Why Are Biopharmaceuticals So Expensive?

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June 12, 2023
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Biopharmaceuticals are a type of pharmaceutical drug derived from living organisms or their components using molecular biology. They have revolutionized the treatment of various diseases and conditions, offering targeted therapies with improved efficacy and fewer side effects compared to traditional small-molecule drugs. However, there are several factors that contribute to the high cost of biopharmaceuticals: research and development costs, manufacturing challenges, regulatory requirements, contamination risks, and limited competition and patent protection.

Developing a biopharmaceutical is a complex and expensive process that involves extensive research, preclinical studies, and clinical trials. The costs associated with discovering and developing a new drug, including the investment in research, equipment, and human resources, can be enormous. The high failure rate in drug development further increases the costs, as the expenses incurred for unsuccessful drug candidates need to be recouped from successful ones.

Biopharmaceuticals are typically produced using living cells or microorganisms, which adds complexity to the manufacturing process. These drugs require specialized facilities, equipment, and highly trained personnel to ensure proper cultivation, purification, and formulation.

The manufacturing process also needs to be carefully controlled to maintain product consistency and minimize the risk of contamination or variation in potency. These factors contribute to the higher manufacturing costs compared to traditional small-molecule drugs. Biopharmaceuticals are subject to strict regulatory oversight, particularly from agencies like the U.S. Food and Drug Administration (FDA). The approval process for biologics is often more complex and time-consuming compared to traditional drugs due to the inherent variability of living organisms and the need to demonstrate safety and efficacy. The rigorous testing and evaluation required to obtain regulatory approval can significantly increase the development costs and time, subsequently, the price of the final product.

Ensuring the sterility and purity of biologics is crucial to maintain their safety and efficacy. Any contamination during manufacturing can lead to batch losses, increased production costs, and potential harm to patients. Stringent measures, quality control procedures, and investments in contamination prevention technologies are necessary to minimize these risks, which can contribute to higher costs.

Biopharmaceuticals often enjoy patent protection, granting exclusive marketing rights to the developer for a specified period. During this time, the manufacturer can charge higher prices to recoup the investment and make a profit. Limited competition from generic versions due to the complexity of manufacturing biosimilars also contributes to the sustained high prices. It's worth noting that efforts are being made to address the high costs of biopharmaceuticals. Biosimilar development, regulatory reforms, and pricing negotiations are some of the strategies being explored to enhance affordability and access to these important treatments.

Developing Biopharmaceuticals

The time required to develop a biopharmaceutical can vary significantly depending on several factors, including the complexity of the product, the nature of the disease being targeted, the availability of resources, and regulatory requirements. On average, it can take anywhere from 8 to 15 years to develop a biopharmaceutical from the initial discovery stage to approval for commercialization. However, it's important to note that this is a rough estimate, and the actual timeline can be shorter or longer.

The process of developing a biopharmaceutical typically involves multiple stages. The first stage is the discovery and research phase, which involves identifying a potential target, such as a specific protein, DNA or mRNA pathway related to a disease, and conducting extensive research to understand its function and potential therapeutic applications. This stage can take several years. The second stage is the preclinical development stage which is where the candidate drug is tested in laboratory and animal models to evaluate its safety, efficacy, and pharmacokinetics. It also involves formulation development and optimization. The preclinical development can take around 1 to 3 years. The next stage is the clinical trials stage in which the candidate drug is tested in animals first then in humans through a series of clinical trials, typically conducted in three phases. Phase 1 trials assess the drug's safety and dosage, Phase 2 trials evaluate its effectiveness and side effects, and Phase 3 trials involve larger populations to confirm efficacy and monitor adverse reactions. Clinical trials can take several years to complete, often ranging from 5 to 10 years. The fourth stage is the regulatory approval phase and this is done once the clinical trial data is collected, it is submitted to regulatory authorities, such as the FDA in the United States or the EMA in Europe, for review and approval. The regulatory approval process can vary in duration, ranging from several months to a few years, depending on the agency and the specific requirements. The fifth stage is the manufacturing and quality control stage and this occurs after the biopharmaceutical is approved, it needs to be manufactured on a larger scale to meet market demand. Costs in this stage include establishing manufacturing facilities, acquiring equipment, implementing quality control systems, staff hiring and training, securing access to approved raw materials and ensuring compliance with Good Manufacturing Practices (GMP).

The costs associated with clinical trials can be substantial and depend on factors such as the number of participants, trial duration, monitoring, data analysis, and site management. The expenses include protocol development, patient recruitment, clinical trial site fees, investigator fees, monitoring, data management, and analysis. The costs for clinical trials can range from several million to hundreds of millions of dollars, depending on the complexity and duration of the trials. Costs in the regulatory approval phase include regulatory strategy development, preparation of regulatory documents, legal fees, regulatory consulting, and fees associated with the submission and review process. The expenses for regulatory approval can range from hundreds of thousands to several million dollars. Costs in the marketing and commercialization phase include marketing campaigns, salesforce, distribution, and market access activities. These costs can be substantial and depend on the target market, marketing strategy, and competition.

Additionally, factors such as the need for additional research, unexpected challenges, and post-approval studies can further contribute to the overall expenses. It is crucial for pharmaceutical companies to carefully manage their resources and investments throughout the development process.

Failures

High failure rates makes biopharmaceutical research expensive since developing a successful biopharmaceutical is challenging, and the failure rates are high. Many drug candidates do not meet the required safety and efficacy standards during preclinical or clinical development. The costs associated with failed drug candidates, including research expenses, clinical trial costs, and investments in manufacturing infrastructure, contribute to the overall expense of successful drug development. The problem is compounded by the extremely limited amount of preclinical candidates due to the costs of creating variants in large numbers. Typically a single variant is created by an outsourced (CDMO) company and tested at a time. The space of potential variants is so large that attempting to cover a sizable, few percent, number of variants is currently prohibitive expensive.

IP

Intellectual property (IP) protection is essential for biopharmaceutical companies to recover their investments and incentivize innovation. Securing patents and defending them against potential challenges or infringement requires significant financial resources, including legal fees and ongoing IP management.

It's important to note that the cost of biopharmaceutical research is also influenced by market dynamics, pricing strategies, and factors like healthcare system regulations, reimbursement policies, and access to funding. The high costs associated with biopharmaceutical research are partly a reflection of the investments required to bring safe and effective treatments to market while accounting for the inherent risks and complexities involved in the process.

Outsourcing and Contract Development and Manufacturing Organization (CDMOs)

With that all being said, outsourcing is a common practice in creating a biopharmaceutical. Outsourcing in the biopharmaceutical industry refers to the practice of contracting certain aspects of the drug development and manufacturing process to external partners or third-party organizations. This approach allows companies to leverage specialized expertise, access advanced technologies, and optimize resource allocation. Key areas in biopharmaceutical development and manufacturing that are commonly outsourced: research and discovery, clinical trials, manufacturing, quality control and testing, regulatory affairs, and commercialization and distribution.

Biopharmaceutical companies may collaborate with academic institutions, research organizations, or contract research organizations (CROs) to outsource specific research activities. This can include target identification and validation, lead compound optimization, and early-stage preclinical studies. Outsourcing these research activities can help companies tap into additional expertise and resources.

Conducting clinical trials is a critical and resource-intensive part of drug development. Biopharmaceutical companies often partner with clinical research organizations (CROs) to outsource various aspects of clinical trial management. This can include patient recruitment, site selection and monitoring, data management, statistical analysis, and regulatory compliance. CROs specialize in managing clinical trials efficiently and have the necessary infrastructure and expertise to execute these studies effectively.

Biopharmaceutical companies also rely on external laboratories or testing facilities to perform quality control testing and analytical characterization of their products. These facilities can conduct various tests, including potency assays, purity assessments, stability testing, and safety evaluations. Outsourcing quality control and testing helps ensure independent verification and compliance with regulatory requirements.

Biopharmaceutical companies may collaborate with regulatory consulting firms or regulatory affairs service providers to support the preparation and submission of regulatory documents. These organizations assist in navigating the complex regulatory landscape, ensuring compliance, and preparing dossiers and applications for regulatory approvals.

Once a biopharmaceutical receives regulatory approval, companies may outsource certain aspects of commercialization and distribution. This can include marketing, salesforce deployment, market access strategies, and supply chain management. Collaborating with specialized partners can help maximize market penetration, leverage existing distribution networks, and optimize commercialization efforts.

Outsourcing in the biopharmaceutical industry allows companies to focus on their core competencies while leveraging external expertise, infrastructure, and resources. It can help accelerate development timelines, improve cost-effectiveness, and enhance overall operational efficiency. However, it is crucial for companies to establish strong partnerships, maintain effective communication, and ensure regulatory compliance throughout the outsourcing process.

An important part of biopharmaceutical production is CDMO, which stands for Contract Development and Manufacturing Organization. In the context of biopharmaceutical production, a CDMO is a company or organization that provides comprehensive services for the development, manufacturing, and often, testing of biopharmaceutical products on a contract basis. CDMOs specialize in offering a range of services to support biopharmaceutical companies throughout the entire product lifecycle, from early-stage development to commercial manufacturing. These services can include: development services, manufacturing services, quality control and testing, regulatory support, and supply chain management.

CDMOs can assist in the development of biopharmaceutical products, including cell line development, process optimization, formulation development, and analytical method development. They work closely with their clients to refine and optimize the manufacturing processes, ensuring that the final product meets the necessary quality, safety, and regulatory standards. CDMOs have the infrastructure and expertise to manufacture biopharmaceutical products at various scales, from small-scale batches for early-stage clinical trials to large-scale commercial production. They have specialized facilities, equipment, and personnel trained in the specific requirements of biopharmaceutical manufacturing. CDMOs often operate under strict regulatory guidelines such as Good Manufacturing Practices (GMP) to ensure product quality and compliance. CDMOs offer quality control and testing services to ensure that biopharmaceutical products meet the required specifications and regulatory standards. This includes conducting analytical testing, stability studies, and release testing to ensure product safety, potency, purity, and stability. Some CDMOs are experienced in navigating regulatory requirements and can provide guidance and support in preparing and submitting regulatory documents to obtain necessary approvals from regulatory authorities. They understand the regulatory landscape and help their clients comply with regulations throughout the product development and manufacturing processes. CDMOs may also offer supply chain management services, which involve coordinating the procurement of raw materials, managing inventory, and ensuring timely delivery of components required for manufacturing. They help ensure a smooth and efficient supply chain to avoid delays or disruptions in production.

By engaging the services of a CDMO, biopharmaceutical companies can leverage the specialized expertise, infrastructure, and resources of these organizations. This allows companies to focus on their core competencies while outsourcing certain aspects of development and manufacturing to trusted partners. Working with a CDMO can help accelerate development timelines, improve cost-effectiveness, ensure regulatory compliance, and access advanced manufacturing technologies and capabilities. One emerging drawback of working with CDMOs is related to the proprietary nature of the biopharmaceutical. For example, once the exact sequence of a biologic (DNA, mRNA, antibody) is shared with a CDMO, even with a CDA in place, there is always a risk that the information might be used to develop biosimilars or be sold or included in data sets for artificial intelligence to design competitor biologics. There are also emerging geopolitical hurdles to sharing technical know how information between countries as well as concerns about the bio-ethical use of such information.

Gene Synthesis

In pharmaceutical development, genes typically refer to specific DNA sequences that encode instructions for the synthesis of proteins. These genes can be obtained from natural sources, such as human or animal cells, or synthesized using recombinant DNA technology or through purely chemical means, so called Synthetic Biology. Here's an overview of how genes are obtained and used in pharmaceutical development:

Gene Identification: The first step in the process is identifying the specific gene or genes of interest that are involved in a particular disease or therapeutic target. This can be done through various research methods, including genomics, proteomics, and functional studies.

Gene Isolation: Once a target gene is identified, it needs to be isolated from its natural source. This can involve extracting DNA from cells, tissues, or organisms using techniques such as polymerase chain reaction (PCR), restriction enzyme digestion, or other DNA extraction methods.

Synthetic Genes: If the gene needs to be modified from the natural source, in any way, the best way to do it is to use chemical means. Phosphoramidite chemistry is a well established method to synthesize de novo genes. It has the advantage that it doesn't involve any biological material that can lead to contamination: no proteins, no cellular RNA or DNA. The gene is typically produced in picomolar amounts (for 1 kb or longer) or in nanomolar amounts for less than 1 kb. For preclinical testing purposes this amount needs to be amplified by PCR or gene cloning.

Gene Cloning: After isolation, the target gene is typically cloned into a suitable vector. Vectors are small DNA molecules that are used to carry and replicate the gene of interest. Common vectors used in pharmaceutical development include plasmids, viral vectors, or other specialized delivery systems.

Gene Modification: In some cases, the isolated gene may undergo modifications to enhance its function or expression. This can involve altering specific DNA sequences, adding regulatory elements, or introducing mutations to optimize the gene's properties for therapeutic purposes.

PCR: Polymerase chain reaction can amplify the initial amount of gene produced. However, due to accumulation of errors, no more than 25-30 cycles of amplification are advised. Purification of the sample must be done to ensure only the gene of interest without errors is used for gene expression.

Gene Expression: Once the gene is cloned and modified, it needs to be introduced into host cells, where it can be expressed to produce the desired protein. This is often achieved using techniques such as transfection, transformation, or viral-mediated delivery.

Protein Production: The expressed gene within the host cells leads to the production of the desired protein. The protein can then be harvested, purified, and formulated for pharmaceutical use.

In terms of who makes the genes, the process of gene isolation, cloning, modification, and expression is typically carried out by researchers or scientists in academic or industry laboratories. These laboratories may be part of pharmaceutical companies, research institutions, or contract research organizations (CROs) specializing in genetic engineering or biotechnology. The expertise and infrastructure required for gene manipulation and protein production are often found within these organizations, where researchers work to develop new therapies or study the role of specific genes in disease processes. It's important to note that gene manipulation and recombinant DNA technology are highly regulated and subject to strict ethical considerations and regulatory oversight to ensure safety and compliance with applicable guidelines.

Jackie Wagner, Jeff Hoernemann, CFA/American Century Investments

Nanopec Mission to lower the costs of Biopharmaceutical Discovery

Nanopec's mission is to cut both expense and time for discovery of new biopharmaceuticals by a factor of ten at the pre-clinical level. For this purpose Nanopec offers DNA Automation technologies. One such technology is Nanopec's DNAReax nano-porous ceramic films. DNAReax holds hundreds of times more DNA during synthesis than a comparable silicon chip. Contrary to CPG glass beads, the works of the synthetic biology industry, the pore size of DNAReax is extremely narrow, eliminating traps where DNA can't grow (leading to so called 'shortmers') to its full size resulting in contamination. DNAReax pores are all vertical and isolated from one another. This allows inkjet printing of Phosphoramidite reagents at amounts consistent with the biopharmaceutical discovery phase. With traditional glass beads (CPG) each micro-fluid operation to synthesize one piece of a gene, such as pipetting, takes on the order of a few second to complete while inkjet printing on DNAReax can be done at 50-80 kHz (50,000 to 80,000 drops per second). Fluid volumes with CPG are measured in micro-liters while volumes with inkjet printing are measured in pico-liters. With such control of volume and speeds, the synthesis of new genes by purely chemical means can be significantly faster, more precise and use fewer reagents and solvents. By an industry estimate, more than half of the world's production of acetonitrile would be needed if biopharmaceuticals were all made by these synthetic means. Miniaturization and high frequency can lead to a factor of one million on the use of acetonitrile (micro to pico liters). This is analogous to the revolution in electronics when going from vacuum tubes to integrated semiconductor micro-transistors. The advances in speed and density were accomplished through high scale miniaturization (volume) and speeds of processing (nano-second clock speeds).

Nanopec's Distributed Gene Synthesis versus Outsourcing

Lastly, generating genes in-house overnight in large numbers is important for several reasons: research efficiency, flexibility and customization, cost-effectiveness, timeliness and independence. This enables researchers to conduct experiments more efficiently and at a faster pace, accelerating the research process. By having the capability to generate genes in-house, researchers have more flexibility and control over the DNA sequences they work with without long delivery delays. They can customize and modify genes as needed for their specific research objectives, and hypothesis testing. While there may be initial investment costs in establishing the infrastructure and capabilities for gene synthesis, in-house production can save money over time, particularly for organizations that require a high volume of genes for their research activities. Relying on external sources for gene synthesis can introduce delays and dependencies on external providers.

DNA automation refers to the use of automated gene synthesizers as well as robotic platforms to streamline and accelerate the process of gene synthesis. By leveraging advanced technologies and automation, Nanopec aims to rapidly generate large numbers of genes in-house, addressing the need for efficiency, customization, and timely access. High speed synthesizers as described here can perform tasks such as oligonucleotide synthesis, assembly of gene fragments, and purification of DNA in a highly efficient and reproducible manner. This reduces human intervention, minimizes errors, and allows for parallel processing, enabling the generation of large numbers of genes overnight. By creating novel DNA automation technologies, Nanopec aims to support the internal mission of the biopharmaceutical industry to expedite biopharmaceutical development and reduce costs.

It's important to note that achieving such significant reductions in both time and cost required substantial innovation, efficient processes, and advancements in new materials combined with off-the-shelf inkjet technology. The technology is projected to produce on the order of 100 variants of the covid vaccine gene overnight. This amount of variants for pre-clinical testing can be use for leveraging and feeding into artificial intelligence models that could result in highly optimized preclinical candidates, potentially exploring alternative regulatory pathways more fully, over a large design space. Nanopec's mission indicates a commitment to revolutionizing the biopharmaceutical industry and making the development of new treatments more efficient and cost-effective, enabling the future of personalized medicine, to protect, heal and prolong human life.

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What would you do if you could create 100 gene variants in-house, overnight at low cost?