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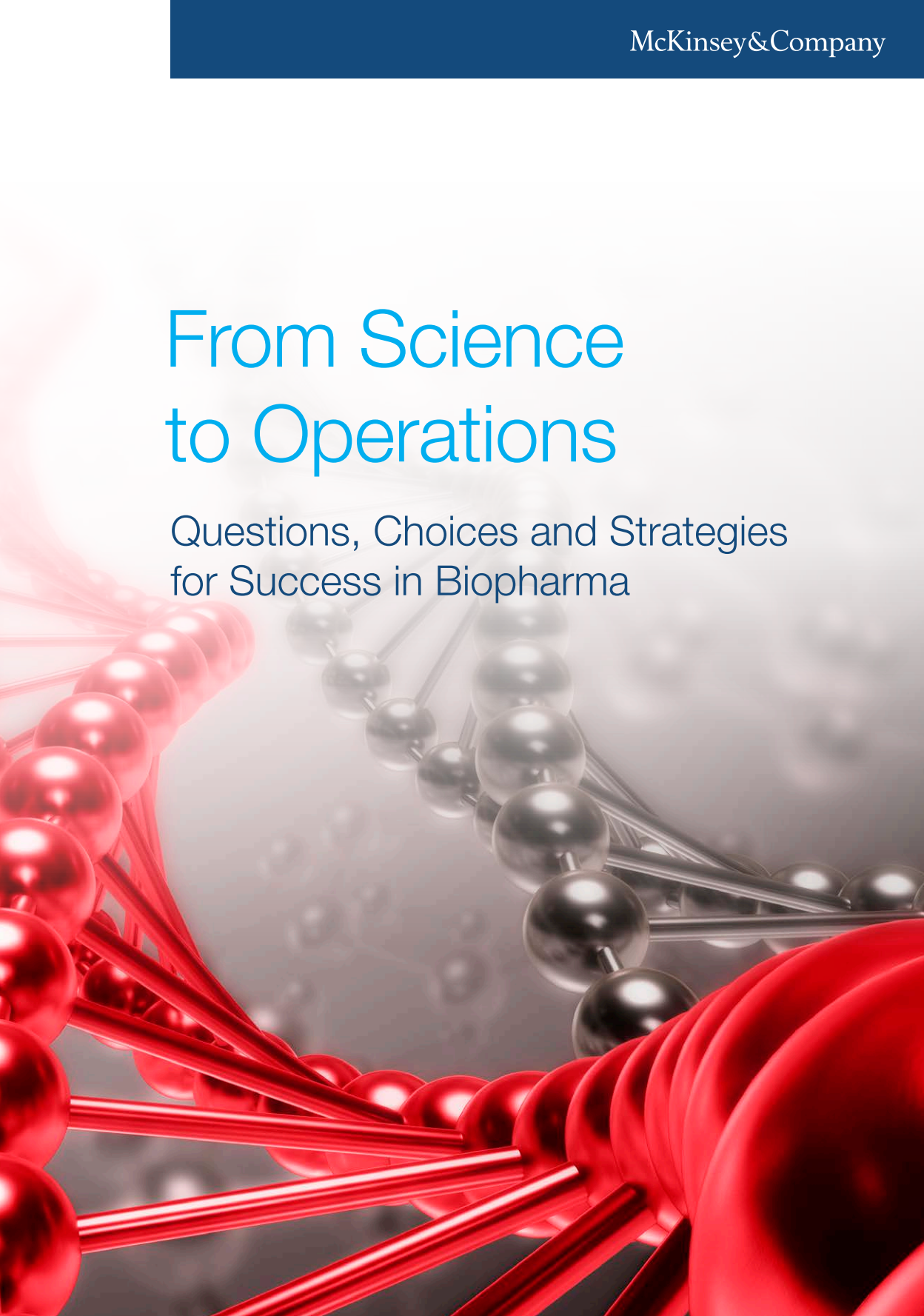
From Science to Operations

Questions, Choices and Strategies for Success in Biopharma



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Questions, Choices and Strategies for Success in Biopharma

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As this book shows very clearly, the technical and business complexity of biopharma is increasing all the time. As a result, the interconnectedness between different players in the life sciences ecosystem is becoming ever more important to efficient and successful drug development and commercialization.

To provide tools, expertise, and improved patient access, disease foundations and patient advocacy groups should be strategically partnering with both academia and industry across all stages of drug discovery, launch, and manufacture. The FDA has piloted several new programs to work more closely with patients and drug developers, manufacturers and payors are being consulted earlier in the development process to address patient access and reimbursement.

Many biopharmas have established strategic relationships both at academic centers and with start-ups through corporate ventures. As complexity in the science and business of drug discovery, launch, and manufacturing operations continues to rise, these kinds of relationship will play a critical role: accelerating the speed and increasing the probability of successfully bringing new treatment to patients.

Gail Maderis
CEO of BayBio (a nonprofit company that supports the life science community)

Over the past 30 years cell-culture technology has moved into the mainstream of the biopharma world. Now an established science, cell-culture-derived medicines have treated more than 40 million patients, often with novel products that could not have been delivered in any other way. The technology has proved to be both safe and versatile, and it continues to yield new approaches to unmet medical needs.

Significant operational challenges await, however. The industry must learn to manage the development, launch, and ongoing production of larger and ever more complex product portfolios. Access to talent threatens to become a significant bottleneck. Growing global demand is stretching production and distribution footprints. And both established and emerging markets are becoming increasingly sensitive to the cost of healthcare provision. This book provides a comprehensive overview of the choices, challenges, and strategic opportunities facing the biopharma industry today. Critically, it encompasses both the next steps in the evolution of established technologies, like mAbs, and the emergence of new ones, like cell and gene therapies. That matters, because even as they tackle today's challenges, biopharma executives must always be looking ahead to tomorrow's opportunities.

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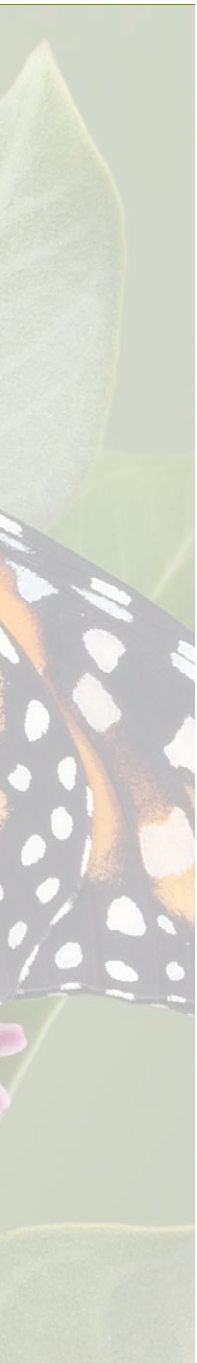


The beauty and the beast: A perspective on biopharmaceuticals

Ralf Otto, Alberto Santagostino, Ulf Schrader

Biopharmaceuticals are increasingly revolutionizing medical treatment and are set to become the core of the pharmaceutical industry. But achieving the next phase of their potential will require a further revolution, not only in the laboratory but also in strategy, technology, and operations.

Biopharmaceuticals are among the most sophisticated and elegant achievements of modern science. The huge, complex structures of these drugs don't just look extraordinary in the 3-D modeling systems used to design them, they also perform their jobs remarkably well, offering high efficacy and few side effects. That the biopharma industry exists at all is testament to the persistence and effectiveness of the scientific community. And those scientists and engineers rely in turn on access to tools of a power and sophistication that would have been unthinkable a generation ago: from computer systems capable of modeling complex molecules, to fast, inexpensive DNA sequencing capabilities leading to in-depth understanding beyond the genome to the proteome and metabolome.

The story of biopharmaceuticals is one of extraordinary success, and it is only just beginning. Early blood and tissue processing resulted in products that still play a critical role in public health, like clotting factors and heparin, which helped to address hemophilia and thrombosis, respectively. If anything, the revolution driven by vaccines was even more important, saving countless lives through prevention rather than treatment and eradicating serious diseases. Now, the industry has moved into the era of recombinant proteins, pioneered by agonistic replacement therapies like the recombinant insulins. Another

class of recombinant proteins—monoclonal antibodies (mAbs)—has become a mainstream technology today, tackling previously untreatable diseases like cancers and autoimmune inflammatory conditions.

There is even more to come. The existing treatment archetypes are evolving and becoming more sophisticated all the time (e.g., conjugates, fab fragments), and continuing research is yielding entirely new types of products. Radically new concepts are making it to the market, like the cell therapy Provenge against cancer and, somewhat further out, gene therapies (e.g., Kynamro, an antisense oligonucleotide) with even more amazing promises of regenerative medicine or disease remission.

Technical challenges

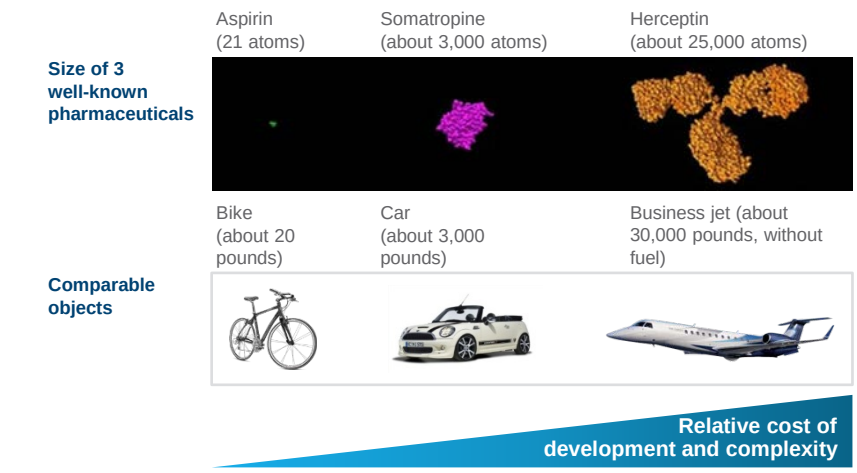
These new products have created their own operational and technological challenges. Reproducing large molecules reliably at an industrial scale requires manufacturing capabilities of a previously unknown sophistication. A molecule of aspirin (chemical) consists of 21 atoms. A biopharmaceutical molecule (protein) might contain anything from 2,000 (interferons) to 25,000 (mAbs) atoms. The "machines" that produce recombinant therapeutics are genetically modified living cells that must be frozen for storage, thawed without damage, and made to thrive in the unusual environment of a reaction vessel. The molecules must then be separated from the cells that made them and the media in which they were produced, all without destroying their complex, fragile structures (Exhibit 1).

All this sophistication comes at great cost. Large-scale biotech manufacturing facilities are expensive: $200 million to $500 million or more (compared with a similar-scale small-molecule facility that might cost just $30 million to $100 million), and they are time-consuming to build (four to five years). These facilities are costly to run too, with long process durations, low yields, expensive raw materials, and, not least, the need for a team of highly skilled experts to operate them.

The rapid growth and increasing importance of the industry are producing a new set of challenges and opportunities. To keep pace, biopharma players will have to revisit and fundamentally reassess many of the strategies, technologies, and operational approaches they currently use.

Exhibit 1

Copying biopharmaceuticals is not a simple task



Note: The molecules are to scale; the objects are not

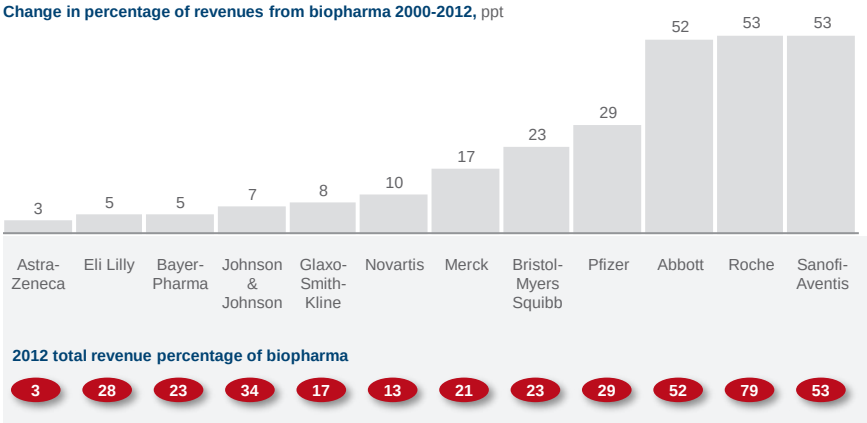
Beauty: Success breeds success

The opportunity in biopharmaceuticals is already big and is growing too rapidly to ignore. Biopharmaceuticals today account for revenues of $163 billion, making up approximately 20 percent of the global pharma market. The segment is by far the fastest growing part of the pharma industry: its current annual growth rate of more than 8 percent is more than twice that of conventional pharma, and growth is expected to continue at that rate for the foreseeable future.

The efficacy and safety of biopharmaceutical products, combined with their ability to address previously untreatable conditions, allows pharma companies to command high prices for innovative drugs. Strong demand has driven significant profits, despite the high cost of goods sold (COGS). Biopharmaceuticals have set new standards for blockbuster drugs as well. Blockbusters are traditionally defined as drugs that earn $1 billion or more in annual sales; the top 15 bio-pharma products each enjoy annual revenues of more than $2 billion, with some, like the anti-inflammatory drug Humira, earning more than $10 billion per year. For many players, the key challenge has been simply making enough product to

Exhibit 2

Many large pharmaceutical companies are shifting their presence to biopharma



Source: EvaluatePharma (November 2012)

sell. Logically, major pharmaceutical companies across the world are increasingly shifting their R&D and sourcing focus to large-molecule products (Exhibit 2).

Investing in biotech R&D has yielded better returns than the pharma industry average. The current biologics development pipeline supports an outlook of continued healthy growth. The number of biotech patents applied for every year has been growing at 25 percent annually since 1995. There are currently more than 1,500 biomolecules undergoing clinical trials, and the success rate for biologics has so far been over twice that of small-molecule products, with 11.5 percent of biopharma products that pass the Phase I trial stage going on to launch.

The success of the clinical pipeline will lead to an unprecedented number of new molecule launches, rising from a handful a few years ago to 10 to 15 per year as biopharma products make up an increasing share of new FDA approvals in the future. A further steep increase is to be expected as multiple players begin to receive approval for the production of biosimilars after 2015.

If anything, the emerging picture of the longer term is even more exciting, with disruptive innovations like immunotherapies, antibody drug conjugates, and gene

and cell therapies all making progress toward commercial launch in the next few years. Biopharma looks poised to transform the industry once more, as increasing understanding of the interaction between drugs and the genetic makeup of patients helps to improve the targeting of therapies. Combined with robust, low-cost genetic profiling, this knowledge will improve treatment outcomes and serve to accelerate and improve the outcomes of clinical trials, helping to reduce the cost of drug development.

The beast: Cost, complexity, and regulatory scrutiny

As biopharma moves from the scientific frontier into the business mainstream, the industry will increasingly be forced to confront the same challenges faced by other businesses: maintaining competitiveness by ensuring affordability, quality, and delivery performance. And the necessary level of performance in each of these dimensions is likely to become considerably more demanding.

Demand for affordability and improved access to care will reshape industry

Downward cost pressure will intensify as health-care systems struggle to balance rising demand with flat or declining budgets. In this environment, payers may find it difficult to justify the annual treatment costs of $50,000 to $100,000 that some biopharma products currently demand. It is hard to imagine that these price premiums will be sustainable for any but the most innovative drugs. Furthermore, governments in emerging markets understand the critical role that biopharma will play in boosting health-care outcomes, and they are aggressively supporting alternative ways to fulfill demand for these products.

The result of these pressures will be the inevitable development of the biosimilars industry. The availability of biosimilar versions of human growth hormones and interferons has already opened access to these products to a far larger number of patients. As patent protection on more complex biopharmaceuticals expires, biosimilars will surely follow the same path.

Early regulatory and customer concern is already being overcome. In June 2013, for example, the European Union approved Remsima, Celtrion's biosimilar version of the mAb Remicade. In emerging markets, where consumers are able to access products only if they are available at considerably lower prices, enthusiasm for biosimilars is likely to be even stronger. The biosimilars industry has the potential to change the commercial landscape as profoundly as generics players have

done in conventional pharma. Pressure from biosimilars will force the innovators to accelerate the search for better products, and will increase pressure on the industry as a whole to reduce its COGS.

Complexity will become a significant hurdle

As the number of products rises and new process technologies, such as continuous manufacturing, are introduced, the complexity of biopharma operations and the biopharma supply chain will increase. Evidence indicates that current production programs are already stretching the industry, with several players failing to deliver to the market. This challenge will only increase as sites move from the current "one line, one product" setup toward nimble and flexible multiple product operations and are required to manage both current and future technologies under one roof.

Supply chain complexity has to be brought under control

The high premium on biopharmaceutical products and the relatively smaller share of revenues they have historically accounted for in big pharmaceutical companies have led to industrywide challenges in the supply chain. Complexity, cost, and service levels are currently far from small-molecule best practices, even considering the additional complexity of cold-chain requirements.

Many more manufacturing technology platforms will come online

The new classes of molecules discussed above, from drug conjugates to the cell and gene therapies arriving in the next five years, will each require its own novel manufacturing, supply, and quality assurance approaches. Today, many companies that are insourcing these products in the late clinical or early commercialization phase are struggling to set up the novel technologies and processes required to produce them. Making the right decision about how to set up operations for an autologous cell therapy is a nonobvious exercise, and there will naturally be many suboptimal solutions before sufficient experience is built.

Quality compliance will increasingly keep the industry on its toes

Quality functions are struggling to keep up with the rising demands of regulators, with the US Food and Drug Administration at head of the list. The industry has received an unprecedented number of warning letters and remediation programs

in the last five years, and the scrutiny is unlikely to decrease. Furthermore, the increasing relevance of global markets (beyond the United States, European Union, and Japan) is adding the complexity of multiple quality standards and regulatory regimes. Compliance, robustness of processes, and efficiency will need to be squared in one equation.

Strategy, technology, and operations: All set to change

The aforementioned trends will fundamentally reshape the industry. Biopharmaceuticals will be the realm of innovators not only in medicine and process sciences but also in operations. The changes will not be the same for everyone; a variety of business archetypes will coexist in the industry, and their strategies and success factors will differ in important ways.

Global innovators will have to drive product innovation in order to continue to command premium prices, shifting the frontier of technology and exploring new operational setups (such as the design and deployment of their future network). Biosimilars players will have to focus on cost, quality, and scale. For them, speed, process innovation, and operational excellence are must-win battles. Players based in emerging-market nations will have to find their own niches with the right operational and quality performance to make the best use of privileged access to, and knowledge of, their local markets. Contract manufacturing organizations (CMOs) will have to be at the leading edge of process innovation and operational efficiency, while retaining or building a spotless reputation for service and performance. Beyond these generic player archetypes, a detailed view of its own strategic position will be pivotal for each company, which will need to ask itself what it stands for in the market and what it needs to do in order to win.

Whatever their competitive niche, companies must continually evolve both their manufacturing technologies and their operational capabilities. Technologies are not yet sufficiently mature to rely only on operational improvement to drive quality and productivity up and cost down. Nor will technological improvements alone be sufficient to do those things.

We believe that the biopharmaceutical companies best positioned to succeed in tomorrow's market will be those that master a broad set of technical and operational capabilities. Decisions that companies are making today will have a critical influence on that success for two important reasons:

- **Operational excellence is a hard-won skill.** Capabilities such as lean, agile, and efficient manufacturing require sustained effort and commitment to develop and hard-wire into the organization.

- **Decisions made today will affect companies' competitive positions years or even decades into the future.** This is particularly true in areas such as footprint design and the choice of core manufacturing technologies.

A full discussion of all the technical and operational decisions facing biopharma companies today and in the coming years is beyond the scope of this article, but here is an overview of some of the most important considerations:

- Reduction of operating cost across manufacturing and quality by methodically adopting lean practices (e.g., eliminating waste, improving labor and asset efficiency) and improving process technology (including possible change controls and regulatory approvals); finding new ways to improve the performance of the production process from titer increases in expression systems, to purification improvement and process stabilization

- Improvements in operational agility and equipment utilization to increase manufacturing-site capacity for individual molecules by debottlenecking existing assets, introducing the ability to run multiple products in fewer lines, and improving the industry's readiness to respond quickly to the needs of a volatile market—all without compromising quality

- Capacity expansion, which may encompass decisions on risk taking for postponement of asset deployment, capital expenditure efficiency, and adoption of new technologies (such as the design of flexible facilities based on stainless steel, disposables, or hybrid systems to suit specific product and market conditions)

- The right make-or-buy decisions, as biopharma CMOs become increasingly capable and available, forcing companies to reevaluate where their core operational skills should lie and how they will ensure the cost, quality, and availability of those they choose to outsource

- Definition of the manufacturing footprint—that is, building, or acquiring, a strong, competitive network with the right suppliers, manufacturing plants, and distribution capabilities to balance cost, service, and customer

acceptance; in particular, a presence in emerging markets and the associated cost, regulatory, and market-access implications need to be considered with great care

- Improving efficiency in the supply chain, to manage inventory, distribution logic, and the complexities of the cold chain

- Streamlining the introduction of new products and new technology platforms, to support the ambition of pushing a far greater number of molecules through technical development and manufacturing launch

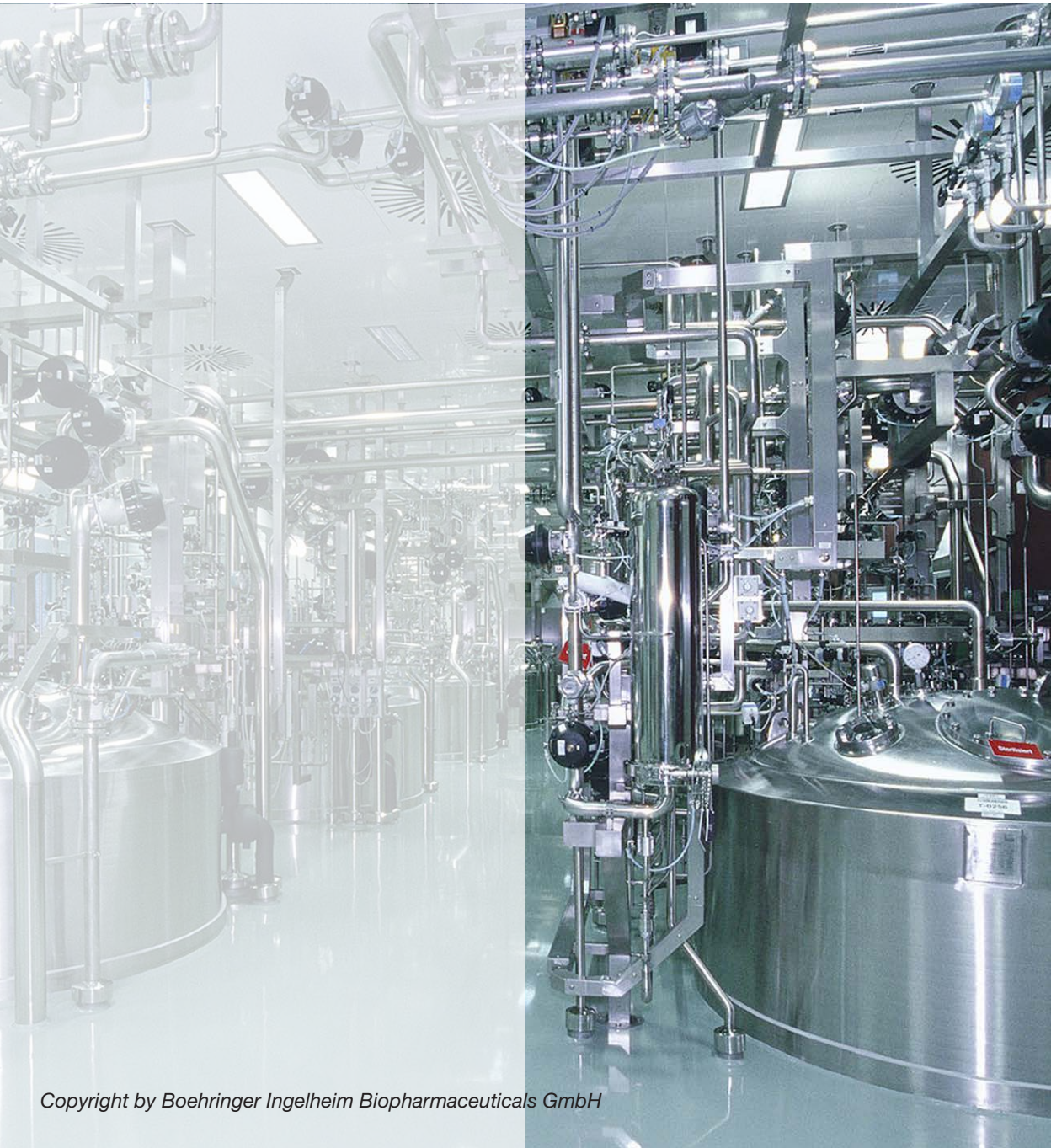
- Deployment of a high-performing organization with access to talent capable of handling these challenges, and the new ones that will inevitably emerge in such a rapidly evolving environment

□ □ □

The prize for organizations that do master these operational challenges will be far more significant than just short-term competitive advantage. Many of the next major opportunities for biotech will require companies to develop new and different technologies and operating models. Today's actions will shape companies' readiness to grasp these opportunities as they come to fruition.

At one end of the scale, for example, the industry must develop the capabilities to quickly and reliably produce the small batches of fully personalized medicines required to deliver cell therapies. At the other, it needs the high-volume, low-cost manufacturing capabilities necessary to deliver inexpensive insulin and vaccines against diseases like malaria that take so many lives today in low- and middle-income countries. Between these two extremes, companies will need to accelerate the development and commercialization of new molecules to allow a broader range of illnesses to be addressed, and they must reduce manufacturing costs, improve quality, and build capacity to broaden access to its life-changing products.

Only through a combination of strong science and deep operational excellence will the biopharma industry be able to fulfill its real potential to transform the health expectations of millions of people across the globe, successfully navigating both the beauty and the beast inherent in the sector.



From science to operations: Questions, choices, and strategies for success in biopharma

Martin Lösch, Ralf Otto, Alberto Santagostino, Ulf Schrader

In 2016, eight of the world's ten top-selling medicines will be biopharmaceutical products, in 2000, just one biopharmaceutical ranked among the top ten. And the full pipeline of biomolecules in clinical development shows that there is much more to come. For an industry that is less than three decades old, the growth and success of biopharma have been remarkable. Yet this revolution is only just beginning. Recombinant proteins led the way, but other, entirely new technologies—from cell therapies to genome editing—are rapidly reaching maturity. They bring with them the promise of treatments, even cures, for many of humanity's most difficult and damaging diseases.

This book isn't about the next disruptive scientific innovation in biopharma, however. It is about another revolution altogether, one that the sector is only now beginning to tackle, and one that McKinsey believes will require just as much creativity, energy, and commitment. This book is about biopharma's industrial revolution.

If biopharma is to fulfill its extraordinary potential—for the pharmaceutical industry and for society at large—its products must move from their current profitable niches into the mainstream. And to do that, the industry must overcome challenges of cost, quality, complexity, and scale.

In this book, we look at those challenges, to see where the industry stands today, where it needs to go, and why it is imperative that

biopharma players make some fundamental choices about that journey—today. Although biopharma leaders have always relied on their strong scientific background to drive business operations, they now need to master the leadership skills to manage change and drive innovation in a global operations setting at full industrial scale. Their scientific curiosity will help them as they transform lessons learned in other industries into biopharma-specific solutions.

The industrial revolution in biopharma will be unique because the industry is like no other. Biopharmaceutical products are hugely complex, consisting of tens of thousands of atoms (compared with the 10 to 50 atoms in a chemical pharmaceutical molecule), and dependent on difficult engineering at the macromolecular level. And the processes needed to build those products aren't just complex, they are also diverse. The techniques used in the production of mammalian antibodies bear little resemblance to the viral vectors used to inject new DNA in autologous cell therapies, for example. That means know-how gained in the development of one manufacturing platform is of little help in the development of another and that the relative maturity of different approaches varies greatly today.

Further, this complexity is not contained within factory walls. Biopharma products are delicate and need careful handling in storage, transportation, and use. Their fragility, together with the increasingly personalized nature of new types of treatment, means that the supply chains and services used to deliver them at scale will also look very different from conventional health-care approaches.

This complexity and diversity mean there will be no such thing as a general biopharma player. Instead, companies in the sector are making difficult strategic choices about the product categories and parts of the value chain in which they want to participate. Access to key technologies and capabilities is also driving make-or-buy decisions, with many companies choosing to outsource activities—not because they don't want to do them, but because they can't.

Choosing where to play won't be the same as winning there. Access to new markets, and sustained competitiveness in established ones, calls for dramatic reductions in manufacturing and distribution costs: in some cases from today's levels of thousands of dollars per dose to ten dollars or less. The evolution of manufacturing technologies will play a role here, but companies are also striving to execute with greatly improved quality, efficiency, and flexibility. McKinsey's research has shown that operating performance in today's biopharma sector is highly inconsistent. To fulfill its potential, the whole industry will aim to close

the performance gap with today's leaders, and tomorrow's leaders will learn to achieve the same sustainable, year-on-year performance improvements that have transformed other industries.

Each of these themes is explored in greater detail through the rest of this book. In "The challenges of biomanufacturing operations," we look at the fundamental and growing differences between biopharmaceuticals and chemical pharmaceuticals, beyond therapeutic proteins to the next generation of technology platforms, and at the implications of the emerging biosimilars market.

In "Strategic choices for biopharma players," we examine the importance of structural design to the performance of biopharma operations and the structural choices that companies face as they seek to maximize effectiveness. We explore the evolution of the biopharmaceutical value chain, including the development of manufacturing networks and the rising importance of effective technical-development and product-launch processes. We assess the new biomanufacturing process technologies coming into play and their implications for the facilities of the future. We also explore the increasingly significant role of contract manufacturing organizations and the changing nature of the supply chain, particularly in the context of the emerging Asian biomanufacturing powerhouses.

Finally, in "Excellence in execution," we look at current and future performance expectations for biopharma players: the need to improve the transparency of current performance with industry benchmarks and the pressure to transform quality, productivity, and flexibility. We then discuss the approaches that will enable such a change, from the sustainable transformation of operational performance using lean methodologies, to how a structured approach can reveal the underlying causes of process yield variability to deliver a radical step change in technical performance.

We hope the content we have gathered here will serve as inspiration to leaders across the biopharma sector. This industry has proved that it is not scared of the most formidable scientific problems. Now, it is time to find novel solutions for some of the world's toughest operational challenges too.