realize the benefit. In this way we created a culture where people thought about what on the surface seemed like outlandish and risky proposals, but ones that we could refine or reject quickly with tailored effort. No one took offense if we dismissed their ideas for not being viable. Through this process, we collected hundreds of ideas and sorted them through our collective experience and available data. When they seemed to remove constraints or clarified previously held assumptions, only then did we consider putting effort into further exploring them.

The decision PIPE

Core to our approach for making decisions was the biotech **PIPE**. PIPE is an acronym for describing **p**roducts, **i**mpurities, **p**rocess, and **e**quipment. Knowledge about each component of the PIPE is fundamental to our process development activities, facility design, operational controls, and decision-making. Underpinning our product and process knowledge was an orthogonal approach to analytical characterization that was applied to assure that our conclusions were valid. With this deep understanding we could then craft creative and flexible strategies for developing robust process development, manufacturing, validation and testing plans in compliance with regulations. This approach supported rapid development activities across a wide variety of product modalities.

BioMarin has developed or partnered in the development of 11 products over the first 25 years of its history. These have included six therapeutic proteins: Aldurazyme, Naglazyme, Vimizim, Brineura, Palynziq, and Voxzogo; four small molecules: Kuvan, Orapred ODT® (prednisolone sodium phosphate), Firdapse® (amifampridine), and Talzenna® (talazoparib); and one gene therapy product (Roctavian). What became evident as the pipeline expanded into a wide range of modalities was that the PIPE approach to drug development could be applied to a diverse set of molecules and provided us a platform approach to process and analytical development.

The key component of the PIPE is the product itself. The International Conference on Harmonization (ICH) refers to critical quality attributes as physical, chemical, or biological characteristics that should be within an appropriate limit or range or distribution to ensure the desired quality attributes. Defining the critical quality attributes of a product requires a comprehensive understanding of the biological mechanism of action and the relationship of molecular structure to function. Analytical characterization for the presence and stability of multiple, critical quality attributes is a fundamental requirement for winning regulatory approval of a therapy.

Consider Vimizim, BioMarin's enzyme replacement therapy for people with MPS IVA, as an example. People with MPS IVA lack the enzyme N-acetylgalactosamine-6-sulfatase, which is needed to breakdown carbohydrates. In the absence of adequate amounts of the enzyme, metabolic waste from improperly broken-down carbohydrates accumulates in the lysosomes of cells throughout the body. Lysosomes normally clear cellular waste, but the accumulation of these long carbohydrate molecules leads to widespread cellular, tissue, and organ dysfunction. Vimizim is a recombinant form of the enzyme these patients lack. By developing an enzyme that could target the lysosome of patients it would be possible to clear the long carbohydrate molecules that accumulate.

There are two essential features of Vimizim that are required for biological function and are defined as critical quality attributes. The first relates to how the enzyme gets inside a cell and gets directed to the lysosome within the cell where waste is processed. This is accomplished

by assuring that the correct carbohydrate structures are present on the protein. The carbohydrates are the key that fits the lock of the receptors located on the cell surface. There is a specific carbohydrate structure on Vimizim referred to as mannose-6-phosphate. The goal of the cell culture and purification scientists that develop the manufacturing process is to assure that adequate amounts of this carbohydrate are present on the protein. The lock on the cell surface that we are trying to open is referred to as the cation-independent mannose-6-phosphate receptor. The carbohydrates on Vimizim bind to this receptor starting a cascade of events that transports the protein to the lysosome in an event referred to as endocytosis.

The other critical quality attribute relates to the desired enzymatic activity. Enzymes are often referred to as molecular scissors with their singular function being the ability to clip big molecules into smaller ones. The cutting occurs at what is referred to as the "active site" of the enzyme. Vimizim is an unusual protein in that it is produced in the cell in an inactive form and must be converted to the active form by another enzyme. Once again, the cell culture and purification scientists are tasked with producing the active form of the molecule. The manufacturing process must be designed to produce and preserve these elements to generate an efficacious product.

The second element of the PIPE strategy involves limiting the quantity and number of impurities in the product, a desirable goal from a safety perspective. Impurities, as defined by ICH, fall into two broad categories: product-related and process-related. Product-related impurities are those that are structurally related to the product itself. During production, the product is susceptible to being cleaved into smaller fragments or can aggregate to form dimers, trimers, or larger aggregates. There are other potential product related impurities resulting from chemical reactions (deamidation, oxidation, or disulfide rearrangements). These product-related impurities may have biologic activity, but often result in the loss of potency. Product-related impurities may also create adverse immunological reactions and may create safety concerns for the patient. They are also difficult to detect as they are structurally similar to the

desired product. Analytical methods that are selective for separating these structurally similar impurities that may be present at low levels from the desired product are required.

In contrast, process-related impurities are associated with the raw materials used during manufacturing or byproducts of the manufacturing process. Process-related impurities differ significantly in structure from the desired product. They can be raw material components that are carried along with the desired product or components (DNA, lipids, or proteins) from the host cell used to manufacture the product. Limiting process-related impurities are most often associated with assuring the safety of the product and less so with its potency. Methods for detecting process-related impurities often need to be specific and can differ significantly from methods used to monitor the desired product.

It is widely understood by health authorities and sponsors that both product- and process-related impurities, at some level, will likely be present in a final drug product. Limit specifications are negotiated with health authorities and established to control the level of these impurities. These limits are arrived at after considering non-clinical and clinical safety and efficacy data established throughout development. Manufacturing and analytical variability are also taken into consideration. The totality of experience and process capabilities come into play in the establishment of specifications. While impurities are controlled by specification or action limits, it is important to distinguish impurities from contaminants. Contaminants are not part of the manufacturing process and are not expected to be in the product at any level. While contamination for biotech products refers primarily to adventitious microbiological contaminates (bacteria, mycoplasma and virus), they can also be chemicals or foreign matter inadvertently added during processing of a product.

Perhaps the most scientifically interesting part of the PIPE refers to the process. The manufacturing process can be broken down into three broad components. The first is referred to as "upstream operations" and involves all aspects of cell culture starting from the establishment of the master cell bank (cells that have been cloned to contain a human gene of interest) through the seed train expansion (the expansion of a starting

group of cells used to produce a desired protein) and ultimately into large scale bioreactors. The goal of the cell culture step is to express the gene of interest to produce protein or vector at the highest concentration possible with the fewest impurities as is reasonable in the shortest time. The upstream process ends with the final step of the process, filtration, or centrifugation, where the cells are removed.

The second stage of the process is referred to as "downstream operations" and involves all aspects of purification. There are two primary goals for downstream operations. The first is to remove water from the product and concentrate it. It is not unusual to start with a volume of up to 25,000 liters of harvested cell culture fluid and reduce the volume 100-fold to 250 liters by the end of the downstream operations. The second goal of the downstream operations is to increase the purity by removing both product and process-related impurities. Downstream operations are expected to increase the purity of the product by three to four orders of magnitude. The reduction in volume and increase in purity involves the use of multiple orthogonal chromatography, filtration, and concentration steps leading to the bulk drug substance. The third step of the process is referred to as "fill-finish" operations. That involves taking the bulk drug substance and filling it into vials, prefilled syringes, or other forms to turn it into what is known as the drug product. This is the form of the product that health professionals or patients use. This step of the process also refers to the formulation work that assures that the product will remain stable and within specifications throughout the full expiry period.

The last element of the PIPE is the equipment used during production. The equipment includes not only the bioreactors, chromatography columns, centrifuges, filtration, and filling equipment that directly touches the product, but also the utility systems (water, steam, HVAC, and autoclaves), the analytic equipment used for in-process monitoring and testing performed throughout production, and the computer systems involved in the collection of process data and alarm generation when process limits are exceeded, which indirectly touch the product.

The facility design and selection of equipment are critical to achieve robust and valid manufacturing processes consistent with regulatory

expectations. The equipment needs to be maintained within established operating limits and provides the interface between the process and the operators running the process. It is vital that analytical monitoring of critical operational control parameters is not only accurate but provided in real time to enable that the process is performing within limits defined through extensive validation and to be able to detect deviations should they occur.

Knowledge about the PIPE accumulates over time. It happens before approval when the number of production runs may be minimal and continues through approval when extensive manufacturing and validation experience is gained. The knowledge gained over time is critical to assuring process consistency and product quality. The interplay between various aspects of the PIPE allows for individual areas of expertise to be optimized, yet to fit back into a greater goal. The PIPE approach generates critical knowledge that allows for informed decision-making about product quality, process parameters, robustness, capacity, cost of goods, and regulatory compliance when applied across a wide range of product modalities. The successful application of the PIPE to our small molecule and recombinant protein products gave us the confidence to apply it to the development of our gene therapy products. Having honed these capabilities, which we applied to the approval of several products, helped us to significantly accelerate the development of our gene therapy programs. We were quickly able to determine the type of facility that needed to be built, the processes that needed to be developed, and the analytical toolbox that needed to be created to characterize both the product and potential impurities. The information garnered was essential in moving our first gene therapy product quickly through development and assuring that we could meet the demand for the largest gene therapy phase 3 study conducted to date and the projected commercial demand once approved.

A top(s)-notch organization

The technical operations group has had an outsized impact on the development of BioMarin throughout its history as the company navigated the

complex world of drug development. TOPS partnered with research and clinical operations to define the critical quality attributes of our products and then developed manufacturing processes to optimize the safety and efficacy of these products. TOPS worked with program management and other administrative functions in the company to enable rapid development, oftentimes within constrained budgets and resources. And TOPS partnered with commercial operations, legal, and compliance departments to help build the distribution systems necessary to support worldwide sales of our medicines. The creation of the TOPS organization provided us a way to develop innovative therapies within aggressive timelines and budgetary constraints so that we could bring our medicines to patients who had few or no therapeutic options.

At the same time, there have been many challenges at BioMarin that were unique to what we were seeking to do. In fact, BioMarin achieved many industry firsts and developed its novel therapies in record time with several products going from first-in-human dosing to approval in three-and-a-half to five years. The rapid development of these therapies put extreme pressure on the TOPS organization to keep pace with clinical development while creating robust and validated manufacturing processes consistent with health authorities' expectations. All that had to be done while assuring an uninterrupted supply of products to enable our commercial operations to expand rapidly to bring these innovative medicines to patients in more than 70 countries worldwide. In many cases, there was no playbook to refer to, or existing solutions to implement.

The lessons learned during the early years in developing enzyme replacement therapies Aldurazyme (to treat MPS I), Naglazyme (to treat MPS VI) and Vimizim (to treat MPS IVA) forged a tenacious, science-driven, and patient-focused company that thrived and overcame substantial challenges. The foundation of these early successes allowed us to develop innovative products that included first-in-class drugs to treat CLN2 disease (Brineura), PKU (Kuvan and Palynziq), and achondroplasia (Voxzogo). We were also able to apply the lessons learned in protein manufacturing to the development of Roctavian, a gene therapy

for treating hemophilia A. The application of our PIPE approach to the approval of Roctavian allowed us to establish a leadership position in the production, characterization, and validation of these complex biologics, and has been integral to establishing the path forward for the industry and health authorities alike.

Delivering a protein to a child's brain by bypassing the blood-brain barrier to inject it directly into the cerebrospinal fluid in the cerebral ventricles of the brain as we do with Brineura or delivering a recombinant bacterial enzyme chronically administered through subcutaneous administration in the case of Palynziq, represented industry firsts. They required us to craft creative solutions by combining science, leadership, and passion from many people across the company. Developing goals that wove together the business needs of the company with the regulatory requirements of health authorities while developing first-and best-in-class protein therapeutics required a culture of curiosity that was willing to embrace new technology.

By leveraging the knowledge gained in developing protein therapeutics, we were able to accelerate the development of our gene therapy programs significantly. Regardless of the modality of a therapy, our approach to manufacturing, quality, and logistics was based on a fundamental understanding of molecular biology, protein structure, analytical chemistry, engineering, and computer systems to deliver therapeutic products against ambitious goals. We applied all of this knowledge directly to our vector biology programs. Often circumstance required we do this with finite resources and time restrictions, necessitating that we maintain the nimbleness and flexibility that has been a hallmark of our product development efforts.

Within TOPS we created a leadership team that not only included the management leads for my direct reports, but also included representation from human resources, legal, finance, information management, and regulatory affairs. It was essential that leaders in all areas of the company provided a clear vision. Together, we could craft strategies that included input from many functional areas. In turn, we created touch points with clinical, research, program management, and commercial

operations so that we were aligned with their activities. While we always had established goals for the company, they were at times more fluid then rigid. Oftentimes we needed to be flexible as a company to respond to new data and feedback from health authorities or clinical outcomes.

The four elements of TOPS

There are four important elements that have driven our operational success. While "TOPS" is an industry term for technical operations, BioMarin also uses the term "**TOPS**" to describe an approach that encompasses **t**echnology, **o**rganization, **p**eople, and **s**cience. Each of these components are intertwined to form a strong bond that allows us to be integrally involved in all aspects of the company's development.

It would have been easy to come into the company with platitudes that we would make a commitment to quality as is often done in our industry. Instead, we focused on how we would attain the quality standards around which the entire company, not just technical operations, could rally. Commitment to science enables compliance. Understanding the critical process parameters in the development of manufacturing processes, coupled with a strong commitment to the use of analytical characterization to define and control the critical quality attributes of the products, were important to establishing consistent manufacturing and integral to a strong commitment to compliance with regulations. This reliance on a science-driven decision-making philosophy was essential in allowing our employees at all levels of the organization to contribute creatively, speak their minds openly, and stay focused on common goals.

Technology is woven into our decision-making processes in that the raw material for making good decisions is information. Using technology to collect and distill information into a useful format is fundamental to our decision-making processes. Whether we are modeling the maximum capacity for production, trending stability data to extrapolate the expiry of the product, or planning the production schedule from raw material to finished products, we leverage technology to our advantage. At the same time, it is important not to be seduced by technical solutions to

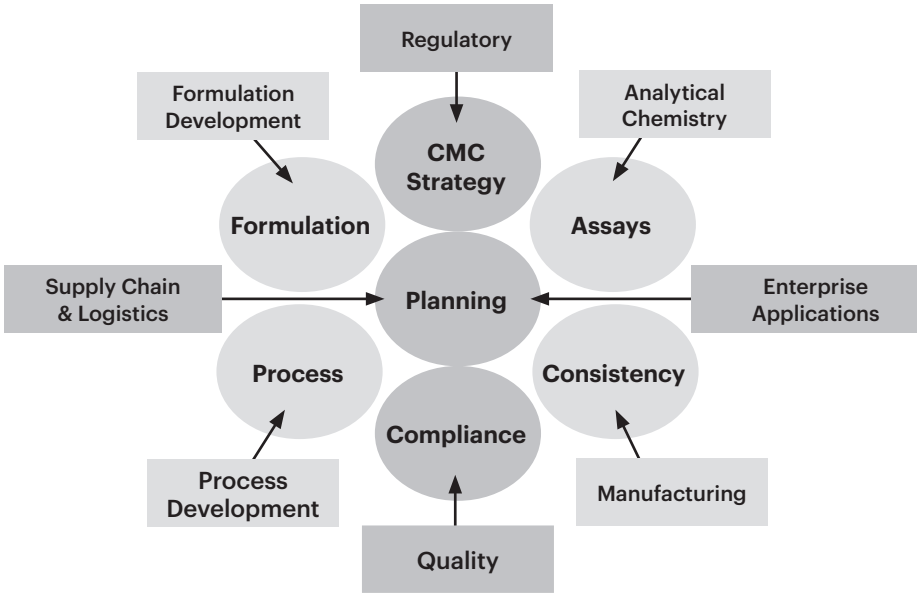
problems. Technology is a means to an end and not the end itself.

Organizational structure can be defined in many ways. The most common way to explain an organizational structure is a hierarchical chart that describes who reports to whom. To be sure, I have spent an enormous amount of time revising the organization chart over time to assure that we could meet our goals. Organizational charts were presented to health authorities during inspections. Within the company, we rarely referred to them. When asked to explain how we were organized we referred to a chart of circles that was philosophically referred to as strategic process development. Strategic process development is a holistic approach leading to high product quality and rapid approval of safe and efficacious therapeutic products for the patients that require treatment.

At the base of the chart was a circle for compliance symbolizing our foundational commitment to quality. Above that was a planning circle as it was fundamental to assuring that we were not haphazard about our approach to identifying and resolving problems in the right order at the right time. Planning was also important to keep aligned all the activities necessary to support eight commercial and multiple development programs across multiple manufacturing facilities and platforms. Planning is where we focused on the assumptions we were making to ensure that they were valid as it would be nearly impossible to make good decisions if our assumptions were not valid. The highest circle on the chart related to CMC strategy. It was paramount that every facility we built, every process we designed, every method we developed, was linked to a defined regulatory strategy that met health authority expectations.

These three circles stacked on top of each other were flanked by process, formulation, and analytical development circles representing activities that support and enable the regulatory strategy. If all of this was done properly, the result would be consistent, robust, and compliant manufacturing. While our products were all very different and did not lend themselves easily to a platform approach, our strategic process development methodology was the platform approach we relied on for a vast array of modalities. The tenets were easily communicated, addressed our core philosophy of science-driven compliance to meet

Strategic Process Development
Holistic approach that leads to high product quality and rapid approval of safe and efficacious therapeutic products for the patients that require treatment



health authorities' expectations, and were aligned with our vision, mission, and values.

People are the critical ingredient of BioMarin's success. That was borne out in the book *A Rare Breed*. Where possible, people we knew, trusted, and shared the same values were recruited. Within technical operations a majority of people were hired straight out of university and trained. We screened the people we hired to determine if they shared our values and commitment to patients, innovation, and rapid development. We looked for the tenacity to see projects through. We looked for people with the ability to process information, be decisive, and make effective decisions. And we selected individuals who could work collaboratively in an evolving team structure and within a fluid environment that was capable of rapid change. We also wanted people who could stay

the course through adversity until we achieved our goals. Our employees were often stretched and challenged as the portfolio of products evolved, as new facilities were acquired or built, or when we would gain approval in new countries around the world. Key to their success was the ability to embrace partnerships with other functions in the company to fashion solutions that in most cases met everybody's needs. As with Alexandre Dumas' Musketeers, it was "all for one and one for all."

Science is fundamental to all that we have accomplished at BioMarin. We have been most successful when we have had a firm grasp of the molecular biology leading to a disease state. Our track record in the development of enzyme replacement therapies reflects our understanding of the pathology of the diseases for which we have developed products. But scientific exploration is not just the domain of research at BioMarin. Science permeates functions throughout the company and is essential to the efforts of TOPS. Rigorous science is applied to process development, analytical characterization, methods development, and validation efforts across a broad spectrum of technologies that include cell culture, purification, engineering, logistics, and materials. It is also applied to formulation and computer systems to improve yield, increase purity, and maintain stability in a consistent fashion. The goal is to keep our scientific eye trained on the structure of the molecules we manufacture to assure they function as intended. A strong commitment to this structure/function relationship is a key component of both the safety and efficacy of the molecules we manufacture. Compliance, from an operational perspective, can be described as being 80 percent derived from good science coupled with a thorough understanding of regulatory expectations. The remaining 20 percent is a function of integrity and commitment. Science, integrity, and commitment focused to meet health authority expectations and the needs of patients is a powerful combination that has been at the core of our drug development efforts from the very beginning.

Understanding the goals of the company and the other functions with which we interacted was essential to good decision-making. Communicating those decisions across functions and appreciating if they met the

needs of the company was just as important. Like many other companies, we developed project teams and their activities were adjudicated through the program management function.

In the early days when we were developing both Aldurazyme and Naglazyme, the project team's membership consisted exclusively of vice presidents. The decisions we were making were so vital to our survival that we did not dare delegate lower down in the organization. As the number of products grew, it became unwieldy for the vice presidents to attend all the project team meetings. At first, within TOPS, we sent more junior delegates and found that they did not have the breadth, experience, knowledge, or authority needed to function as a single voice representing the TOPS organization. Our inclination was to send additional people representing the various TOPS functions. The outcomes were no better, and the size of the project teams were getting too large to have meaningful strategic discussions and decisions made.

Dan Maher came to me when he was head of program management and vented about the challenges he was having with this problem, not just from technical operations but from other functional areas as well. He said that the decisions the junior representatives were making were being overruled by the functional vice presidents. If the project team leaders didn't like the answers, they went opinion shopping until they got an answer they liked. What he said was true.

"Would it be possible to send just one person from technical operations to the project team meetings who could speak and decide for the whole group?" he asked out of frustration.

I got defensive at first and explained how complex and large our function was and how one person could not possibly be able to fulfill that role. He challenged that premise.

"When you are the one person that comes to the project team meetings, things go well," he said. His comment forced me to reconsider my thinking and approach.

During my next staff meeting I relayed the conversation and challenged the team to send just one person to each project team. They were even more defensive than I had been with Maher. As we discussed that

the work being performed in their groups was not being appreciated, the conversation shifted to what the challenges were and how they might be addressed. Maher's request had merit and we were determined to work on a viable solution.

Over the next several weeks, we developed a vision for what came to be known as our **SCOUTS** initiative. Our goal was to make informed decisions that are communicated and in the best interest of the company and to have a single representative to each core team that is sufficiently informed and authorized to make decisions for TOPS. Though we started with the dictionary definition of scouts as people sent out to obtain information by examining, inspecting, and observing, SCOUTS too was another acronym:

Single core team representative
Completely informed, organized, and prepared
Obligated and authorized to communicate and make decisions
Uninhibited communicators fostering cross-functional dialogue
Thinks globally about the ramifications of issues
Strategically focused on meeting corporate goals

We put in place a comprehensive support team to facilitate and assist the SCOUTS. There were now too many core teams to support individually so we created several sub-teams within TOPS that were to serve as a common resource. There was an analytical team to address any specific assay requirements. There was a microbiology team that was tasked with minimizing the risk of contamination so that the plants were always available for production along with facilitating microbiologic-based analytical methods as needed. We created a computer sciences team to streamline the collection and organization of data to facilitate decision-making. And we created our own project management team that was tasked with organizing our goals and commitments so that progress could be monitored and resources reassigned if warranted.

The technical teams met regularly and on an ad hoc basis as issues arose. The project management team and all the directors within TOPS along with the SCOUTS, myself, and my leadership team met monthly to

review progress and the evolving needs of the core teams. In addition, I met on a regular basis with the SCOUTS individually, as needed, to better understand the core team requests and to define how we would meet those requests, or occasionally, when we would push back against the request if necessary.

We paired each of the SCOUTS with an executive sponsor from the pool of my direct reports. We were not asking the SCOUTS to make their own independent decisions, but to bring issues back to our leadership and the sub-teams to define and design our strategy and then to communicate that to the core team in a timely fashion. As time went on, we continually refined this approach and incorporated resource planning and budgeting into the project management meetings.

Our SCOUTS were generally two levels down within the organization and they were some of the best and brightest technical experts within our group. They were seasoned professionals who spoke their minds and whom their peers respected. They didn't give up their day jobs but were expected to incorporate these new responsibilities into their current work schedules. This was not a tested concept, and we didn't want to burden the experiment with a bunch of organizational changes. The first four people we tapped were a microbiologist from quality control, as the representative to the Palynziq core team; an analytical chemist, as the representative to the Voxzogo core team; and two process development scientists, as the representatives to the Vimizim and Brineura core teams.

From a career perspective, SCOUTS were developing critical thinking and leadership skills while being exposed to planning activities in other parts of the company and at the highest level of TOPS. These now became coveted roles where talented people could be coached and mentored on strategic decision-making by having direct and frequent access to senior management. The core team leaders, at first concerned that having these more junior people on the team would result in a drop off in engagement, were ecstatic to have a single point of contact for TOPS. The coaching and mentoring we provided them, along with the strict requirement that they bring core team issues to senior management in a timely fashion,

improved decision-making immediately. It didn't take the core team leaders long to figure out that the days of opinion shopping were over. We stood in solidarity with the collectively defined decisions that had been communicated to the core teams. When team leaders came to me or my direct reports looking for a different answer than they had heard at the core team meeting, they were not forthcoming.

Coordination with my peers about the decisions we were making, the positions we were taking, and the rationale was occurring in the background to gain cross-functional alignment. This took effort and resources, but once up and running it took on a life of its own as the habits we were creating were being ingrained in the organization and led to better decision-making and the establishment of goals that were more clearly aligned with corporate initiatives. We now had a self-sustaining process where no one person, namely me, was being asked to make all the decisions and the decision-making abilities of the group improved immensely. Other groups in the company emulated the approach and the overall impact on core team decision-making improved. Decisions were now being vetted by management as they were being made rather than being critiqued by management after they had been made. The SCOUTS concept, while simple in design, was effective in action.

Built to last

The hiring of Jean-Jacques Bienaimé in 2005 brought stability at the CEO level. Within the TOPS organization, stability was also being established. An organizational structure emerged with clear roles and responsibilities for six major functions important to technical operations: quality, manufacturing (internal and contracted), process development, logistics, engineering, and project management. Due to the previous five years of organizational instability, technical operations also took on responsibility for important support functions including good laboratory practice testing, compliance, and a variety of information management and financial functions. It would take another ten years for the support functions to mature and allow technical operations to divest these support functions and sharpen our focus on drug development.

By 2011, the company and TOPS had nearly tripled in size. With that growth came complexity. We expanded the converted Birkenstock sandal factory known as the Galli facility into three suites, with each referred to as points on a compass. Galli West and Galli East supported cell culture operations including perfusion and fed batch processes while Galli North supported bacterial manufacturing. With Aldurazyme and Naglazyme sales increasing, and the Vimizim phase 3 study fully enrolled, we anticipated the need for additional capacity and drove the acquisition of the Shanbally facility. With the acquisition of a second manufacturing facility located 6,000 miles away from headquarters, an organizational realignment became necessary. These organizational changes evolved from 2011 to 2014 as the plans for the Shanbally plant were developed and integrated into the company.

The most obvious aspect of the organizational changes came within manufacturing. We consolidated Galli West, Galli East, and Galli North into a single leadership team that coordinated all Novato site-related activities. This resulted in more efficient scheduling and increased the flexibility of these facilities as a total of six commercial products (Aldurazyme, Naglazyme, Vimizim, Brineura, Palynziq, and Voxzogo) using both perfusion and fed batch technology for the cell culture products, and fermentation for the bacterial products were in simultaneous production on a campaign basis. The Galli facility's flexibility enabled it to be rearranged as necessary to make a diverse set of proteins through three different technologies.

A parallel leadership team was established at Shanbally. Though activities there at first were limited to quality testing and release of products, the plant eventually became fully integrated with bulk manufacturing for both Vimizim and Brineura, along with label and packaging for nearly all our products. The ten-year journey at Shanbally followed the model laid out for the Galli facility. We brought capabilities online in a strategic and pragmatic fashion driven by the clinical and commercial growth of our pipeline.

The contract manufacturing activities had seen significant growth as we had medicines delivered in vials, tablets, sachets, and pre-filled

syringes. Contract manufacturing was previously aligned with the logistics function. This reorganization provided the opportunity to align the bulk manufacturing that occurred in Galli and Shanbally with the fill-finish activities performed by contractors. We organized global manufacturing into a single, cohesive function with responsibilities for Galli, Shanbally, and contract manufacturing. This added clarity of responsibility and focus and provided a streamlined organizational structure that allowed for the incorporation of the gene therapy facility when that came online in 2017.

From a technical perspective, process development and quality functions had responsibilities for developing process and analytical control systems for a variety of products and modalities. The complexity relating to process development and testing for a pipeline that included small molecules, proteins, oligonucleotides, and eventually gene therapies required seamless technical integration. Ensuring robust manufacturing required the development of process knowledge. Process knowledge was gained through the interrogation of product quality using highly sensitive and selective analytic methods. We created a regulatory strategy integration group. The role of this group was to collate, integrate, and coordinate the development of documentation for applications health authorities required to begin human clinical trials and to gain marketing approvals. This group worked with our regulatory affairs team to address technical responses from health authorities. The coordination of these functions together improved efficiency and allowed us to introduce process improvements to enhance product quality and capacity rapidly.

The logistics function played a critical role in budgeting, project management, engineering, scheduling, and distribution to ensure that projected clinical and commercial demand requirements were fulfilled on a global basis. This was a challenging task as we were always projecting product demand two or more years into the future. This was even more complicated to do during the first years of product launches where commercial demand was unpredictable. With initial product launches for Vimizim (2014), Kuvan powder (2017), Brineura (2018), Palynziq (2019), Voxzogo (2021), and Roctavian (2022) coming closely together,

we lived in a world of uncertainty that constantly tested our abilities, our systems, and our people. We made a distinction between the facilities groups that supported the Galli and Shanbally plants that reported directly to the site heads and the more global engineering functions that supported larger projects for technical operations and the rest of the company. The logistics group coordinated a number of computer systems that were integral to track production, quality testing, release, and product distribution. By having the logistics group organize budgeting, project management, and various other support functions, it enabled the manufacturing, quality and process development groups to focus on the scientific challenges associated with manufacturing, compliance, and regulatory strategies.

8.

The Bus Came By and I Got On, That's When It All Began

"If you would be a real seeker after truth, it is necessary that at least once in your life you doubt, as far as possible, all things."

René Descartes

Shortly after BioMarin won regulatory approval of Aldurazyme, my son was studying Taekwondo. During one of his tests to advance the color of his belt, I had the chance to watch a brown belt take his test to ascend to black belt. The test went on for three hours challenging the physical, mental, and emotional preparedness of the student. The brown belt was skilled, knew all the katas, and completed them with confidence. He showed no sign of hesitancy when instructed to do something. He made it look easy, although it was evident that he had trained for many years to acquire those skills.

Sitting in the front row, the corollary to the development of technical operations was evident. We were trying to master the diverse skills needed to be successful as a fully integrated pharmaceutical company competent in drug development. Mastering the scientific, engineering, and business skills were insufficient to solving the many challenges we faced. Success would require us to be focused, organized, and committed in developing well designed regulatory strategies that would be rooted in science, executed compliantly and would necessitate the development of

a decision-making paradigm willing to embrace a tolerance for the risk inherent in the biotechnology industry. Coordinated execution across the company was also necessary. Occasionally, good fortune was helpful.

Each product approval is unique where manufacturing and clinical challenges abound. Along the way, we often faced doubt about success up until the day of approval. While all approvals are meaningful for patients, there are some that stand out either because of technical hurdles overcome, innovative solutions implemented, compromises reached, or lessons learned. While it would be challenging to rank the approvals in terms of importance, Aldurazyme signified a liberating metamorphosis for the company indicative of the challenges met and overcome as it paved the way for many more successes.

The blueprint that emerged was essential to the ongoing success of the company. What became apparent was that technical training and mastery is necessary but insufficient to unravel the mysteries of science, biology, and medicine. Well-crafted strategies, executed with persistence, integrity, and shaped by scientific curiosity, are essential, along with a willingness for continual learning fueling iterative problem solving. Working with talented and motivated people provided the catalyst for transforming scientific knowledge and passion for patients into products. An ethos for data-driven decision-making, combined with experience and vision, enables taking calculated risks where time is of the essence, budgets finite, and doubts exist. Finding the sweet spot for timely and effective decision-making requires striking a balance between knowing when it is necessary to gather more information or proceeding with the knowledge at hand. Deciding before sufficient information is available increases the risk of making poor decisions. Wait until all uncertainty is removed and costly time delays are inevitable. It is essential to plan scenarios for the evolution of knowledge as the results from ongoing studies and experiments become available. Course corrections due to the shifting scientific, business, and regulatory winds require a skilled hand on the tiller. When more information becomes available, it is often necessary to reevaluate decisions to determine if minor or major changes are needed, or if prudence argues for staying the course. Changing plans can create enormous work, confusion about priorities, and frustrations throughout the organization.

It is important to resist the urge to make changes unless the need or benefit is extremely high. When changes are made, they must be communicated so everyone understands the rationale and remains aligned with the goals.

Both positive and negative events can drive organizational changes. Organizing around function, rather than people, requires a commitment to assessing the evolving needs and requirements of the company as it grows while never losing sight of the fact that it is the people in the organization who make the progress we hope to achieve. Organizational decisions made during growth spurts are easier to manage compared to retrenchments that are driven by clinical, technical, or business realities and uncertainties. These tenets were essential elements in the development of the company throughout its first 25 years and provide solid underpinnings for the ongoing drug development efforts that will come in the next 25 years.

We worked diligently to develop strategies, implement tactics, and build facilities and capabilities that did not exist previously against a backdrop of evolving health authority expectations, budgetary constraints and scientific uncertainty. From a distance, what we did may have looked easy or could have been ascribed to just following the path established by other companies. But it involved hard work, ingenuity, and vigorous training to establish standards that we held ourselves accountable to and the commitment to improve our operations continuously while bringing eight innovative products to market in our first 25 years. In many cases, the uncharted nature of our development efforts required trailblazing solutions negotiated with health authorities around the world. Successful negotiations with one health authority upped the ante for negotiations with other health authorities as drug development efforts for ultra-rare disorders often necessitated a single-minded approach to manufacturing and clinical studies due to the small patient populations and the lack of validated endpoints. There were times we had to take a step backward before we could go forward. Most times, we charted a path along the road less traveled.

Over time, we honed our expertise annealing new skills, knowledge, and capabilities necessary for innovative solutions to intractable problems in record-setting time. The goal was not to eliminate risk, but to get better at assessing risk. When we encountered doubts, we were prepared

to be bold, yet humble enough to be prudent as warranted. Our obsession with getting the science right paid dividends by allowing us to devise processes and procedures that were grounded in a solid understanding of biology, chemistry, and physics. The process knowledge we created allowed us to devise strategies to bring capacity and capabilities on-line as needed. Timelines and budgets pressed us to get things right the first time and more times than not we succeeded. Beyond the science, we maintained a clear link to regulatory strategies. We viewed our approach through the lens of health authorities and devised strategies that resonated with them.

Preserving a culture

In the book *Good to Great*, Jim Collins uses the metaphor of a bus for a company. He talks about first having the right people on the bus, then getting the wrong people off the bus, and finally making sure everyone is in the right seat including the driver. When BioMarin CEO Jean-Jacque Bienaimé shared Collin's book with the management team shortly after he arrived, a six-year journey to organize technical operation's bus, assuring the right people were on it, was still evolving.

The acquisition of the Shanbally facility six years later required a reorganization of who was on the bus and where they were seated, as did the build-out of our capabilities for the production of gene therapy vectors five years later. As the company grew ten-fold, and then three-fold more, it felt like we were surfing on the edge of a large and fast-moving wave. Maintaining balance required not only a constant assessment of risk, but a willingness to embrace it. Even when doubts existed, it was necessary to accept and embrace risk based on well-honed plans to bring our innovative therapies rapidly to patients who were in dire need of a therapeutic option. This was not about cutting corners. Our methodology was focused on meeting regulatory expectations in novel and creative ways only if standard approaches were not feasible or implementable. We did not reinvent the wheel. If well-established approaches were available and appropriate, we used them.

The challenge was exhilarating, and at times exhausting. The occasional failures, and there were a few, provided perspective on the difficulties associated with drug development. The approvals were a vivid reminder

of why we work so hard and that nothing comes easily. The scientific and business intent never wavered: develop first-in-class or best-in-class therapies to address unmet medical needs for the benefit of patients. The ability to react quickly and to communicate across the organization with a single purpose required ongoing refinements to our strategies and tactics. The culture of the company that was so instrumental to our success had to be preserved, protected, and nurtured. We also needed to distill it and communicate it to hundreds of new employees as we grew. The lore of a sandal factory, Pink Palace, or fishbowl would have little meaning to new employees if it was not somehow connected to challenges overcome and linked to defining our mission, values, and culture that had been forged in the crucible that led to the approvals of such innovative products.

Preserving culture is not about reliving the glory days of the past as much as we might want to revel in our past successes. We had to address new and more complex challenges as we racked up approval after approval. The approach that enabled our success was codified into simple and easy to understand acronyms PIPE, TOPS, and SCOUTS, leading to decision-making that was grounded in science and targeted compliance. As the company grew, evolution of a holistic approach to strategic process development was communicated broadly and practiced in plain sight for all to see. In response to growth, we implemented town halls and all-hands meetings to communicate goals, purpose, and process. We reveled in our successes and spoke transparently about our challenges.

At our first Technical Leadership Global Summit, where 100 directors from functional groups around the company were in attendance, we explored the powerful yet simple message from *Beyond Measure* by Margaret Heffernan. In it, she describes the big impact small cultural changes can have on a company and how high levels of social capital produce trust that makes conflict safe, vigorous, and open. She argues that without high degrees of social capital, the debate that hard problems demand won't take place. This was important in a company that had grown to 3,500 people in multiple worldwide locations.

Maintaining connection to the values that were integral to our success could be easily lost if not attended to as the company grew. It was crucial to share the essential values of the company as we grew so that newly

hired employees knew not only what we did and why we did it, but how we were going to continue doing it. Remaining open to new approaches and the contributions made by the people we hired was crucial to evolving our systems as the company grew. Building trust in one another was essential as the company grew. Layers of trust were laid down in day-to-day interactions in a safe and collegial environment where ideas could be proposed, challenged, refined, and then implemented with conviction. Traditions rooted in our earliest successes were continued and expanded so that we could interact with one another on a more personal level. Socializing on campus in what we referred to as "coolers" was initially implemented in 2001. These were themed gatherings that provided the opportunity for banking social capital for more challenging times. As management and employees mingled at these gatherings, discussions inevitably focused on the challenges of the day. Just as often, though, discussions drifted to more personal topics that helped form connections among the team. Cross fertilization was an additional benefit of these low-key gatherings, as many strong and vital connections were made. When we won approval for a product, members of management, core teams, and the company at large would gather to bang a gong. Banging a gong when products were approved created a tradition symbolic of the cross-functional cooperation and sustained efforts required to bring products to patients. The culture created was collegial and cooperative, driven by science and focused on patients, and was uniquely BioMarin.

The Technical Leadership Global Summit was successful at driving common understanding within TOPS aligned with corporate initiatives. As strategies, tactics, and challenges were openly discussed, we generated novel cross-functional ideas. A year later, we held a second Technical Leadership Global Summit where we shared the book *Dare to Lead* by Brene Brown and discussed the role that doubt plays in our drug development efforts and how it can help drive us to results, inspire curiosity, foster collaboration, and demand that we act with integrity. In empathetic and powerful ways, each of the leaders within TOPS presented their own journey, motivation, and expectation for themselves to the directors. That provided a powerful link between the mission, values, and goals of the company and the role that TOPS played in achieving those goals.

We had struck a nerve, or perhaps more appropriately, tapped into our soul. The feedback from the summit was overwhelmingly positive. It was not just one of those feel-good moments that sometimes happens at company offsites only to wither once the strain of day-to-day activities commences when attendees are back at their desk or lab bench. We purposely defined approaches and different ways to work with each other to reenforce our ethos and to enhance efficiency while improving compliance. We committed ourselves to maintaining our rapid and innovative approach to drug development while assuring that our systems evolved to meet our expanding pipeline. It was apparent weeks and months later that the learnings were being put into everyday practice. It felt like we not only had all the oars in the water but that we were pulling together in a synchronized fashion. The power of organizational vision and alignment liberated people to change how we got work done without jettisoning the culture of why we were doing the work in the first place.

What became clear from these two summits was that some arcane systems had been developed and the manual nature of numerous operations were inefficient. The result of going fast for so many years had led to the development of some systems that were not scalable and had the potential to fail. We committed ourselves to assuring that operational controls and procedures matched our scientific acumen—not an easy task in 2016 when we were responsible for three plants, 25 contractors, four commercial products with the prospect of more on the way, and a half-dozen development programs including gene therapy. The challenge was to create more robustness in our operational procedures and controls while maintaining the existing business and continuing to rapidly develop the pipeline.

The following year we shared James Clear's *Atomic Habits* where we further explored how being purposeful about our habits was critical to our decision-making and continuous improvement efforts. Working closely with many functions in the company over the course of four years, we implemented a manufacturing execution system (MES) in Shanbally that eliminated paper-based batch and assay history records and developed the procedural controls to release product based on exceptions. An adjunct to the MES project was undertaken simultaneously that

focused on reducing the number and frequency of deviations. This required a thorough understanding of root causes combined with effective corrective actions. The emphasis on deviations was not a new initiative as we had been focused on this important element of compliance for many years. What was new was the realization that the zeal of going fast was juxtaposed with the need to develop more robust processes and procedures earlier in the lifecycle of a product. The initiatives on efficiency held the promise of allowing us to realize the benefits sooner than we had in the past. The result was a measurable decrease in deviations, reduction in inventory held, increase in manufacturing robustness, and clarity in expectations for processes without encumbering our innovative scientific approach for rapid drug development.

We streamlined the lot release process to accelerate the release of product and were able to free up capital as we reduced inventory levels across the commercial products. These initiatives were a long way from biology and product development, but there was enthusiasm for taking them on as it increased efficiencies across multiple groups, decreased cost of goods, and enhanced compliance while providing us with scalable and robust processes to enable future growth. These initiatives were communicated broadly and supported vigorously by management. The goal was less about saving pennies and more about focusing on how we could develop more innovative products for patients. As was often the case, the TOPS organization embraced the initiatives first and took the lead in extolling the benefits as it encouraged other groups to streamline their practices. As we built new facilities and added new capabilities, the learnings were incorporated as part of the normal course of business.

None of the books that formed the basis of the three Global Summits were technical books, but their simple, yet powerful, messages were crucial to maintaining alignment across a growing company with operations in more than 70 countries that was developing some of the most innovative products on the planet. It allowed for an honest discussion of what worked and what did not work. It identified the things we needed and wanted to keep—namely being bold, resourceful, innovative—while being science-focused. Of course, we wanted to maintain the can-do spirit that was so contagious. It also helped us define the characteristics

we needed to refine in terms of efficiency, scalability, and consistency. The old and the new bridged together to create sustainability for our purpose. How we did things evolved for the better while why we did things maintained a solid footing in the bedrock of our mission, values, and culture.

Never give up

As the black belt test proceeded, next came the sparring portion. There were twelve other black belts in attendance. The brown belt had to spar with each one of them separately for about a minute with little to no rest in between for him. The black belts were noticeably more skilled than the student as he struggled to defend himself. When he was sparring with the fifth black belt, he walked into a spinning roundhouse kick, and it was evident that the kick hit him hard and knocked the wind out of him. He was given barely a moment to recover before he was being challenged by the next black belt. During a moment of rest between the eighth and ninth black belts, he turned to me. "How many more?" he asked. I told him just a few more.

Once again, the corollary to technical operations was evident as we endured times of hardship and challenge. We had the will and tenacity to protect and defend the last hope our patients had of gaining a treatment option. We were not about to give up or give in. We spoke honestly about constraints on budgets, timelines, and capabilities in establishing challenging goals that were met and consistently exceeded. When things went awry, and they sometimes did, we focused on contingent solutions. We went through a lesson learned exercise to determine what we had failed to consider. We never placed the blame on an individual or a group. Because of that, people were willing to speak up, think creatively, and make themselves vulnerable. This allowed others in the group to rally the support necessary to keep projects on track. We encouraged a no-surprises mentality and developed project tracking systems that allowed us to identify issues early. This enabled us to correct course and reallocate resources as necessary before things became critical. We routinely developed contingency plans that were vetted and ready to go as an essential component to our planning to maintain flexibility and stay on track with our drug development aspirations. The development of a project tracking system

combined with extensive contingency planning was crucial to assure that we did not get gut-punched by things we had not seen coming.

The brown belt survived his battles with the remaining black belts even though he was nearing exhaustion. As he rearranged his gi and caught his breath, the end of the test was near. At that point, his sensei told him that they had a surprise. Three junior black belts, all under 13 years of age, came on to the mat and started attacking him all at once. Although they were smaller, they were as relentless as raptors. In his exhausted state they took an additional toll on his remaining strength and willpower. It didn't seem fair. If he fought back, he was likely to hurt a child. If he just stood there, he was going to get hurt. He gently tossed each of the junior black belts across the mat, finding a middle ground. He managed to protect himself while not injuring the young black belts.

Yet again there was a corollary to the development of technical operations. Deciding when to be aggressive and when to be passive, when to take risks and when to be cautious, was not instinctual. Trial-and-error learnings could not be tolerated for long when the cost of failure could be measured not only in time and money but in the lives of patients for whom we were trying to develop treatments. We had to get it right the first time. Like the brown belt, we were being attacked from multiple directions. We were accountable to budgets, timelines, regulatory requirements, and had to overcome scientific and business challenges that were ever-present. We planned for various scenarios and devised multi-pronged strategies that provided us with options in the face of the unknown. Science was our compass as we developed pragmatic and innovative solutions to our technical and business challenges. We tracked our execution against these plans, and when necessary, modified them when new information became available.

For the final part of the test, the student had to break three pine boards held up by one of the other black belts. Even in his state of exhaustion you could sense the frustration that had built up during this grueling test and years of training. When he hit the boards, they cracked easily under the power of his strong punch. It was almost as if that punch was meant to say, "I told you I could do it."

Each of our product approvals conveyed a sense of accomplishment tinged with just a bit of defiance. The approvals carried significance, conveyed validation, and emboldened us to try again. It gave us the confidence to develop molecules independent of modality and complexity as we applied lessons learned in terms of molecular biology, clinical design, technical operations, and commercial distribution on a worldwide basis. Support from administrative functions (Information Management, Human Resources, Legal, Program Management, Finance, Compliance, Business Development, and Investor Relations) matured and developed in lockstep with clinical, technical, and commercial operations, providing, clarity, focus, and support.

Our connections were held together through constant, consistent, and adaptive planning and communication. There certainly was vigorous debate about the best approach, but at the end of the day, the management team and their corresponding functions pulled together to execute on the chosen course of action. With scientific cunning, efficient execution, and knowledge of regulatory expectations, we developed innovative first-in-class medicines that addressed unmet medical needs in record setting time.

Finally, all that remained was to award the student his black belt. As he knelt in the middle of the mat the sensei first put the black belt around his own waist and then removed the young man's brown belt and then placed the black belt around the student's waist. The sensei then asked him, "Do you know what having a black belt signifies?" The young man was confused, exhausted, overwhelmed, and unprepared for the question and said nothing. "This black belt does not mean you are an expert," the instructor said. "It means that you are no longer a beginner."

The corollary to the technical operations group and the company's journey was evident. The approval of BioMarin's first therapy Aldurazyme, significant as it was, only meant that we were no longer beginners. There was still much for us to accomplish and learn, and in fact, the expectations were significantly higher. Having crested the peak of approval, we challenged ourselves to do it again and again and again. Our understanding of biology grew and fueled the development of even

more innovation. There was no reason we could not continue to innovate for the benefit of patients. Small molecules as cofactors (Kuvan) for misfolded proteins led to restoration of function, direct injection of enzymes into the brain (Brineura)—bold and risky as it was—overcame the hurdle of penetrating the blood brain barrier, PEGylating bacterial enzymes (Palynziq) provided cloaking for chronic administration, molecular biology studies focused on debilitating bone growth disorders resulting in a novel approach (Voxzogo) to treating dwarfism, even when experts in the field scoffed at our approach. The recent approval of Roctavian, a gene therapy for treating hemophilia A, represents a milestone in medicine that expands BioMarin's approach to the development of drugs to address the unmet medical needs of patients.

We took the time as a group to enjoy the accomplishment in overcoming so many hurdles and took away learnings of what worked well and what needed to be improved. We immediately got back to the business of our drug development roots and recommitted ourselves to the basic yet important tenets underpinning our culture: providing support to each other, working cross-functionally to maintain alignment, and averting problems and conflicts rather than resolving them after they occur. Only then can you bring out the best in people, set audacious goals, and succeed at them consistently.

The lessons learned were easy to understand yet difficult to master. The manner in which we overcame challenges generated a steadfast approach that was a guiding light throughout our development efforts: stay true to the science, remain persistently focused on tasks and goals, be willing to take risks, do not fear making mistakes, apply imagination and experience in fulfilling regulatory expectations, and create value while always maintaining your integrity. These simple but powerful messages are at the core of a sustainable scientific and leadership philosophy. When you get to a point where your compass always points to true north, and you no longer have anything to prove to yourself or to others, then your approach to problem solving can be truly liberated. Let the attainment of difficult goals provide you with the freedom to be bold and to grow as a person and as a team.

For sure, technical operations at BioMarin continues to evolve and the capabilities developed not only benefit the patients for whom products have been approved, but the many other products that are and will move through development. Product approvals are the ultimate measure of our efforts and technical operations has been at the core of BioMarin's many product approval successes. It has been a value-creating asset for the company from both a tactical and strategic perspective. The strategies developed and lessons learned will continue to facilitate rapid development of products for the benefit of patients for years to come. As new challenges arise, this time-tested approach provides us with a template to continue the rapid development of innovative technology and to deliver hope in the form of medicine to patients so desperately in need.

APPENDIX: DRUG INFORMATION

ALDURAZYME prescribing information

The first and only enzyme replacement therapy for MPS I.

INDICATION

ALDURAZYME® (laronidase) is indicated for patients with Hurler and Hurler-Scheie forms of mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established.

ALDURAZYME has been shown to improve pulmonary function and walking capacity. ALDURAZYME has not been evaluated for effects on the central nervous system manifestations of the disorder.

LIMITATIONS OF USE

The risks and benefits of treating mildly affected patients with the Scheie form have not been established.

ALDURAZYME has not been evaluated for effects on the central nervous system manifestations of the disorder.

WARNING: RISK OF ANAPHYLAXIS

Life-threatening anaphylactic reactions have been observed in some patients during ALDURAZYME® infusions.

Appropriate medical support should be readily available when ALDURAZYME is administered.

Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions and require additional monitoring.

ALDURAZYME® (laronidase) is an enzyme replacement therapy designed to address the underlying cause of mucopolysaccharidosis I (MPS I). ALDURAZYME is manufactured by BioMarin and commercialized by Sanofi Genzyme in the US, EU, and internationally.

MPS I is an inherited lysosomal storage disorder caused by a deficiency of alpha-L-iduronidase, a lysosomal enzyme normally required for the breakdown of certain complex carbohydrates known as glycosaminoglycans (GAGs). If the enzyme is not present in sufficient quantities, the normal breakdown of GAGs is incomplete or blocked. The cell is then unable to excrete the carbohydrate residues and they accumulate in the lysosomes of the cell. This accumulation disrupts the cell's normal functioning and gives rise to the clinical manifestations of the disease.

continued

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Anaphylaxis and Hypersensitivity Reactions

Anaphylaxis and serious hypersensitivity reactions have been observed in patients during or up to 3 hours after ALDURAZYME infusions. Some of these reactions were life-threatening and included respiratory failure, respiratory distress, stridor, tachypnea, bronchospasm, obstructive airways disorder, hypoxia, hypotension, bradycardia, and urticaria.

If anaphylactic or other serious hypersensitivity reactions occur, immediately discontinue the infusion of ALDURAZYME and initiate appropriate medical treatment.

Caution should be exercised if epinephrine is being considered for use in patients with MPS I due to the increased prevalence of coronary artery disease in these patients.

Interventions have included resuscitation, mechanical ventilatory support, emergency tracheotomy, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and IV corticosteroids.

In clinical studies and postmarketing safety experience with ALDURAZYME, approximately 1% of patients experienced severe or serious allergic reactions. In patients with MPS I, pre-existing upper airway obstruction may have contributed to the severity of some reactions. Because of the potential for recurrent reactions, some patients who experience initial severe reactions may require prolonged observation.

The risks and benefits of re-administering ALDURAZYME following an anaphylactic or severe hypersensitivity reaction should be considered. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

Acute Respiratory Complications Associated with Administration

Patients with an acute febrile or respiratory illness at the time of ALDURAZYME infusion may be at greater risk for infusion reactions. Careful consideration should be given to the patient's clinical status prior to administration of ALDURAZYME and consider delaying ALDURAZYME infusion.

Sleep apnea is common in MPS I patients. Evaluation of airway patency should be considered prior to initiation of treatment with ALDURAZYME. Patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments readily available during infusion in the event of an infusion reaction or extreme drowsiness/sleep induced by antihistamine use.

Risk of Acute Cardiorespiratory Failure

Caution should be exercised when administering ALDURAZYME to patients susceptible to fluid overload or patients with an acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusions.

continued

Appropriate medical support and monitoring measures should be readily available during ALDURAZYME infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient.

Infusion Reactions

Because of the potential for infusion reactions, patients should receive antipyretics and/or antihistamines prior to infusion. If an infusion-related reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms.

Adverse Reactions

Patients 6 years of age and older

The most common adverse reactions reported in ≥10% of patients were infusion reactions (32%). These included rash (36%), flushing (23%), injection site reaction (18%), and paresthesia (14%). Other common adverse reactions included upper respiratory infection (32%), hyperreflexia (14%), and poor venous access (14%).

Patients 6 months of age and older

The most common serious adverse events were otitis media (20%) and central venous catheterization required for ALDURAZYME infusion (15%). The most common adverse reactions reported in ≥10% of patients were infusion reactions (35%). These included pyrexia (30%), chills (20%), blood pressure increased (10%), tachycardia (10%), and oxygen saturation decreased (10%).

Please see Full Prescribing Information including Boxed WARNING for Aldurazyme:
https://www.biomarin.com/our-treatments/products/aldurazyme-laronidase-for-mps-i/

BRINEURA prescribing information

The first approved treatment for any form of Batten disease.

Brineura® (cerliponase alfa) is indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency. Brineura is the first enzyme replacement therapy to be directly administered into the fluid of the brain, treating the underlying cause of CLN2 disease by helping to replace the deficient TPP1 enzyme missing in affected children.

Due to the potential for anaphylaxis, appropriate medical support should be readily available, and patients should be observed closely, during and after Brineura infusion. If anaphylaxis occurs, immediately discontinue infusion and initiate appropriate medical treatment. Inform patients/caregivers of the signs and symptoms of anaphylaxis and to seek immediate medical care should these occur. Consider the risks and benefits of readministration of Brineura following an anaphylactic reaction.

CLN2 disease is an ultra-rare and rapidly progressing brain disorder that affects an estimated 20 children born in the United States each year–less than one in a million Americans.

INDICATION

Brineura® (cerliponase alfa) is a prescription medication used to slow loss of ability to walk or crawl (ambulation) in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

IMPORTANT SAFETY INFORMATION

Brineura is a prescription medicine. Before treatment with Brineura, it is important to discuss your child's medical history with their doctor. Tell the doctor if they are sick or taking any medication and if they are allergic to any medicines. Your child's doctor will decide if Brineura is right for them. If you have questions or would like more information about Brineura, contact your child's doctor.

Brineura is only given by infusion into the fluid of the brain (known as an intraventricular injection) and using sterile technique to reduce the risk of infection. An intraventricular access device or port must be in place at least 5 to 7 days prior to the first infusion. Intraventricular access device-related infections, including meningitis, were observed with Brineura treatment. If any signs of infection or meningitis occur, contact your child's doctor immediately. The signs and symptoms of infections may not be readily apparent in patients with CLN2 disease. Your doctor should vigilantly be looking for signs and symptoms of infection, including meningitis, during treatment with Brineura.

Your child's intraventricular access device should be replaced prior to 4 years of single-puncture administration of Brineura, because the device may deteriorate due to repeated use.

Brineura should not be used in patients with active intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection, including meningitis),

continued

symptom of acute, unresolved localized infection around the device insertion site (e.g. cellulitis or abscess), or and with shunts used to drain extra fluid around the brain. Your child's doctor should inspect the scalp and collect samples of your child's cerebrospinal fluid (CSF) prior to each infusion of Brineura, to check that there is no device failure or infections present.

Low blood pressure and/or slow heart rate may occur during and following the Brineura infusion. Contact your child's doctor immediately if these reactions occur.

Undesirable or hypersensitivity reactions related to Brineura treatment, including fever, vomiting, and irritability, may occur during treatment and as late as 24 hours after infusion. Your child may receive medication such as antihistamines before Brineura infusions to reduce the risk of reactions. Serious and severe allergic reactions (anaphylaxis) may occur. If a reaction occurs, the infusion will be stopped and your child may be given additional medication. If a severe reaction occurs, the infusion will be stopped and your child will receive appropriate medical treatment. If any signs of anaphylaxis occur, immediately seek medical care.

Safety and effectiveness in pediatric patients below 3 years of age have not been established.

The most common side effects reported during Brineura infusions included fever, problems with the electrical activity of the heart, decreased or increased protein in the fluid of the brain, vomiting, seizures, hypersensitivity, collection of blood outside of blood vessels (hematoma), headache, irritability, and increased white blood cell count in the fluid of the brain, device-related infection, slow heart rate, feeling jittery, and low blood pressure. Intraventricular device-related side effects included infection, delivery system-related complications, and increased white blood cell count in fluid of the brain.

These are not all of the possible side effects with Brineura. Talk to your child's doctor if they have any symptoms that bother them or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to BioMarin Pharmaceutical Inc. at 1-866-906-6100, or the FDA at 1-800-FDA-1088 or go to www.fda.gov/medwatch.

See full Prescribing Information at www.Brineura.com.

The first treatment for PKU.

Kuvan® (sapropterin dihydrochloride) Tablets and Powder for Oral Solution is the first FDA-approved medication for phenylketonuria (PKU). Kuvan is a form of BH4, the cofactor of the PAH enzyme, which helps the enzyme break down Phe. Kuvan is to be used in conjunction with a Phe-restricted diet.

WHAT IS KUVAN?

KUVAN® (sapropterin dihydrochloride) Tablets for Oral Use and Powder for Oral Solution are prescription medicines used to lower blood Phe levels in adults and children over one month of age with a certain type of phenylketonuria (PKU). KUVAN is to be used along with a Phe-restricted diet.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about KUVAN?

KUVAN can cause serious side effects, including:

Severe allergic reactions including anaphylaxis. Stop taking KUVAN and get medical help right away if you develop any of these signs or symptoms of a severe allergic reaction:

—Wheezing, coughing, or trouble breathing

—Feeling flushed, nauseous, lightheaded, or you faint

—Rash

—Inflammation of the lining of the esophagus or stomach (esophagitis and gastritis). Your doctor will monitor you for symptoms of inflammation in your upper gastrointestinal tract, including your stomach and esophagus. If untreated that inflammation can lead to serious side effects including narrowing of the esophagus, ulcers, and bleeding. Call your doctor right away if you have any of these signs or symptoms:

—Pain in the upper abdomen (stomach area), esophagus, or throat

—Nausea, trouble swallowing, loss of appetite, or vomiting

—Blood in your vomit or stool

—Black, tarry stools

—Phe levels that are too low. Patients have experienced low blood Phe during treatment with KUVAN. Low blood Phe is more common in children under the age of 7 who take high doses of KUVAN each day.

Too much or constant activity (hyperactivity) can happen with KUVAN. Tell your doctor if you have any signs of hyperactivity, including:

—Fidgeting or moving around too much

—Talking too much

continued

—**What should I tell my doctor before I take KUVAN?** Before you take KUVAN, tell your doctor about all your medical conditions, including if you:

—Are allergic to sapropterin dihydrochloride or any of the ingredients in KUVAN

—Have poor nutrition or have a loss of appetite

—Are pregnant or plan to become pregnant

—Are breastfeeding or plan to breastfeed. It is not known if KUVAN passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take KUVAN.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal and dietary supplements. KUVAN and other medicines may interact with each other. Especially tell your doctor if you take:

—A medicine that contains levodopa

—An antifolate medicine such as methotrexate, valproic acid, phenobarbital, trimethoprim

—Sildenafil (Revatio, Viagra), tadalafil (Adcirca, Cialis), vardenafil (Staxyn, Levitra)

—Tell your doctor if you are not sure if your medicine is one that is listed above. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take KUVAN?

See the detailed "Instructions for Use" that comes with KUVAN for information about the correct way to dissolve and take a dose of KUVAN tablets or KUVAN powder for oral solution.

—KUVAN does not work for everyone. It is not possible to know if KUVAN will work for you until you start taking KUVAN. Your doctor will check your blood Phe levels when you start taking KUVAN to see if the medicine is working.

—Take KUVAN exactly as your doctor tells you

—You can swallow KUVAN tablets whole or dissolve the tablets in water or apple juice

—KUVAN powder for oral solution should be dissolved in water or apple juice

—KUVAN should be taken with a PKU-specific diet. Any change you make to your diet may affect your blood Phe level. Follow your doctor's instructions carefully and do not make any changes to your dietary Phe intake without first talking with your doctor. Even if you take KUVAN, if your blood Phe levels are not well controlled, you can develop severe neurologic problems.

—Your doctor should continue to monitor your blood Phe levels often during your treatment with KUVAN to make sure that your blood Phe levels are not too high or too low and frequent monitoring for pediatric patients is recommended. Both high and low Phe can result in serious problems. Active management of dietary Phe intake while taking KUVAN is required.

—If you have a fever, or if you are sick, your blood Phe level may go up. Tell your doctor as soon as possible so he or she can change your dose of KUVAN to help keep your blood Phe levels in the desired range.

continued

—If you forget to take your dose of KUVAN, take it as soon as you remember that day. Do not take 2 doses in a day.

—If you take too much KUVAN, call your doctor for advice

The most common side effects of KUVAN are: headache, runny nose and nasal congestion, sore throat, diarrhea, vomiting, and cough.

These are not all the possible side effects of KUVAN. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to BioMarin at 1-866-906-6100.

See full Prescribing Information: https://www.biomarin.com/our-treatments/products/kuvan/

The first and only treatment for MPS VI.

NAGLAZYME® (galsulfase) is an enzyme replacement therapy for the treatment of mucopolysaccharidosis VI (MPS VI). Naglazyme provides a recombinant version of the enzyme missing in individuals diagnosed with MPS VI.

> Severe and life-threatening allergic reactions can occur during NAGLAZYME (galsulfase) infusions and up to 24 hours after infusion. Typical signs of an allergic reaction include shock, difficulty breathing, wheezing, swelling of the throat, and low blood pressure. Please see the Important Safety Information below and Full Prescribing Information.

MPS VI, also known as Maroteaux-Lamy Syndrome, is an inherited lysosomal storage disorder caused by the deficiency of an enzyme normally required for the breakdown of glycosaminoglycans (GAGs). If the enzyme is not present in sufficient quantities, the normal breakdown of GAGs is incomplete or blocked. The cell is unable to excrete the GAG residues, which then accumulate in the lysosomes of the cell. This accumulation disrupts the cell's normal functioning and gives rise to the physical manifestations of the disease. Only about 1,100 people in the world are thought to live with MPS VI.

INDICATION

NAGLAZYME® (galsulfase) is indicated for patients with mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy Syndrome). NAGLAZYME has been shown to improve walking and stair-climbing capacity.

IMPORTANT SAFETY INFORMATION

Severe and life-threatening allergic reactions can occur during NAGLAZYME (galsulfase) infusions and up to 24 hours after infusion. Typical signs of an allergic reaction include shock, difficulty breathing, wheezing, swelling of the throat, and low blood pressure. If a severe allergic reaction occurs during infusion, the infusion should be stopped immediately and you should receive medical attention. Contact your doctor or get medical help right away if you develop any severe symptoms after infusion.

In clinical trials, most patients developed antibodies to NAGLAZYME treatment. There was no clear relationship between antibody formation and the safety or effectiveness of NAGLAZYME.

Serious and severe infusion reactions are associated with NAGLAZYME, including hives, chest pain, rash, abdominal pain, difficulty breathing, swelling, fever, and eye irritation. You should receive medication such as antihistamines before NAGLAZYME infusions to reduce the risk of infusion reactions. If an infusion reaction occurs, the infusion should be slowed or stopped and you may be given additional medication.

The most common side effects of NAGLAZYME seen in clinical trials were rash, pain, hives, fever, itching, chills, headache, nausea, vomiting, abdominal pain and difficulty breathing. The most

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common side effects requiring medical attention are infusion-related effects.

These are not all of the possible side effects with NAGLAZYME. Talk to your doctor if you have any symptoms that bother you or that do not go away.

NAGLAZYME is a prescription medicine. Before treatment with NAGLAZYME, it is important to discuss your medical history with your doctor. Tell your doctor if you are taking any medication and if you are allergic to any medicines. Your doctor will decide if NAGLAZYME is right for you. If you have questions or would like more information about NAGLAZYME, contact your doctor.

Spinal cord damage may occur due to the natural MPS VI disease process. Signs of spinal cord injury include back pain, loss of bladder and bowel control, numbness, and paralysis. Contact your doctor immediately if you develop any of these symptoms.

Call your doctor for medical advice about side effects. You may report side effects to BioMarin at 1-866-906-6100 and the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

For more information, call BioMarin RareConnections™ at 1-866-906-6100.

See full Prescribing Information at:
https://www.biomarin.com/our-treatments/products/naglazyme-galsulfase-for-mps-vi/

PALYNZIQ prescribing information

The first and only enzyme therapy approved for adults living with PKU.

WARNING: RISK OF ANAPHYLAXIS

PALYNZIQ can cause a severe allergic reaction (anaphylaxis) that may be life-threatening and can happen any time during treatment with PALYNZIQ.

For more information, read the Important Safety Information below or see the full Prescribing Information and Medication Guide at PALYNZIQ.com.

PALYNZIQ® (pegvaliase-pqpz) Injection is the first FDA-approved enzyme substitution therapy for adults with PKU (phenylketonuria) who have uncontrolled blood Phe (phenylalanine) levels above 600 micromol/L (10 mg/dL) on their current treatment. PALYNZIQ is a once-daily self-administered therapy that acts independently of the phenylalanine hydroxylase (PAH) enzyme, so it is an option for all eligible adult patients living with PKU.

IMPORTANT SAFETY INFORMATION

What is PALYNZIQ?

PALYNZIQ® (Pal-lin-zeek) (pegvaliase-pqpz) is a prescription medication used to lower blood levels of phenylalanine (Phe) in adults with PKU (phenylketonuria) who have uncontrolled blood Phe levels above 600 micromol/L (10 mg/dL) on their current treatment. You should discuss the potential benefits and risks of PALYNZIQ with your healthcare provider.

What is the most important information I should know about PALYNZIQ?

PALYNZIQ can cause a severe allergic reaction (anaphylaxis) that may be life threatening and can happen any time during treatment with PALYNZIQ.

PALYNZIQ® (Pal-lin-zeek) (pegvaliase-pqpz) is a prescription medication used to lower blood levels of phenylalanine (Phe) in adults with PKU (phenylketonuria) who have uncontrolled blood Phe levels above 600 micromol/L (10 mg/dL) on their current treatment. You should discuss the potential benefits and risks of PALYNZIQ with your healthcare provider.

Severe allergic reactions are a serious but common side effect of PALYNZIQ.

You will receive your first injection of PALYNZIQ in a healthcare setting where you will be closely watched for at least 1 hour after your injection for a severe allergic reaction.

Your healthcare provider will prescribe auto-injectable epinephrine for you, and will teach you (or your caregiver) and your observer, if needed, when and how to use it if you have a severe allergic reaction.

If you have a severe allergic reaction during treatment with PALYNZIQ, you will need to receive an injection of epinephrine immediately and get emergency medical help right away.

Your healthcare provider will decide if you (or your caregiver) are able to give the PALYNZIQ injections, recognize the signs and symptoms of a severe allergic reaction, give an injection of epinephrine, and call for emergency help, if needed.

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Your healthcare provider may recommend that an adult observer (or your caregiver) be with you when you give your PALYNZIQ injection and for at least 1 hour after your injection to watch you for signs and symptoms of a severe allergic reaction and, if needed, give you an injection of epinephrine and call for emergency medical help.

Stop injecting PALYNZIQ and get emergency medical care right away if you have any of the following symptoms:

—Fainting (passing out)
—Dizziness or lightheadedness
—Sudden confusion
—Trouble breathing or wheezing
—Chest discomfort or chest tightness
—Fast heart rate
—Swelling of your face, lips, eyes, or tongue
—Throat tightness
—Flushed skin
—Skin rash, itching, or raised bumps on skin
—Nausea, vomiting, or diarrhea
—Losing control of urine or stools

Keep the auto-injectable epinephrine with you at all times during treatment with PALYNZIQ. Read the Patient Information that comes with the auto-injectable epinephrine that your healthcare provider prescribes for you for more information.

If you have a severe allergic reaction, do not continue to take PALYNZIQ until you talk with your healthcare provider. Your healthcare provider will tell you if you can continue treatment with PALYNZIQ.

People taking PALYNZIQ have also experienced allergic reactions other than anaphylaxis. Talk to your healthcare provider if you experience any allergic reactions when taking PALYNZIQ.

PALYNZIQ REMS: PALYNZIQ is available only through a restricted program called the PALYNZIQ REMS (Risk Evaluation and Mitigation Strategy). Talk to your healthcare provider about the PALYNZIQ REMS and how to enroll.

What should I tell my healthcare provider BEFORE starting PALYNZIQ?

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Before injecting PALYNZIQ, talk to your healthcare provider right away if you cannot or will not use auto-injectable epinephrine to treat a severe allergic reaction. If you are pregnant or plan to become pregnant while taking PALYNZIQ, talk to your healthcare provider to discuss the risks and benefits of taking PALYNZIQ during pregnancy to you and your unborn baby. If you are breastfeeding or plan to breastfeed, talk to your healthcare provider about the best way to feed your baby if you take PALYNZIQ.

Before injecting PALYNZIQ, read the Medication Guide and Instructions for Use that come with your PALYNZIQ injection.

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What should I watch for AFTER starting PALYNZIQ?

PALYNZIQ may cause serious side effects, including:

Severe allergic reactions (anaphylaxis)

Other allergic reactions to PALYNZIQ can happen during treatment with PALYNZIQ. Contact your healthcare provider right away if you have any of the following symptoms of an allergic reaction including: rash, itching, or swelling of the face, lips, eyes, or tongue. Your healthcare provider may change your dose of PALYNZIQ, stop your treatment with PALYNZIQ for a period of time, or prescribe medicine for you to take before your PALYNZIQ injection to help reduce the symptoms of an allergic reaction.

The most common side effects of PALYNZIQ include injection site reactions (such as redness, itching, pain, bruising, rash, swelling, or tenderness), joint pain, headache, skin reactions that spread and last at least 14 days (such as itching, rash, or redness), nausea, stomach pain, vomiting, cough, mouth and throat pain, itching, diarrhea, stuffy nose, feeling very tired, dizziness, anxiety, and low levels of Phe in your blood.

These are not all of the possible side effects of PALYNZIQ. Speak with your healthcare provider right away about any side effects.

IMPORTANT NOTES

Blood Phe testing and diet

Your healthcare provider will monitor your blood Phe levels during PALYNZIQ treatment

Monitor the amount of protein and Phe that you eat or drink. Your healthcare provider may change the amount of protein and Phe you should have in your diet during treatment with PALYNZIQ, depending on the levels of Phe in your blood. Follow your healthcare provider's instructions about the amount of protein and Phe you should have in your diet.

Missed dose

If a dose is missed, take your next dose as scheduled and do not take 2 doses of PALYNZIQ to make up for the missed dose.

Pregnancy Surveillance Program

There is a pregnancy surveillance program for females who take PALYNZIQ during pregnancy, or who become pregnant while receiving PALYNZIQ or within 1 month after their last dose of PALYNZIQ. The purpose of this program is to collect information about the health of you and your baby while taking PALYNZIQ. Talk to your healthcare provider about how you can take part in this program or call BioMarin at 1-866-906-6100.

You may report side effects to BioMarin at 1-866-906-6100.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

See full Prescribing Information and Medication Guide at:
https://www.biomarin.com/our-treatments/products/palynziq/

VIMIZIM prescribing information

The first and only treatment for Morquio A syndrome (MPS IVA).

> Life-threatening allergic reactions, known as anaphylaxis, can occur during VIMIZIM® (elosulfase alfa) infusions. Typical signs of anaphylaxis include cough, rash, throat tightness, hives, flushing, changes in skin color, low blood pressure, shortness of breath, chest pain, and gastrointestinal symptoms such as nausea, abdominal pain, retching, and vomiting. Contact your doctor or get medical help right away if these symptoms occur during or after VIMIZIM infusions. If you have a respiratory illness, you may be at risk for a sudden worsening of your condition, and you may require additional monitoring.

Vimizim® (elosulfase alfa) is the first approved enzyme replacement therapy designed to address the underlying cause of Morquio A syndrome, or mucopolysaccharidosis IVA (MPS IVA) — a deficiency in the enzyme N-acetylgalactosamine-6 sulfatase (GALNS). VIMIZIM works at a cellular level to help with deficient enzyme activity.

Morquio A is a rare and progressive inherited disease that affects major organ systems in the body. People living with Morquio A are missing an enzyme essential in the breakdown and removal of the glycosaminoglycans (GAGs) called keratan sulfate (KS) and chondroitin-6-sulfate (C6S).

INDICATION

VIMIZIM® (elosulfase alfa) is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

IMPORTANT SAFETY INFORMATION

VIMIZIM is a prescription medicine. Before treatment with VIMIZIM, it is important to discuss your medical history with your doctor. Tell your doctor if you are sick or taking any medication and if you are allergic to any medicines. Also tell your doctor if you are pregnant, planning to become pregnant, or are a nursing mother. Your doctor will decide if VIMIZIM is right for you. If you have questions or would like more information about VIMIZIM, contact your doctor.

Anaphylaxis can occur during any VIMIZIM infusion and up to three hours after any infusion, and hypersensitivity reactions have been observed as early as 30 minutes from the start of infusion but as late as six days after infusion.

Serious and severe reactions can happen with VIMIZIM treatment, including life-threatening allergic reactions (anaphylaxis), hives, swelling, cough, shortness of breath, and flushing. You should receive medication such as antihistamines before VIMIZIM infusions to reduce the risk of reactions. If a reaction occurs, the infusion should be slowed or stopped and you may be given additional medication. If a severe reaction occurs, the infusion should be stopped immediately and you will receive appropriate medical treatment.

If you have acute febrile or respiratory illness at the time of VIMIZIM infusion, you may be at higher risk of life-threatening complications from hypersensitivity reactions. If you use supplemental oxygen or continuous positive airway pressure (CPAP), you should have it available during your infusion in the event of a sudden reaction, or extreme drowsiness/sleep from antihistamines.

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Spinal cord damage may occur due to the natural MPS IVA disease process. Signs of spinal cord injury include back pain, numbness and paralysis, and loss of bladder and bowel control. Contact your doctor immediately if you develop any of these symptoms.

The most common side effects reported during VIMIZIM infusions included fever, vomiting, headache, nausea, abdominal pain, chills, and fatigue. These are not all of the possible side effects with VIMIZIM. Talk to your doctor if you have any symptoms that bother you or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to BioMarin at 1-866-906-6100 and the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

For more information, call BioMarin RareConnections™ at 1-866-906-6100.

Please see full Prescribing Information, including important warning:
https://www.biomarin.com/our-treatments/products/vimizim/

VOXZOGO prescribing information

The first and only therapy approved to increase linear growth in children with achondroplasia aged 5 years and over with open growth plates.

VOXZOGO™ (vosoritide), a once-daily injection, is an analog of C-type natriuretic peptide (CNP) approved to increase linear growth in individuals or children with achondroplasia 5 years and older with open epiphyses (growth plates). Children on VOXZOGO have regular check ups to measure weight, growth, and physical development and adjust their dose. VOXZOGO should be stopped upon confirmation of no further growth potential, when growth plates are closed.

VOXZOGO may cause serious side effects including a temporary decrease in blood pressure in some patients. To reduce the risk of a decrease in blood pressure and associated symptoms (dizziness, feeling tired, or nausea), patients should be well fed and hydrated in the hour before receiving VOXZOGO. Please see below for Important Safety Information, full Prescribing Information, and Patient Prescribing Information.

INDICATION

VOXZOGO™ is a prescription medicine used to increase linear growth in children with achondroplasia who are 5 years of age and older with open bone growth plates (epiphyses). This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

What is VOXZOGO used for?

VOXZOGO is a prescription medicine used to increase linear growth in children with achondroplasia who are 5 years of age and older with open growth plates (epiphyses).

It is not known if VOXZOGO is safe and effective in children with achondroplasia under 5 years of age.

VOXZOGO is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

What is the most important safety information about VOXZOGO?

VOXZOGO may cause serious side effects including a temporary decrease in blood pressure in some patients. To reduce the risk of a decrease in blood pressure and associated symptoms (dizziness, feeling tired, or nausea), patients should eat a meal and drink 8 to 10 ounces of fluid within 1 hour before receiving VOXZOGO.

What are the most common side effects of VOXZOGO?

The most common side effects of VOXZOGO include injection site reactions (including redness, itching, swelling, bruising, rash, hives, and injection site pain), vomiting, joint pain, decreased blood pressure, and stomach ache. These are not all the possible side effects of VOXZOGO. Ask your healthcare provider for medical advice about side effects, and about any side effects that bother the patient or that do not go away.

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How is VOXZOGO taken?

VOXZOGO is taken daily as an injection given under the skin, administered by a caregiver after a healthcare provider determines the caregiver is able to administer VOXZOGO. Do not try to inject VOXZOGO until you have been shown the right way by your healthcare provider. VOXZOGO is supplied with Instructions for Use that describe the steps for preparing, injecting, and disposing VOXZOGO. Caregivers should review the Instructions for Use for guidance and any time they receive a refill of VOXZOGO in case any changes have been made.

Inject VOXZOGO 1 time every day, at about the same time each day. If a dose of VOXZOGO is missed, it can be given within 12 hours from the missed dose. After 12 hours, skip the missed dose and administer the next daily dose as usual.

The dose of VOXZOGO is based on body weight. Your healthcare provider will adjust the dose based on changes in weight following regular check-ups.

Your healthcare provider will monitor the patient's growth and tell you when to stop taking VOXZOGO if they determine the patient is no longer able to grow. Stop administering VOXZOGO if instructed by your healthcare provider.

What should you tell your doctor before or during taking VOXZOGO?

Tell your doctor about all of the patient's medical conditions including

If the patient has heart disease (cardiac or vascular disease), or if the patient is on blood pressure medicine (anti-hypertensive medicine).

If the patient has kidney problems or renal impairment.

If the patient is pregnant or plans to become pregnant. It is not known if VOXZOGO will harm the unborn baby.

If the patient is breastfeeding or plans to breastfeed. It is not known if VOXZOGO passes into breast milk.

Tell your doctor about all of the medicines the patient takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

You may report side effects to BioMarin at 1-866-906-6100. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

See additional safety information in the full Prescribing Information and Patient Prescribing Information: https://www.biomarin.com/our-treatments/products/voxzogo/

"The lessons learned were easy to understand yet difficult to master. The manner in which we overcame challenges provided a steadfast approach that was a guiding light throughout our development efforts: stay true to the science, remain persistently focused on tasks and goals, be willing to take risks, do not fear making mistakes, apply imagination and experience in fulfilling regulatory expectations, and create value while always maintaining your integrity."

—Robert Baffi, Ph.D.

retired President of Global Manufacturing
& Technical Operations for BioMarin

How Technical Operations Paved the Way for BioMarin's Success

Even to the most sophisticated industry observers, the role of technical operations is often overlooked, undervalued, or misunderstood. In many biopharmaceutical companies, process development, manufacturing, and quality often remain invisible. These activities only come into view during times of product shortages or when lack of regulatory compliance becomes public. This book offers an account of the critical role that technical operations have played in the success of BioMarin. By shining a light on this part of the organization, many hard-fought lessons learned emerge and provide an understanding of what it takes to rapidly develop safe and effective medicines for patients whose lives depend on them and match the urgency they feel.