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Biopharma Manufacturing Trends

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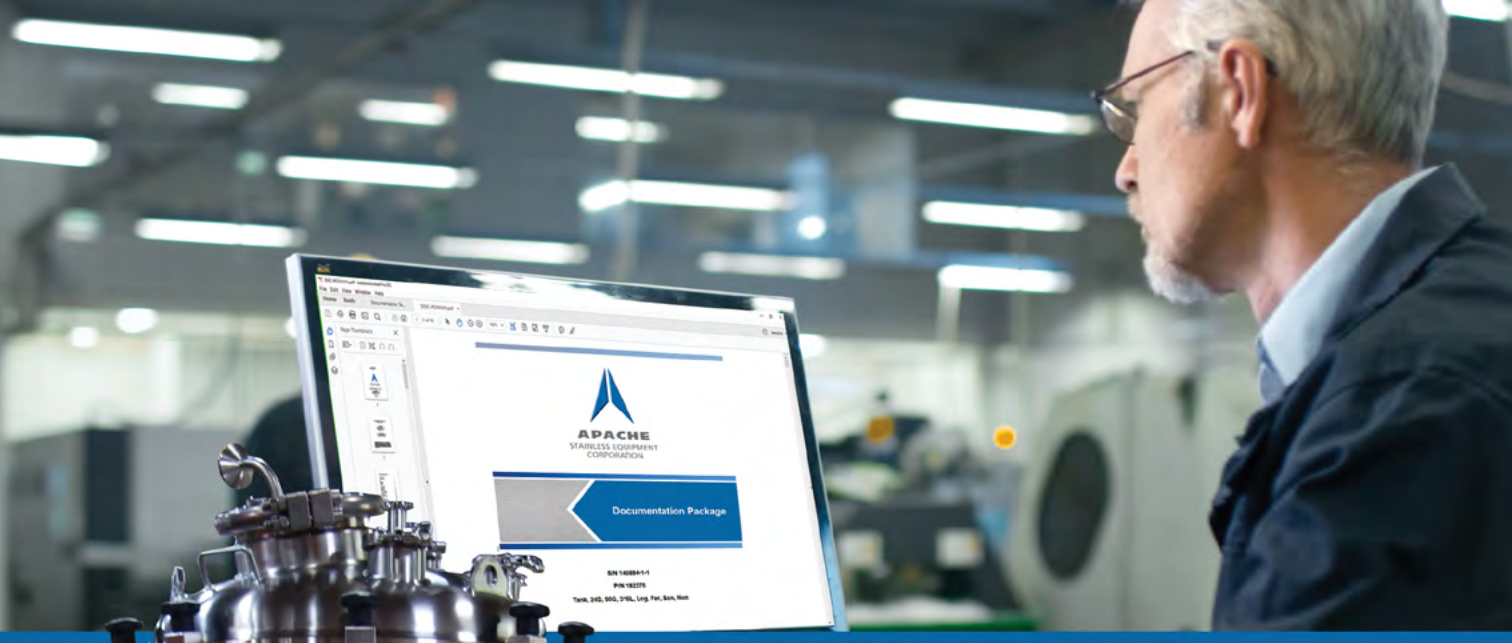

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TABLE OF CONTENTS

AD INDEX

BioPharma Market: An Inside Look

Survey results reveal how slow-motion trends are driving biopharma growth

By Ronald A. Rader, Senior Director, Technical Research, BioPlan Associates and
Eric S. Langer, President, BioPlan Associates

The biopharma sector has seen incredible growth in recent decades, with growth the major long-term trend. Total annual revenue has increased from about $4.4 billion in 1990 to now about $275 billion, an increase of 6,250 percent, with biopharmaceuticals now more than 25 percent of the total pharmaceutical market.

For over two decades, the biopharmaceutical manufacturing industry has created a body of industrial knowledge and institutional experience. The sector can be considered mature, and the trends relatively stable. This can be good for future planning, and it can allow time for things like novel bioprocessing technologies to shake out glitches as they make it through the R&D and the regulatory pipeline. Of course, investors may not get nearly as excited about the molasses-speed of new product introduction, compared with other industries where inventions can make it to the market in months, rather than years. But the situation is much the same in the broader drugs (chemical substances as APIs) sector.

On the other hand, the bioprocessing market segment has grown remarkably consistently for the past 15 years we've been measuring supplier performance, at between 12-15 percent annually. Even when the data are broken out by growth in services, materials and equipment, the expansion shows notable stability; a good environment for risk-averse investors. This also matches the rate of growth in sales of biopharmaceuticals globally, as well. The upside of a highly regulated market

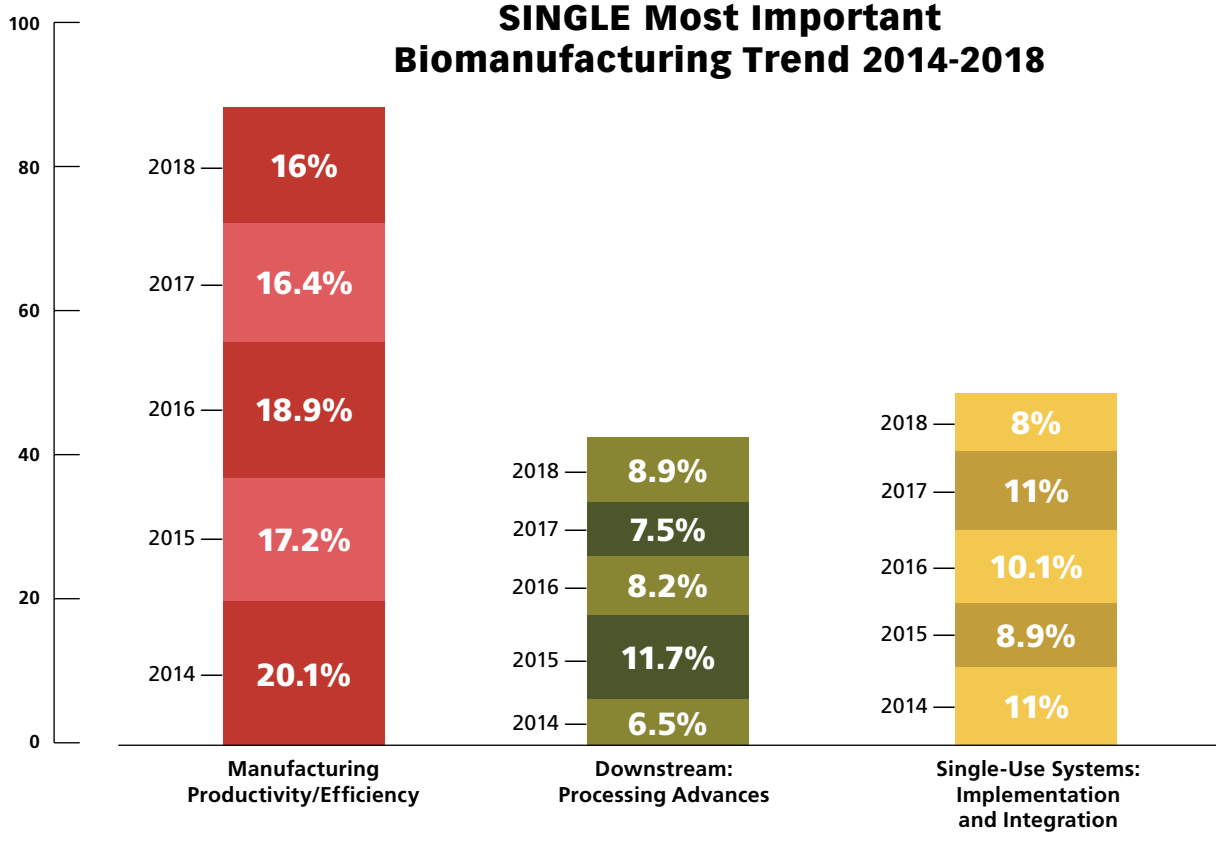
that includes slow-motion trends is that its environment is relatively easy to track over time, and the data can be used to assess future movement more accurately.

This article presents trends and findings from BioPlan's 15th (2018) Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, and discusses the impact of some of our findings.[1] This survey and study provides a composite view and trends analysis from 222 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations in 22 countries, and includes over 130 direct suppliers of materials, services, and equipment. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the major markets in the U.S. and Europe.

TOP TRENDS AND THEIR IMPACT

Despite the overall, slow-motion nature of the biopharma industry, the significance

Exhibit 1



and impact of events most definitely affect decision-makers, strategy development and investments in new facilities and technologies. Because decision-makers are affected differently by diverse shifts and trends, there are no real "top trends," but rather, the trends have broad impact on the biopharma environment and how the industry responds.

The Importance of Manufacturing Efficiency and Productivity

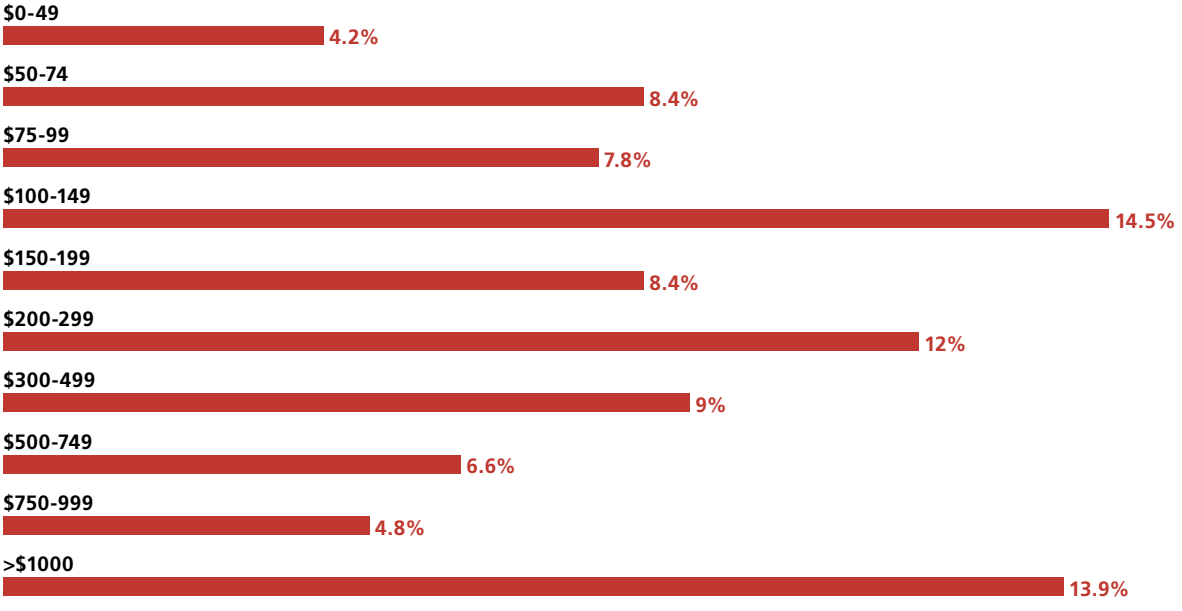
This year when respondents were asked to choose the "single most important trend or operational area," the largest portion of respondents, 16 percent, cited "manufacturing productivity/efficiency," with this largely unchanged from last year (Exhibit 1). Over the past six years, we have consistently seen a high interest this area. This affects virtually all stake-holders. Suppliers need to gear their new technologies toward making biologics cheaper, better and faster. Biopharmas need to plan for the future now, and must decide if the facilities and equipment they own or specify will be future-proofed. Will what they do be efficient and still operating well enough a decade from now, using then likely legacy, inefficient technologies?

Bioprocessing Productivity Continues to Increase

This year, the average titer reported at both clinical and commercial scales was 3.20 g/L. Annual survey data and other sources confirm that bioprocessing efficiency and productivity, in terms of upstream titers

Exhibit 2

DISTRIBUTION: Average Cost/Gram for Recombinant Protein Manufacture



Source: 15th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity, April 2018)

The upside of a highly regulated market that includes slow-motion trends is that its environment is relatively easy to track over time, and the data can be used to assess future movement.

and downstream yields, will continue to increase. BioPlan has reported rather steady increases in bioprocessing productivity, particularly upstream bioprocessing, over the past 30 plus years, since the first adoption of recombinant technologies.[2]

Biosimilars Bringing More Products and Players

Biosimilars/biogenerics are bringing many new bioprocessing players and facilities; and with these products facing considerable competition, cost-effective manufacturing is a basic requirement.[3] The Biosimilars/Biobetters Pipeline Database reports more than 1,000 biosimilars (including biogenerics) in development or marketed worldwide.[4] There are now over 300 biogenerics marketed in lesser- and non-regulated commerce in developing countries, each of which could perhaps be upgraded for major market entry. Over 750 companies are involved in follow-on (biosimilar, biobetter and biogenerics) products, with many new entrants in both developed and developing regions.

Facility Constraints Create Bottlenecks

The factor most frequently cited (50 percent) as likely to cause capacity constraints at respondent facilities in five years (2023) was "facility constraints." This has remained the No. 1 cited factor since starting to ask this question in 2008.

"Develop better continuous bioprocessing — downstream technologies" was the area most commonly cited, by 42.2 percent as needing to be addressed to address (fix or avoid) future capacity constraints. Continuous downstream processing is also cited in responses to several other questions as needed and expected to resolve many of the current problems, with purification operations being the primary bottleneck in bioprocessing.

Lowering Manufacturing Costs

A majority of respondents continue to report efforts seeking to reduce bioprocessing costs, with 64 percent reporting that they have "implemented programs to reduce operating costs" at their facility

within the past 12 months. Working to reduce bioprocessing costs has become a routine activity. This was the first year we surveyed about the cost/gram for recombinant protein manufacture. The average reported cost was $306.8/gram for respondents' primary recombinant protein product, usually a monoclonal antibody (Exhibit 2).

Supplier Growth

Besides overall annual growth in the industry generally being above 12 percent over the past 20-plus years, the equipment and supplies sector is reporting health and even better growth.[5] Surveyed supplier staff reported an average of 13.7 percent sales growth. "Equipment and instrumentation" took the top spot for growth with 16.8 percent average growth. Average growth reported in "raw materials and consumables" was 13.3 percent and "services (e.g., CMOs, CROs, consultants)" was 12.1 percent.

Bioprocessing Budgets are on the Rise

This year, no budget decreases were reported in any of the areas surveyed. Budgets for new capital equipment continued to be an area of significant growth, with respondents reporting an average increase of 8.2 percent in facility bioprocessing budgets for 2018. Much of this involves construction of new facilities, retrofitting, and the addition of capacity at existing facilities, (with an increasing number turning to single-use systems).

Single-Use Systems are Still the Rage

Again this year, over 90 percent of respondents reported currently using single-use equipment, with "tubing or disposable operations" alone cited the most, (90.6 percent), followed by "disposable filter cartridges," (86.2 percent) and "bags, empty," (81.8 percent). About 77 percent reported the use of single-use bioreactors. BioPlan estimates that more than 85 percent of pre-commercial product manufacturing now primarily involves single-use systems.

The Rise of Capacity in Asia

BioPlan's free database ranks the top 1,000-plus biomanufacturing facilities worldwide. The current breakdown of worldwide bioprocessing capacity includes:

- US/Canada: 6 million L (37 percent)
- W. Europe: 5.5 million L (33 percent)
- Asia Pacific: 4.7 million L (25 percent)
- China: 876,000 L
- India: 833,000 L

Overall, the fastest growth (from low baselines) is in Asia, particularly China.

China Becoming an Industry Leader

In a survey of 50 biopharma executives in China by BioPlan staff, the largest portion, 58 percent, cited a "more innovative biopharma pipeline" as what China must possess to expand globally. This was followed by 50 percent citing both need to develop an "overall quality image" and "capacity, commercial scale."

The trends show that biopharma manufacturing is continuously growing, evolving, demanding and adopting (albeit slowly) new and improved technologies to reduce costs, increase efficiencies, improve product quality, and improve development pipelines.

China has recently moved ahead of India in terms of bioprocessing capacity. Also, BioPlan's directory of the top 60 biopharma manufacturing facilities in China portrays an embryonic industry working to expand its GMP-quality manufacturing capacity to supply domestic needs while also aiming to becoming a major global player in innovative and follow-on biopharmaceuticals.[6]

IMPACTS OF TRENDS

Collectively looking at its past, current status and trends, the biopharmaceutical industry is very healthy, and continues to grow at its usual rather steady pace, with most growth-related parameters, such as industry revenue, generally annually increasing by about 12 percent or more. In fact, there are hardly any significant negative trends. Despite any industry-related growth rates below the norm considered by some in the industry to be negative growth or contraction (with about 12 percent growth so long the norm, it's considered the baseline), the roughly 12 percent annual biopharma industry growth rates are considerably higher than for most other established industries and the growth rates of developed countries. In the meantime, biopharmaceutical industry-related growth rates are even higher in the rest-of-the-world, particularly in the major Asian bioprocessing markets, although growth has only recently started from much lower or even near zero baselines.

The trends show that biopharma manufacturing is continuously growing, evolving, demanding and adopting (albeit slowly) new and improved technologies to reduce costs, increase efficiencies, improve product quality, and improve development pipelines. Ongoing industry trends support an optimistic vision of the future that includes more:

- Biopharma facilities worldwide, in both major markets and Asia
- Biopharma products
- Revenue and added-value for patients from innovations in products and processes
- Diversity in products in development and marketed, e.g., cellular and gene therapies
- Follow-on products and manufacturers, including biosimilars and biogenerics
- Flexible manufacturing facilities, including use for manufacture of multiple products
- Adoption of single-use systems at pre- and clinical scales, as well as for commercial manufacture
- Efficient bioprocessing — titers and yields will continue to increase
- Use of continuous processing, including for downstream processing
- Automation, monitoring and process control
- Use of bioprocess modeling, data mining, PAT, QbD
- Use of high-tech expression systems and other genetic engineering advances
- Modular facilities, including cloned facilities in developing countries and for regional cellular/gene therapies manufacturing
- Complex regulations which drive many other specific needs, advances and trends

WHAT THE FUTURE HOLDS

The current situation in the biopharmaceutical industry is exciting, with new technologies and markets, such as continuous processing, biosimilars, cellular and gene therapies, and many new opportunities in emerging markets causing constant changes that must be adapted to.

Overall, the primary impetus for trends in bioprocessing is innovation. Innovation opens new opportunities and makes existing ones more attainable. It also speeds discovery, increases choices/options, and can drive down costs and improve productivity. The industry will see some (relatively) rapid changes in the coming years, including the rise of new classes of products, notably cellular and gene therapies; and expanded adoption of new(er) technologies, such as continuous bioprocessing. There will also be regulatory changes, such as more in-depth risk assessments related to leachates/extractables and other potential bioprocessing-associated risks to patients and staff.

However, changes in the bioprocessing sector, particularly any major advances and shifts in bioprocessing, take a long time. For example, it has taken over a decade for single-use systems to fully dominate pre-commercial biomanufacturing, despite the cost savings over stainless steel. Because new technologies are generally only adopted for new products, major changes in bioprocessing are inherently slow, generally take a decade or more. In the meantime, incremental innovation in improved manufacturing

productivity continues. This ongoing adoption of new technologies, not dramatic paradigm shifts, is the general rule; and is the primary driver for many biopharmaceutical trends.

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SURVEY METHODOLOGY

THE 2018 FIFTEENTH ANNUAL REPORT AND SURVEY of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from 222 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 22 countries. The methodology also included over 130 direct suppliers of materials, services, and equipment to this industry. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the major markets in the U.S. and Europe.

Bio's Bad Apples

Can unproven therapies spoil the sector's sweet success?

By Karen Langhauser, Chief Content Director

Few will dispute the enormous potential of cellular therapy — and for patients suffering from vision loss, leukemia or lymphoma who have had life-changing experiences with these new treatments, cell-based therapies are nothing short of a miracle.

Although they lack a globally harmonized classification system, cell therapies fall under the broad umbrella of regenerative medicine. There are several types of cells that can be used for cell therapy and the type of cells administered depends on the treatment. Collectively, these therapies are heralded for their ability to promote the repair of diseased, dysfunctional or injured tissue. What this ultimately means is that cellular therapies offer the potential to treat conditions for which few, if any, treatments exist.

Around the world, there are clinics making dramatic claims about cure-all cell-based treatments that have not gone through regulated clinical trials — which means their safety and efficacy has not been proven to regulatory bodies. If this confusion surrounding cell therapies isn't addressed, it could become a problem that ultimately discredits a whole industry on the brink of booming.

It is estimated that the unproven cell therapy market is currently worth $2.4 billion and treats approximately 60,000 patients annually.[1] While it's difficult to identify exactly how many clinics exist, a 2016 analysis of online direct-to-consumer marketing activity in the U.S. found 351 distinct businesses offering interventions at 570 physical locations — and this number has undoubtedly grown.[2]

The potential for miracle cures also brings with it the potential for large financial gain, which has sparked the growing private interest in the cell therapy space.

But when it comes to cell therapy, "potential" is still the key word in the discussion. Currently, the only stem cell-based products approved by the U.S. Food & Drug Administration consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood — and there are fewer than 10 of these products on the market.[3] Kite Pharma, Novartis and Dendreon hold the only immune cell therapy approvals in the U.S. This is likely to change in the future, however. According to the FDA, there are nearly 800 active cell therapy Investigational New Drugs (INDs) on file with the agency.[4]

The potential for miracle cures also brings with it the potential for large financial gain, which has sparked the growing private interest in the cell therapy space. While the pharmaceutical industry might be quick to dismiss these bogus cell therapy clinics, the unfortunate reality is that the general public is still confused. And in that confusion arises a genuine concern that the popularity of unproven cell-based therapies will have a negative impact on the future of legitimate, science-based cellular therapies — which is an issue the industry should not dismiss.

FDA DOING ITS PART

The FDA is not ignoring the rise of unproven cell therapy clinics and has acknowledged the role that regulatory gaps have played in the proliferation of direct-to-consumer cell therapy treatments.

In August 2017, the agency stepped up its efforts to enforce regulations and oversight of stem cell clinics. When this was announced, FDA Commissioner Scott Gottlieb acknowledged that new, complex therapies are challenging the traditional approach to regulations.

"The field of regenerative medicine, because of the very nature of the science and the rapidly evolving clinical developments, not infrequently lends itself to often close calls between what constitutes an individualized treatment being performed by a doctor within the scope of his

medical practice on the one hand, and what constitutes a medical product that is currently subject to the authorities Congress has already charged the FDA with exercising," said Gottlieb.5

Part of the allure of unproven cell therapy clinics is that they promise to solve unmet medical needs. When a potential cure to an ailment is tied up in the FDA approval process, patients are more likely to seek help elsewhere. In order to find a balance between safety concerns and innovation, the FDA made a major move in November 2017 to modernize product licensing pathways by introducing an additional expedited program in which a product could be designated as a regenerative medicine advanced therapy (RMAT). The expedited RMAT program — like the fast-track designation, priority review, accelerated approval, and breakthrough therapy designation that were introduced a year prior with the 21st Century Cures Act — is now helping to speed the development of new regenerative therapies, particularly those aimed at life-threatening conditions.

Last May, the FDA stayed true to its promise to increase oversight and enforcement to "protect people from dishonest and unscrupulous stem cell clinics"6 and sought permanent injunctions against clinics in Florida and California after they failed to address violations outlined in FDA warning letters, including serious cGMP violations.

GOOD GUYS DON'T ALWAYS WEAR WHITE HATS

Unfortunately, the pharmaceutical industry continues to struggle with its image problem. Many patients still perceive the pharma industry as impersonal and rapacious. Unproven cell therapy

WHAT IS AN UNPROVEN CELLULAR THERAPY?

- Unclear scientific rationale to suggest potential efficacy
- Lack of understanding of the mechanism of action and/or the biological function to support clinical use
- Insufficient data from in vitro assays, animal models and clinical studies regarding the safety profile to support the use in patients
- Lack of a standardized approach to confirm product quality and ensure consistency in cell manufacturing
- Inadequate information disclosed to patients to enable proper informed consent
- Use within non-standardized or non-validated administration methods
- Uncontrolled experimental procedures in humans

Positioning a Scientific Community on Unproven Cellular Therapies: The 2015 International Society for Cellular Therapy Perspective

clinics are capitalizing on this stigma, and creating environments that appear to be warm, welcoming and highly personalized.

"Providers of unproven cell are seen as entities which are really taking care of patients versus pharma, which is perceived as unconcerned with personal needs. Pharma is seen from the patient perspective as more concerned about business, while unproven cell therapy clinics seem to be the good guys — which, in reality, is the opposite of the truth," says Massimo Dominici, M.D., associate professor of medical oncology and head of the Laboratory of Cellular Therapies at University/Hospital of Modena, Italy.

Formerly serving as the president of the International Society for Cellular Therapy (ISCT), Dominici is now chairing the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell and Gene Therapies. Established in 1992, ISCT is a growing global organization of clinicians, regulators, researchers, technologists and industry partners dedicated to translating cell and gene therapies for the benefit of patients worldwide. Its unproven cell therapy task force is a major player in the fight to characterize unproven and unethical cell and gene interventions, and promote safe and effective practices worldwide.

What it comes down to is that unproven clinics are doing a much better job of branding themselves. One Connecticut-based clinic's website, for example, features personalized testimonials as well as the Buddhist quote, "When love meets pain it becomes compassion."

"The marketing around unproven clinics is quite similar to that of five-star hotels. Essentially this is what people are looking for and how they want to be treated," says Dominici. "But at the end of the day…it's fake."

THE DANGERS ARE REAL

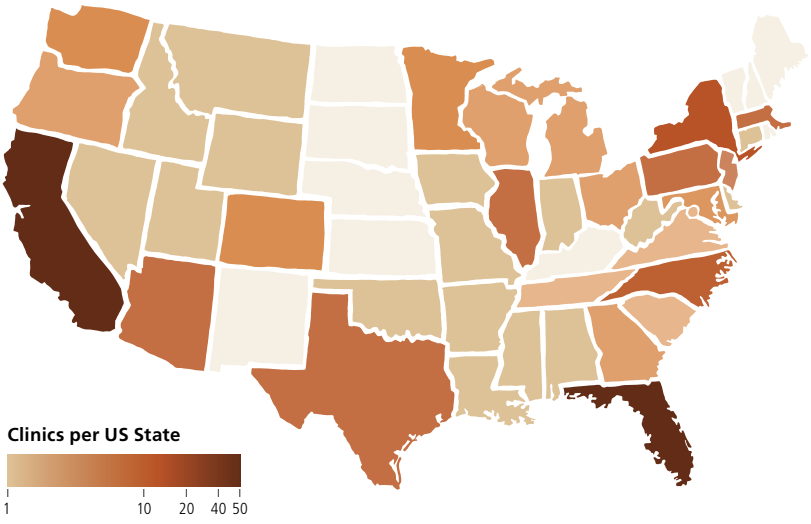
The most obvious danger linked to unproven cell therapy treatments and clinics is patient safety. Without a detailed evaluation of the manufacturing facility and process, there's no way to assess the general safety and risk factors of a specific cell therapy product. And without going through the proper channels outlined by registered clinical trials, there's no standard for logging, reporting or following up adverse events — and plenty have occurred already.

So far, there has been several cases of poor outcomes linked to unproven cell therapy treatments performed in clinics including documented deaths, a patient who became blind due to an injection of stem cells into the eye and another patient who grew a spinal tumor after receiving a spinal cord injection.

There is also a certain degree of psychological harm that can come from unproven

treatments related to side effects, possible financial loss (treatments can cost up to $40,000), and unrealistic expectations that do not yield tangible results.

Not only do safety and ethical issues negatively impact patients — they also affect the future of the entire cell therapy community. Negative experiences with unproven cellular therapy can erode financial confidence, which could restrict investment decisions.



Top five states: CA (49), FL (35), NY (15), PA (11), and AZ (10). (No sites were recorded in HI or Alaska)

Courtesy of Stem Cell Reports, ISSCR

"Unproven cellular therapies, which are marketed as safe and effective, can have a destabilizing influence on financial sector confidence that emerging cell therapies are well-founded and ready for development," stated ISCT in its latest reference guide.7

WHAT CAN PHARMA DO?

When it comes to the fight against unproven cell therapy treatments, pharma's voice is somewhat missing from the battlefield — and this might actually be a wise approach.

For pharma, part of the solution involves a cultural shift. The industry has already begun to realize that in this new era of personalized medicines, it is necessary to interface with patients much earlier in the drug development process and continue that relationship all the way through commercialization. This approach will invariably generate higher levels of patient trust, which in turn will help improve pharma's "bad guy" image.

But cultural shifts don't happen overnight, and the issue of unproven cell therapies is immediate. So why are the drugmakers who are investing millions of dollars in the development of legitimate cell therapies not fighting back?

Because the issue is a delicate one, and has to be dealt with carefully, explains Dominici. In a situation where patients don't entirely trust the pharma industry, fueling the fire may just make things worse.

"Yes, I would call for bigger commitment from pharma,

but not alone. If they stand up by themselves, they risk fire-back. This is why the involvement of organizations like ISCT is so important," says Dominici.

Third parties, such as ISCT, are already hard at work raising awareness of the dangers of unproven therapies. Pharma's collaboration with such organizations is crucial, and will allow drugmakers to add their voices to a trusted, unified front against unproven therapies. Partnerships that include academia, industry, regulatory bodies and patient advocates will enhance credibility and minimize potential concerns about an industry-biased conflict of interest.

The ISCT Presidential Task Force on Unproven Cell and Gene Therapy is working towards a series of initiatives, including establishing a global, publicly-accessible, cell therapy patient safety registry and providing additional tools to patients that can be used as guidance in evaluating a potential treatment.

"Teaching and communication — not policing — are key," says Dominici.

Around the world, drugmakers are expanding cellular therapy portfolios, putting their faith in the future potential of this emerging class of therapies. A collaborative, concerted effort from all parties is needed to ensure that the true potential of cellular therapies is not lost in the shadows of unproven treatments.

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China's Biopharma Growth: Can it Continue?

A new study shows a projected doubling of sales volume by 2021, as China strives to catch up with the global market

By Vicky (Qing) Xia, Senior Project Director, BioPlan Associates

China is a relative newcomer to the biopharmaceutical industry. Biological therapeutics by multinational corporations in China have been on the market only since the 1990s,[1] but the country has been making rapid and significant progress ever since.

The sales of biopharmaceuticals in China's market grew from $9.4 billion to $22.8 billion from 2012 to 2016 — nearly 25 percent annually. BioPlan's newly released report, "Advances in Biopharmaceutical Technology in China," estimates that the market will continue to grow at this rate — meaning that by 2021, the sales volume is expected to reach $48.8 billion. This far surpasses the growth rate in North America, Europe and Japan.[1]

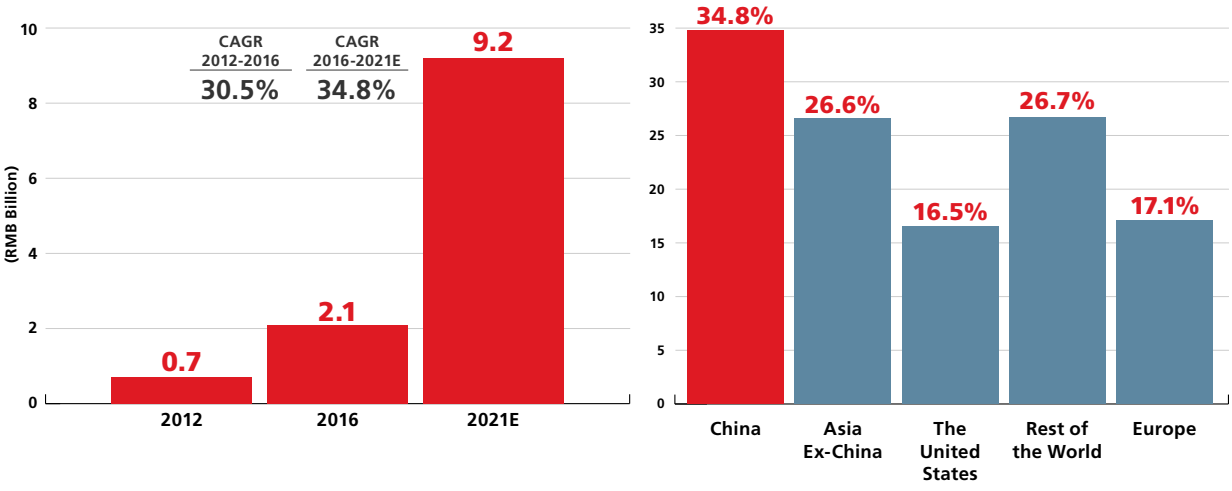
What does China need to do to continue on this upward path?

BRIDGING THE GAP IN THERAPEUTIC MABS

Multiple sources identify a major gap between China and the rest of the world with regard to the use of therapeutic monoclonal antibodies (mAbs). These products make up a large percentage of biologics globally, but only seven percent of the Chinese biologics market. So far, of the nearly 70 mAb therapeutics approved in the United States, only 12 have been approved by the Chinese Food and Drug Administration (CFDA) and made available in the Chinese market.[2]

Analysts attribute the gap to several factors:

China Biopharmaceutical Service Market 2012-2021



Source: Xia, V.Q., et al, Advances in Biopharmaceutical Technology in China

For many Chinese patients, the price of imported mAbs, even biosimilars, can put them out of reach, as the national health insurance does not cover many of them.

There is a lack of biosimilar mAbs from domestic drug makers, which tend to be cheaper.

It is widely accepted that biosimilar/better drugs from domestic drug makers will be more likely to be put on the National Reimbursement Drug List (NRDL) and made more affordable for Chinese patients, thus holding strong potential for growth in the next decade.

Despite its relatively late start, the Chinese therapeutic antibody market, however, is catching up quickly. The CFDA granted 1,653 approvals for biologics manufacturing, more than 95 percent of which have resulted in therapeutic biologics being launched in the Chinese market. At the same time, the agency accepted 7,060 regulatory applications for biologics, of which about six percent are for therapeutic antibodies. As of early 2018, there were 401 antibodies in the pipeline in China,3 of which 288 were in active development. Among those, 77 were initiated abroad and 211 by domestic companies.

ROBUST SERVICE SECTOR GROWTH

China's biopharmaceutical service sector, including contract manufacturing organizations, has been growing at close to 30 percent CAGR, and is projected to reach $1.4 billion in 2021.[7] Although there are presently many regulatory hurdles for CMOs in China, these are being resolved, and this segment is demonstrating growth, including the establishment of a number of international and domestic manufacturers in recent years.

Total healthcare expenditure in China more than tripled over the past decade. These trends lay a solid foundation for the growth of the biological therapeutics industry.

There are a number of major driving forces pushing the robust growth of China's biopharma industry. These include:

Economic development: China's reform and open-door policy has led to robust growth of the general economy, and ascension into the World Trade Organization has made China, in many ways, the world's factory. In terms of GDP, China is currently second only to the U.S., representing 19.7 percent of the world's economy.[2] Strong economic development has enriched the quickly expanding middle class in China. Greater purchasing power has made therapeutic biologics less of a luxury for the Chinese middle class, who tend to pay more attention to health issues.

Rising healthcare expenditure; enhanced reimbursement policies: China has become older and richer, and healthcare reform has increased accessibility to insurance and reimbursement for hundreds of millions of people. According to the head of the Ministry of Human Resources and Social Security, Ying Weimin, Urban Residents Basic Medical Insurance, Urban Employee Basic Medical Insurance, and new rural cooperative medical systems combined covered China's 1.3 billion members in 2015.

Meanwhile, commercial healthcare insurance is also getting more popular among the middle-class urban population. Projections have been made that show commercial healthcare insurance in China will more than quadruple from 2015 to 2020. Total healthcare expenditure in China more than tripled over the past decade. These trends lay a solid foundation for the growth of the biological therapeutics industry.[1]

New biological therapeutics from international and domestic drugmakers: In the past two decades, dozens of biological drugs have been launched in China, from both multinational corporations and domestic drugmakers. These include cytokines, enzymes, recombinant vaccines, insulin and its analogs and therapeutic mAbs.

CAN THIS GROWTH CONTINUE?

The Chinese industry will likely keep growing, but may have difficulty maintaining a double-digit CAGR over the next decade as economic development cools and enters a "new normal." With healthcare expenditure growing faster than economic growth, there is concern that the national healthcare insurance fund has reached or will soon reach overdraft status. Therefore, the Chinese government has made control of healthcare expenditure a policy priority.

In November 2015, the State Council issued a decree to control of the increase of healthcare expenditure from public hospitals (the Chinese healthcare system is still dominated by a public hospital system). Other policy moves include more stringent compliance standards, price negotiations with drugmakers by the Ministry of Human Resources, and "zero markup" for drug prices at hospital pharmacies. All these will put pressure on biopharmaceutical sales, and as was the case with Roche's Lucentis, many new biological therapeutics may need to have reduced prices to get on China's National Reimbursement Drug List (NRDL). It is highly possible that revenue from biopharmaceutical therapeutics will maintain a healthy growth rate, but a lower profit margin.

CHINESE PHARMA MOVES TO BIOLOGICS

With the new State Drug Administration (SDA) reforms streamlining the approval process of new drugs originating overseas and the launch of biosimilar versions of mAbs by domestic companies, the structure of China's pharmaceutical consumption will shift toward a greater market share of biological therapeutics, especially more complex molecules. Although China is still an under developed market in this sector, the penetration rate, especially of the more complex biologics, will increase. Multiple sales statistics show that the biopharma market grows faster than the pharma industry as a whole, and that mAb therapeutics market grows faster than the biopharma market. BioPlan's internal research also shows that China is likely to approve new gene therapy/cell therapy products in the next decade, since dozens of them are already at the clinical trial stage, although possibly only after the approval of such products in the U.S. and EU.

CHINA'S EXPORT AMBITION

Besides the growth of China's domestic market, biopharma manufacturers are strongly motivated to export their products to the global market, including the regulated market in the U.S. and EU. BioPlan's 2017 research, including interviews with 50 biopharmal manufacturing executives in China, confirmed that the country is making efforts to become a global contract bioprocessing hub.[4] Multiple executives from

CDMOs in the industry, including Dr. Li Zhiliang, CEO/founder of AutekBio, are confident that biopharmaceutical will be the next sector that China will lead as a contract manufacturer. As Zhiliang puts it, "This industry is not unique at all. What has already happened in the textile, toy, and mobile industries will happen in the biopharmaceutical sector as well."

With government subsidies and an influx of returning scientists, contract manufacturing of biologics in China has the potential to offer a cost advantage for global biopharma companies, which will see multiple therapeutic biologics go off-patent in the next decade. Outsourcing the manufacturing of these older products will also enable companies to focus on developing core products.

Despite its relatively late start, a number of major driving forces are pushing the robust growth of China's biopharma industry, as well as driving the country's efforts to become a global contract bioprocessing hub.

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