



ELEVENTH ANNUAL

Report and Survey of Biopharmaceutical Manufacturing Capacity and Production

A Study of Biotherapeutic Developers and Contract Manufacturing Organizations

APRIL 2014



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Manufacturing Organizations*

April 2014



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- AusBiotech (Malvern, Victoria, Australia)
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To ensure global coverage for this project, this year we invited major ***Media Partners*** to support our outreach to biopharmaceutical decision-makers. This year, our media sponsors helped ensure broad and representative coverage of industry participation:

- Biopharm International (Iselin, NJ)
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The early participation of our authors and sponsors in evaluating the areas and trends to be surveyed this year ensured the project was designed to cover the most relevant issues in biopharmaceutical manufacturing today. Their support was, again this year, critical to the success of the project.

Eric S. Langer
Editor

ABOUT BIOPLAN ASSOCIATES, INC.

BioPlan Associates, Inc. is a biotechnology and life sciences market analysis, research, and publishing organization. We have managed biotechnology, biopharmaceutical, diagnostic, and life sciences research projects for companies of all sizes since 1989. Our extensive market analysis, research and management project experience covers biotechnology and biopharmaceutical manufacturing, vaccine and therapeutic development, contract research services, diagnostics, devices, biotechnology supply, physician office labs and hospital laboratory environments.

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METHODOLOGY

This report is the eleventh in our annual evaluations of the state of the biopharmaceutical manufacturing industry. The strength of this study's methodology remains in its breadth of coverage, which yields a composite view from the respondents closest to the industry. This year, BioPlan Associates, Inc. surveyed 238 qualified and responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations in 31 countries; plus 178 industry vendors and direct suppliers of materials, services and equipment to this industry segment. Using a web-based survey tool, we obtained and evaluated information regarding respondents' current capacity, production, novel technology adoption, human resources, quality, and outsourcing issues. We assessed respondents' projected reasons for bottlenecks, and their perception of how these bottlenecks might be resolved.

This year, we provide additional in-depth analysis of specific issues affecting the industry. These Monographs cover the events shaping the past year, and evaluate how they will affect, or create trends that will shape biopharmaceutical manufacturing over the next five years.

To ensure comprehensive global coverage, we partnered with world-wide organizations to ensure the most accurate overview of the worldwide biopharmaceutical industry. Our industry partners are included in our acknowledgment section. In addition, to support this coverage, we also include acknowledgment of our media partners, whose assistance enabled us to reach the high quality of respondents required in this quantitative analysis.

Further information on methodology, breakouts on specific segments, and data from earlier surveys may be obtained by contacting us at the address below.

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CHAPTER 0: DEMOGRAPHICS

Survey respondents include a diverse group of biopharmaceutical senior managers and executives covering a spectrum of global biopharmaceutical and CMO firms. In addition, in Chapter 12, we include responses from global suppliers and vendors to this industry. As in previous years, we included firms of all sizes, and while we specifically sought input from larger manufacturers with substantial current capacity, we also obtained data from mid-tier and smaller companies with clinical scale production, and also from companies using CMOs for product manufacture and from CMOs. Respondents had a broad range of responsibilities, though all were directly involved with manufacturing in some way. Most were senior staff within their organizations.

This was an international effort, and we received responses from organizations around the world, including input from facilities in 31 countries.

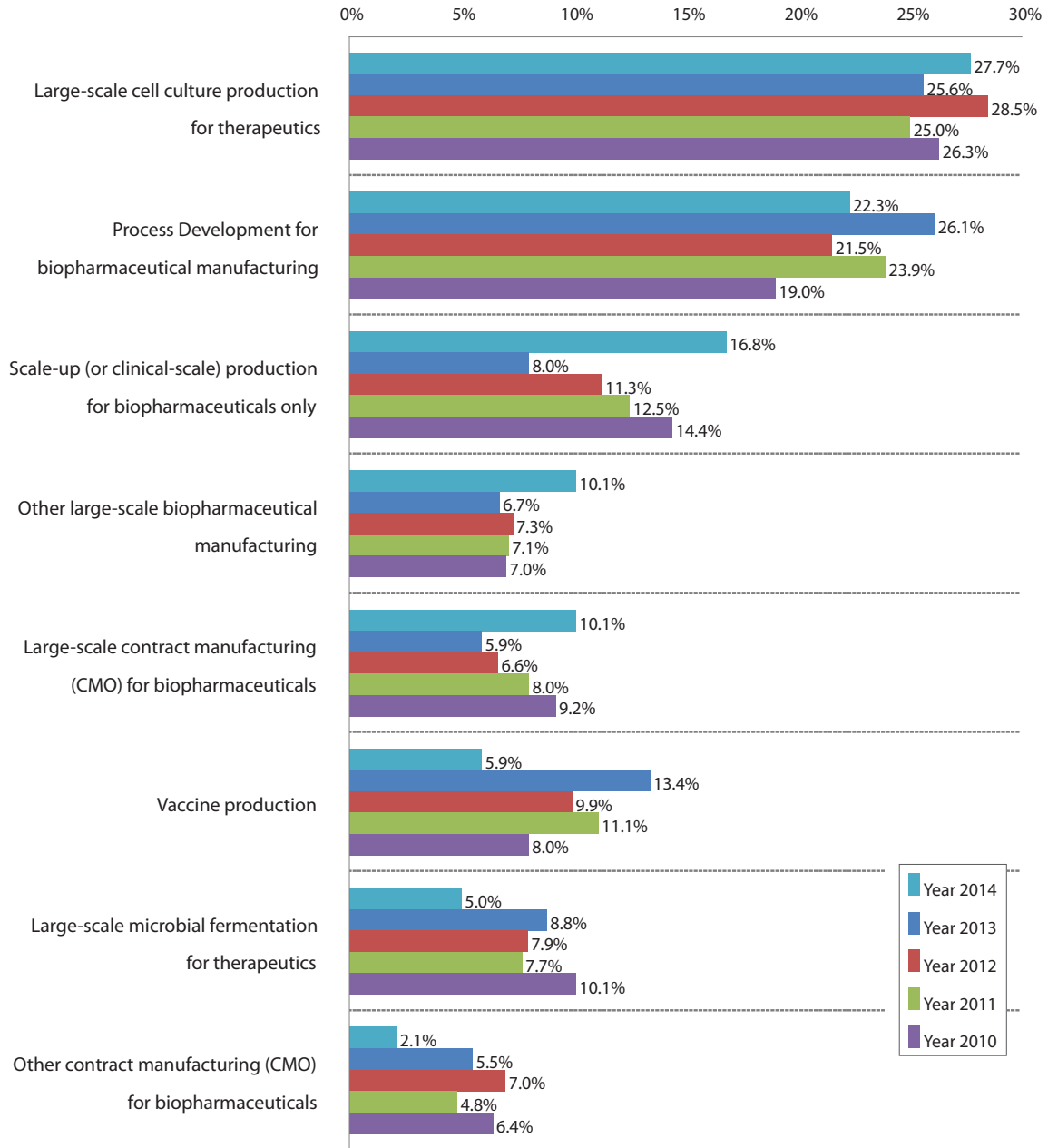
The diversity of respondents provides a comprehensive view of the industry from those closest to the present state of their organizations; those with a good understanding of the current and future business drivers, and manufacturing plans and needs. This offers a means for understanding the industry and its future course. The breakdown of organizations into CMO's and biotherapeutic manufacturers provides insights into two major segments of the industry. These two types of organizations have different business drivers, risk profiles, and costs of capital.

Respondents' Area of Involvement

Of the 238 biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) staff responding to this year's survey, 27.7% were primarily involved in large-scale cell culture production for therapeutics, up from 25.6% last year; 22.3% were involved primarily in process development for biopharmaceutical manufacturing, down from 26.1% last year; and 16.8% were involved in scale-up (or clinical-scale) production for biopharmaceuticals only, a significant increase from 8.0% last year and other prior years. Those involved with large-scale microbial fermentation for therapeutics accounted for 5.0%, and 5.9% of respondents indicated they were primarily involved in vaccine production, with both of these showing significant decreases from recent years. Other large-scale biopharmaceutical manufacturing accounted for 10.1%. 'Other' contract manufacturing (CMOs) for biopharmaceuticals accounted for 2.1% of respondents, down from 5.5% last year; and 10.1% were employed in large-scale contract manufacturing (CMOs) for biopharmaceuticals. Overall, the makeup of respondents continues to be consistent with prior year's studies.

Fig 0.1: Area of Primary Involvement in Biopharmaceutical Manufacturing, 2010 to 2014

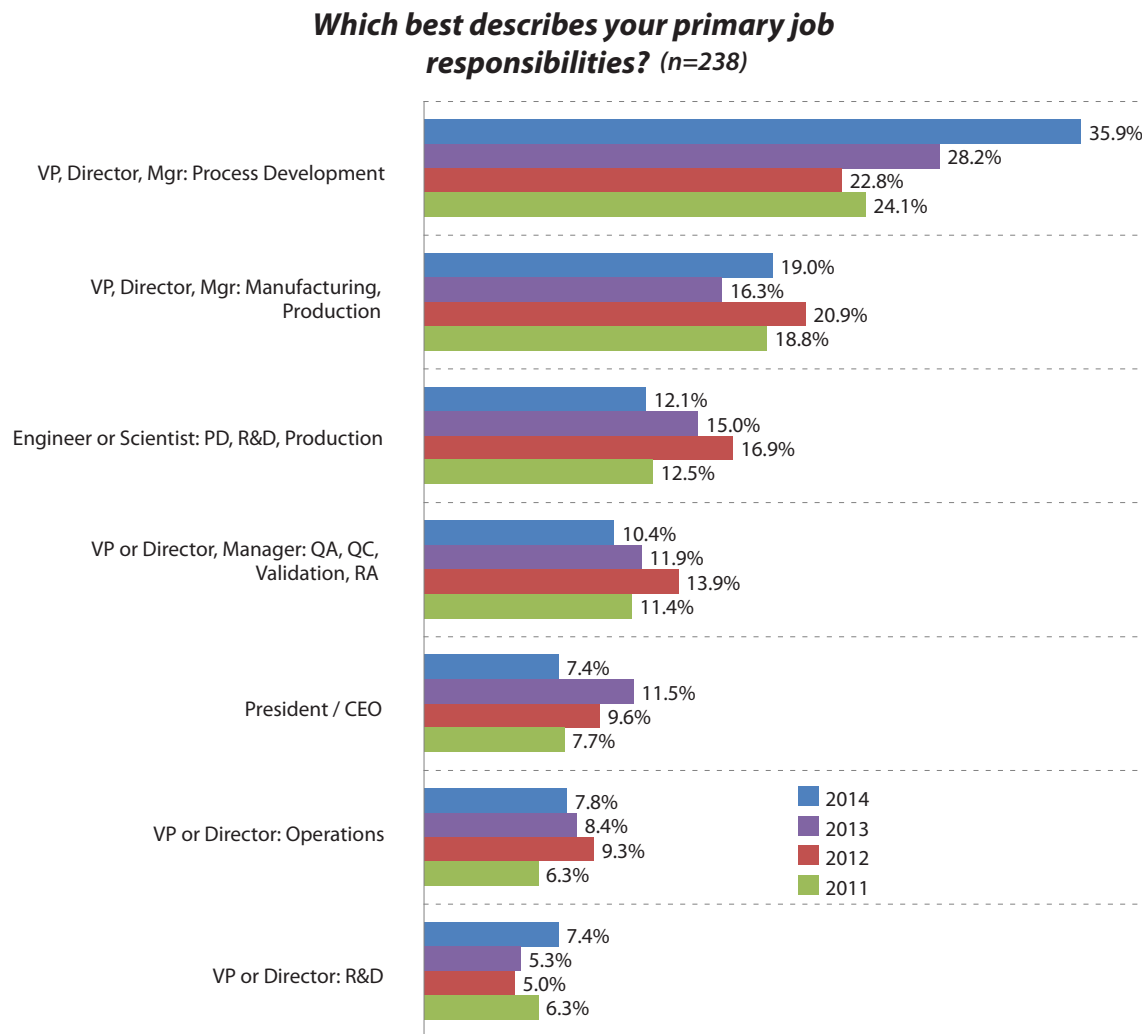
"In which area of biopharmaceutical manufacturing is your organization currently involved?"
Comparison 2010 to 2014



Respondents' Titles

Respondents were asked about their areas of responsibility, as indicated by job titles. Almost 88% had titles of VP, Director or President/CEO. VP's or directors of manufacturing, production, and operations, Directors and managers primarily involved in process development comprised 35.9% of respondents. Combining VPs with manufacturing and process development managers, the percentage comes to 54.9%. Biopharmaceutical scientists or engineers lacking VP/Director/Manager responsibilities in process development, R&D or production made up 12.1%, down from 15.0% last year. This year, 10.4% of respondents indicated they were VP's or directors of QA, QC, and validation. Presidents/CEO's represented 7.4% of respondents. VPs or Directors of R&D accounted for 7.4% of respondents. The largest percentage increase this year was in those reporting "VP, Director, Mgr.: Process Development" responsibilities.

Fig 0.2 Respondents' Job Responsibilities, 2011 - 2014

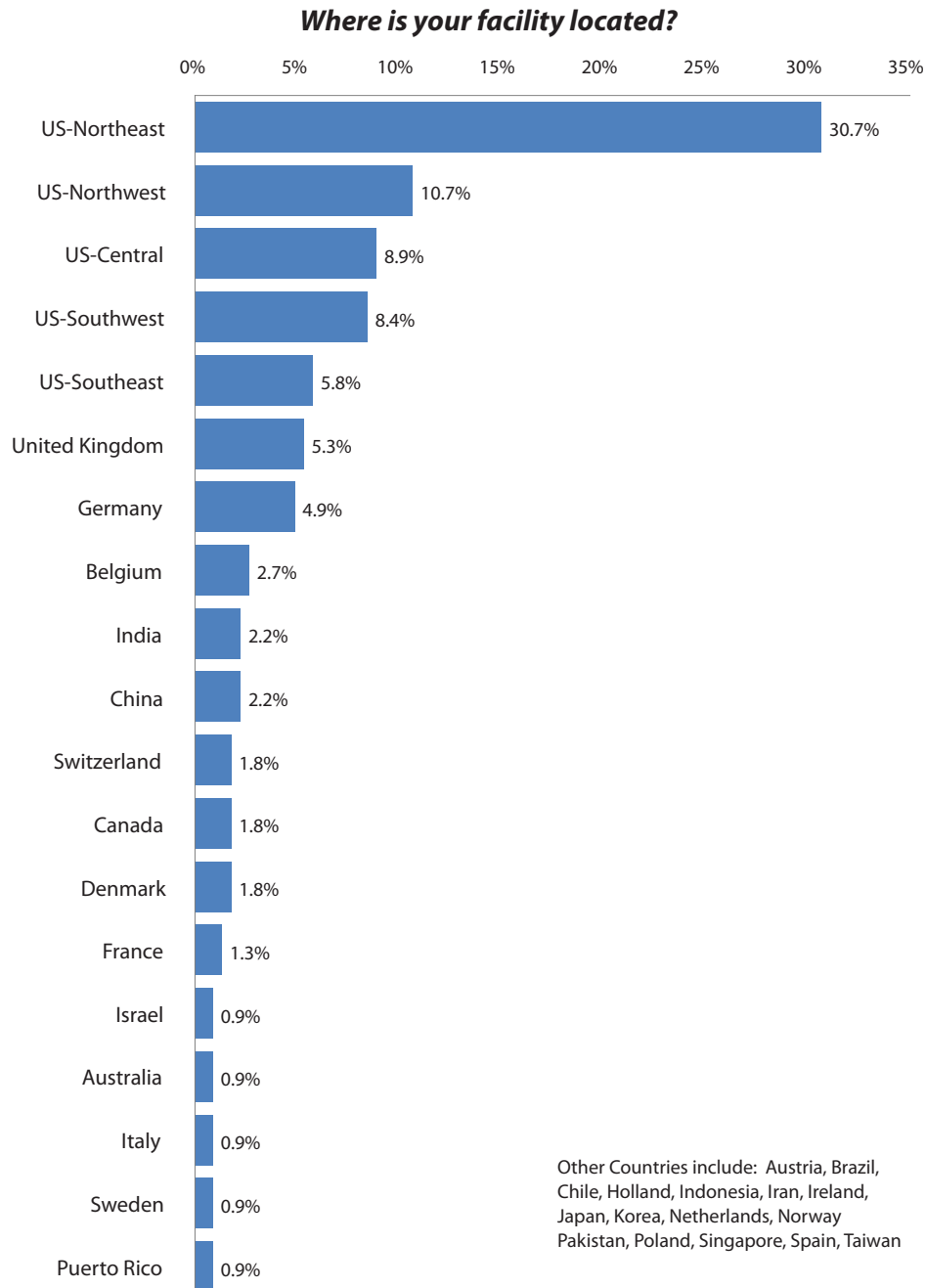


Respondents' Facility Locations

This year we surveyed respondents in 31 countries. Over 64% of the respondents were from the United States, with the Northeastern U.S. representing 30.7%. Respondents from Western Europe made up over 20% of the total. Other countries in the survey ("Rest of World") made up almost 16% of the respondents, down from 22% last year.

Further information about biopharmaceutical manufacturing facilities worldwide is available at the Top 1000 Global Biopharmaceutical Facilities Index Web site from BioPlan Associates (www.Top1000Bio.com.)

Fig 0.3: Facility Location

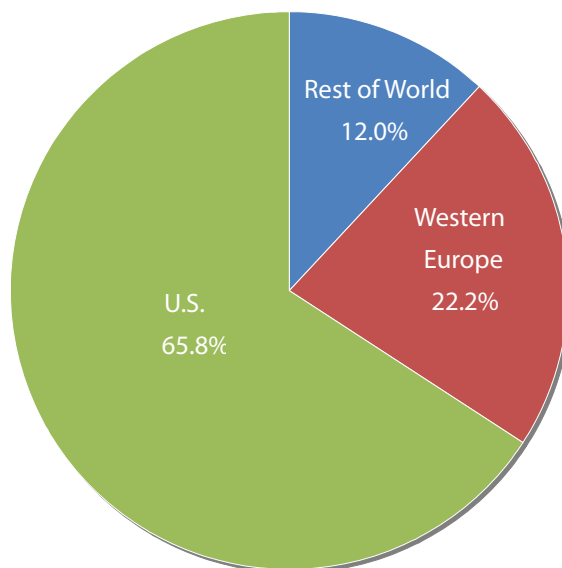


We note that U.S. respondents rose to 65.8% this year, significantly up from 55.0% in 2013, 60.9% in 2012 and 61.7% in 2011. Western European responses have been relatively constant at 22.2% for this year, 22.9% in 2012 and 20.2% in 2011.

This year ROW responses declined significantly to 12.0%, from 22.0% last year. This decline may be the result of difficulties in communicating with ROW bioprocessing professionals and/or developed country-based, particularly U.S., bioprocessing professionals being more motivated to participate in this and other industry surveys.

Fig 0.4: Facility Location, by Region

**Respondents' Facility Location by Region
(Biotherapeutic Developers and CMOs)**



Respondent countries in Western Europe include: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.

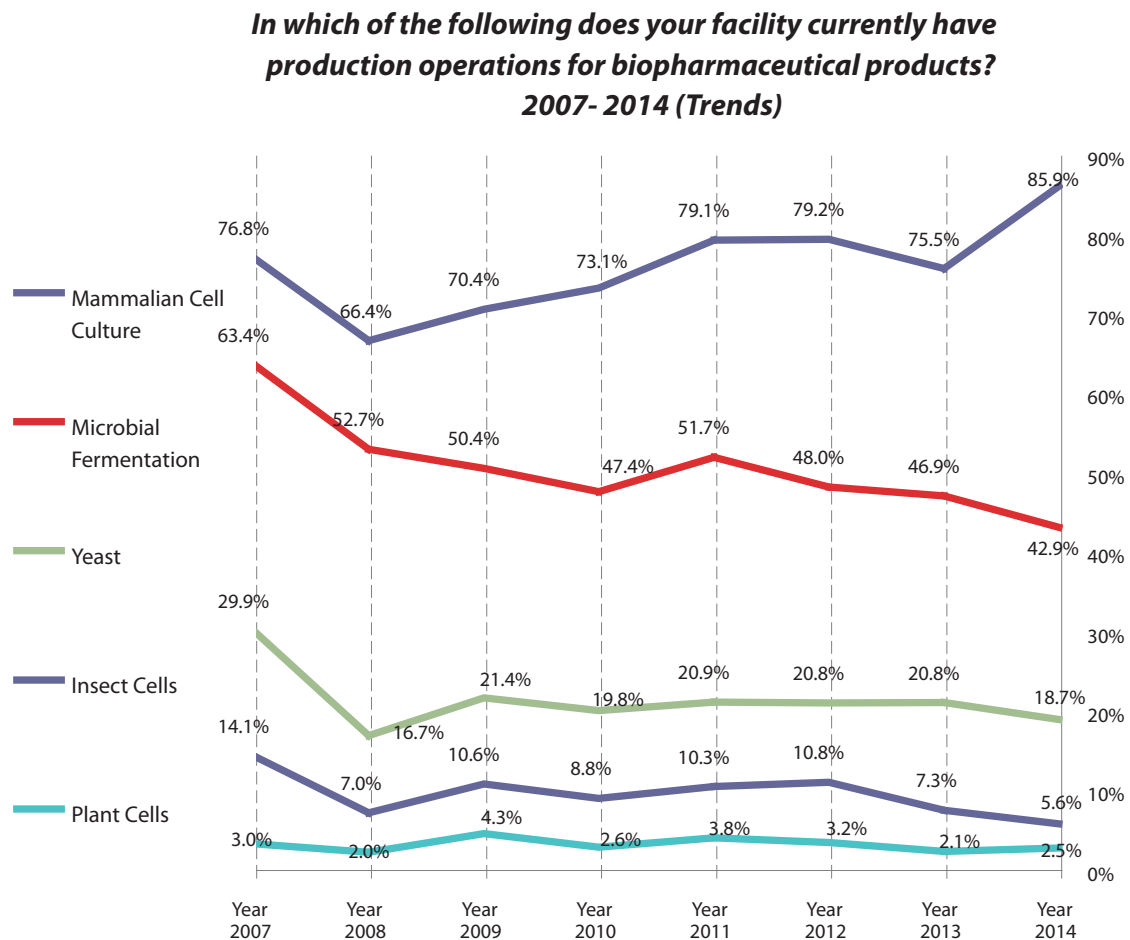
Respondent countries in "Rest of World" include: Canada, Australia, India, China, India, Singapore, Egypt, Japan, Russia, Estonia, Israel, Argentina, Brazil, Bulgaria, Cuba, Korea, Lithuania, New Zealand, Poland, Slovenia, South Africa, and Taiwan.

Respondents' Areas of Biopharmaceutical Manufacturing Operations

This year, almost 90% of respondents indicated that they were involved in mammalian cell culture (85.9%.) This is up from last year's study in which 75.5% of respondents were involved in mammalian cell culture. For microbial fermentation, 42.9% of respondents noted involvement in this area, down from the previous year (46.9%.) For this year, 18.7% said that their facility had production operations in yeast, down from 20.8% last year. The percentage of those involved with microbial, including yeast, manufacture is tending to slowly decrease, with mammalian cell culture generally dominating product development and manufacture.

Since 2009 the overall percentage of respondents in each system has declined, except for mammalian cell culture. Almost every system reported showed a slight drop in participation from 2013 to 2014, except for mammalian cell culture and plant cells. The increasing use of mammalian systems is likely associated with increased adoption of mammalian systems as standardized broad platform technologies within facilities, preferably using the same mammalian systems for manufacture of as many products at possible. With increases in mammalian system yields, even products that could be manufactured in microbial systems are now often manufactured in mammalian systems, if these will get the job done, such as to produce pre-clinical or early clinical supplies.

Fig 0.5: Biopharmaceutical Manufacturing Systems, (2007-2014) Trends



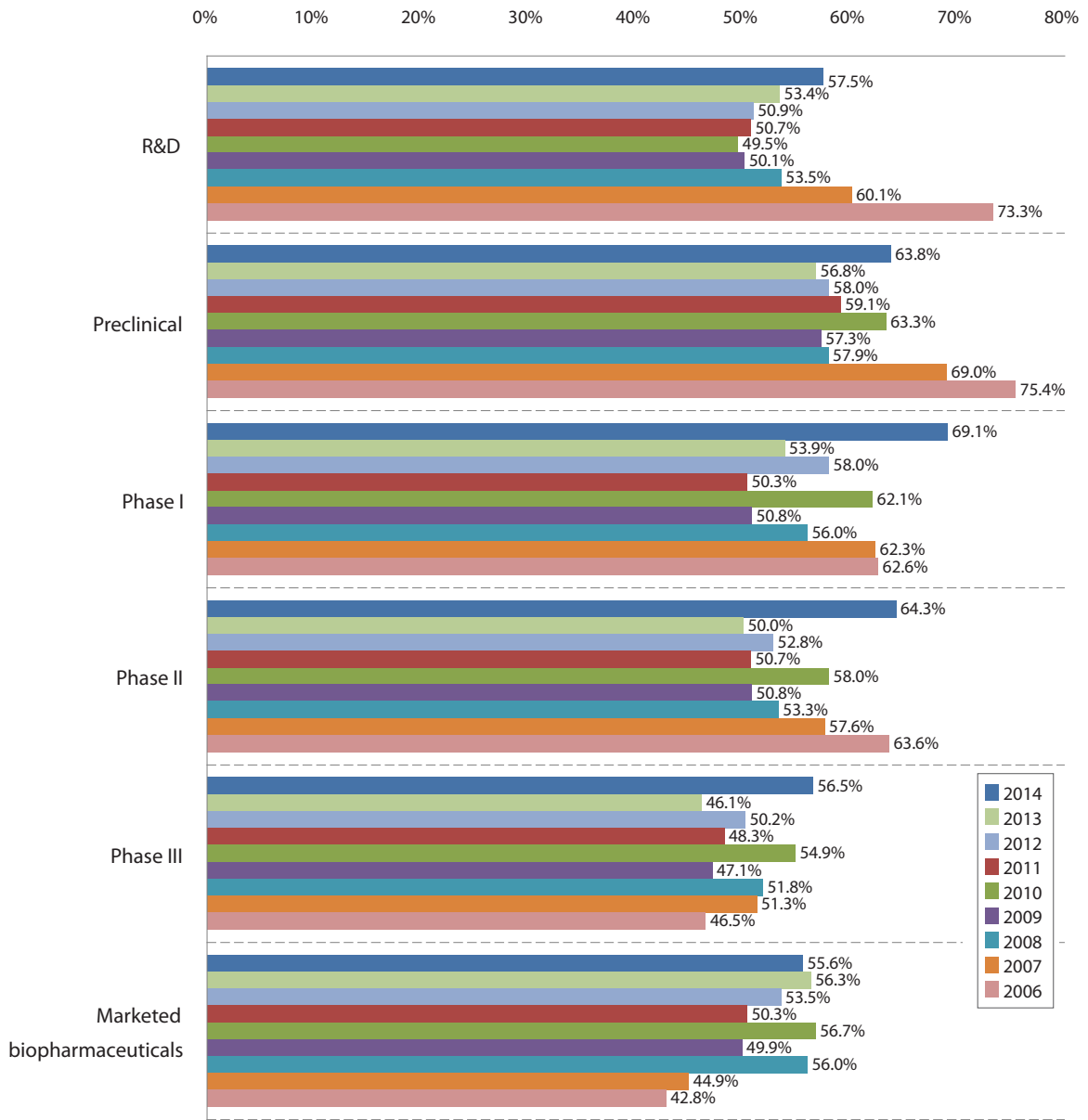
Respondents' Production Operations, Phase of Development

We identified the phases of clinical development in which respondents' organizations (companies) had products. In 2014, almost 60% (57.5%) of respondent companies had R&D biopharmaceutical operations, and 63.8% had preclinical operations. Respondent organizations involved with R&D were 73.3% in 2006, down in 2007 and continuing downward in 2008, then leveling off at 50.7% in 2011. This has continued to climb each year to 50.9% in 2012 and 53.4% in 2013. Preclinical started at 75.4% in 2006, down to 69.0% in 2007, and continuing downward to 57.9% in 2008. It spiked to 63.3% in 2010, with downward years in 2011 and 2012, at 59.1% and 58.0%, respectively, and has risen back past 2010 levels.

The percentage of respondents whose companies have biopharmaceutical products on the market has risen since 2006, from 42.8% in that year, to 55.6% this year (a slight decline from 56.3% last year.) This continues to show industry maturation, with most respondents now employed by companies with revenue streams from marketed biologics. In fact, 2009 has been widely noted as the year the biopharmaceutical industry finally, as a whole, turned a profit. Of interest may be the slight increases in the percentages of manufacturers that also have products in the R&D pipeline. This may represent consolidation within the industry as smaller R&D based companies are absorbed by larger companies, or the industry may simply be devoting more resources to R&D, including having recovered from recent prior year's economic difficulties.

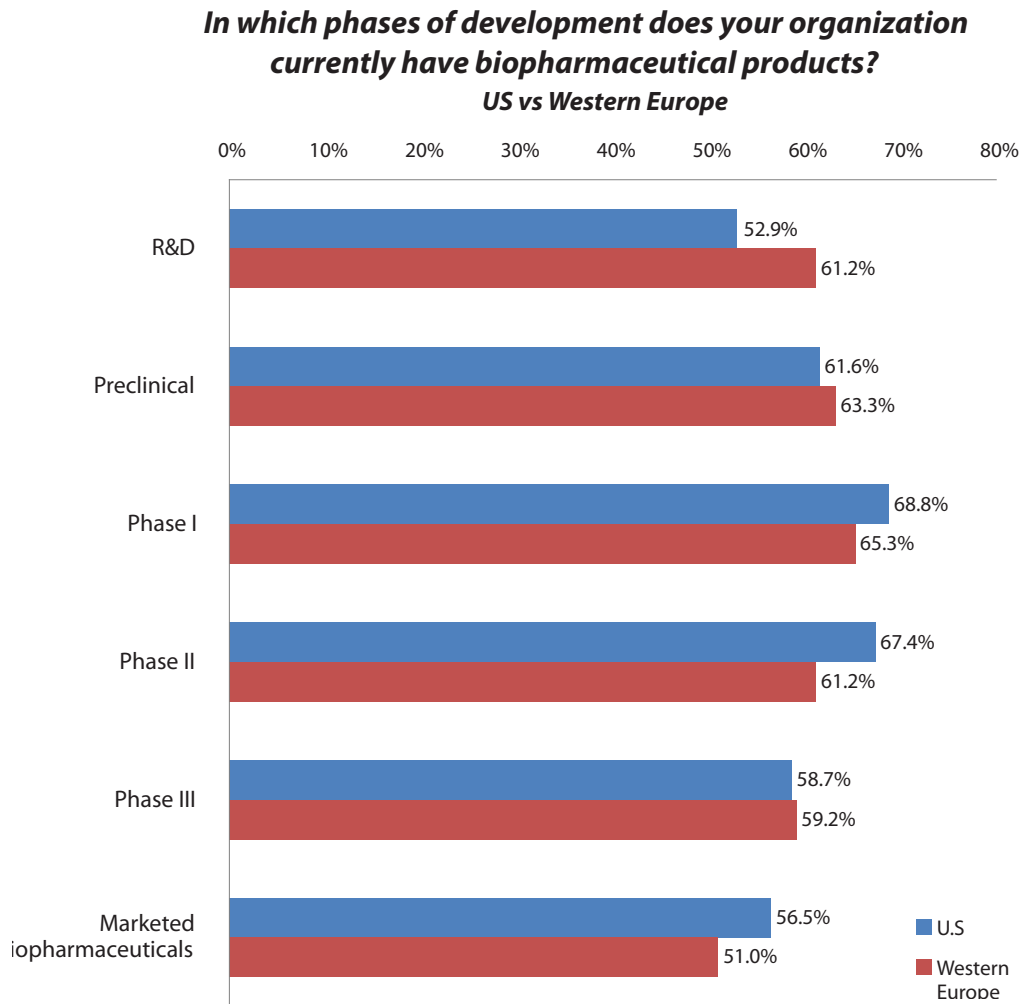
Fig 0.6: Phase of Development of Surveyed Respondents

***In which phases of development does your organization currently have biopharmaceutical products?
2006-2014***



The U.S. has higher responses indicating involvement with commercial products, 56.5% for the U.S. and 51.0% for Europe. Western Europe, compared to the U.S., has significantly higher percentages of respondent companies involved in early R&D and slightly higher percentages in preclinical development, and has slightly higher percentages involved with Phase III clinical trials than the U.S. However, the U.S. has significantly higher percentages in Phase I and Phase II clinical trials this year vs. Western Europe, an increase from previous years. Overall, the phases of development of bioprocessing organizations are rather well spread over the full spectrum from product R&D through commercial products manufacture, confirming that this is a vital and growing industry.

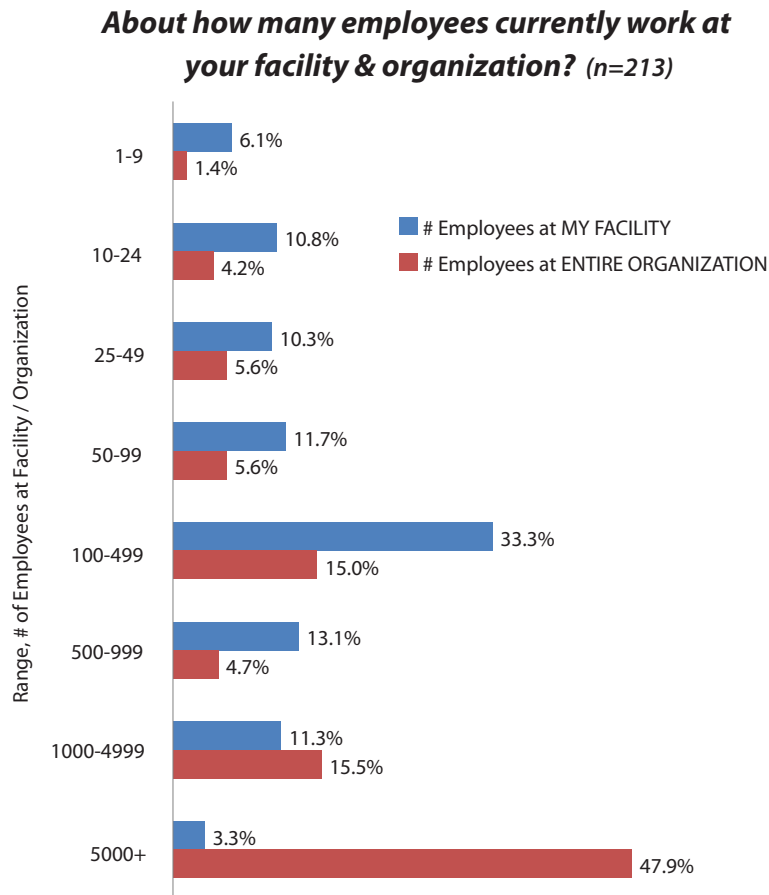
Fig 0.7: Phase of Development of Surveyed Respondents, 2014 (U.S. vs. Western Europe)



Employees at Facility

To evaluate issues such as capacity, disposables usage and other factors, we asked the number of staff within their own facility, and within their total organization. Within the survey group, the largest percentages of respondents were at facilities with 100-499 employees, continuing the trend from previous years. However, the largest numbers of respondents, nearly 50%, were from organizations with greater than 5,000 employees. This distribution reflects the distribution of bioprocessing and other professionals employment in the (bio)pharmaceutical industry, and larger company dominance of R&D and products marketing.

Fig 0.8: Distribution of Employees at Facility, and Organization

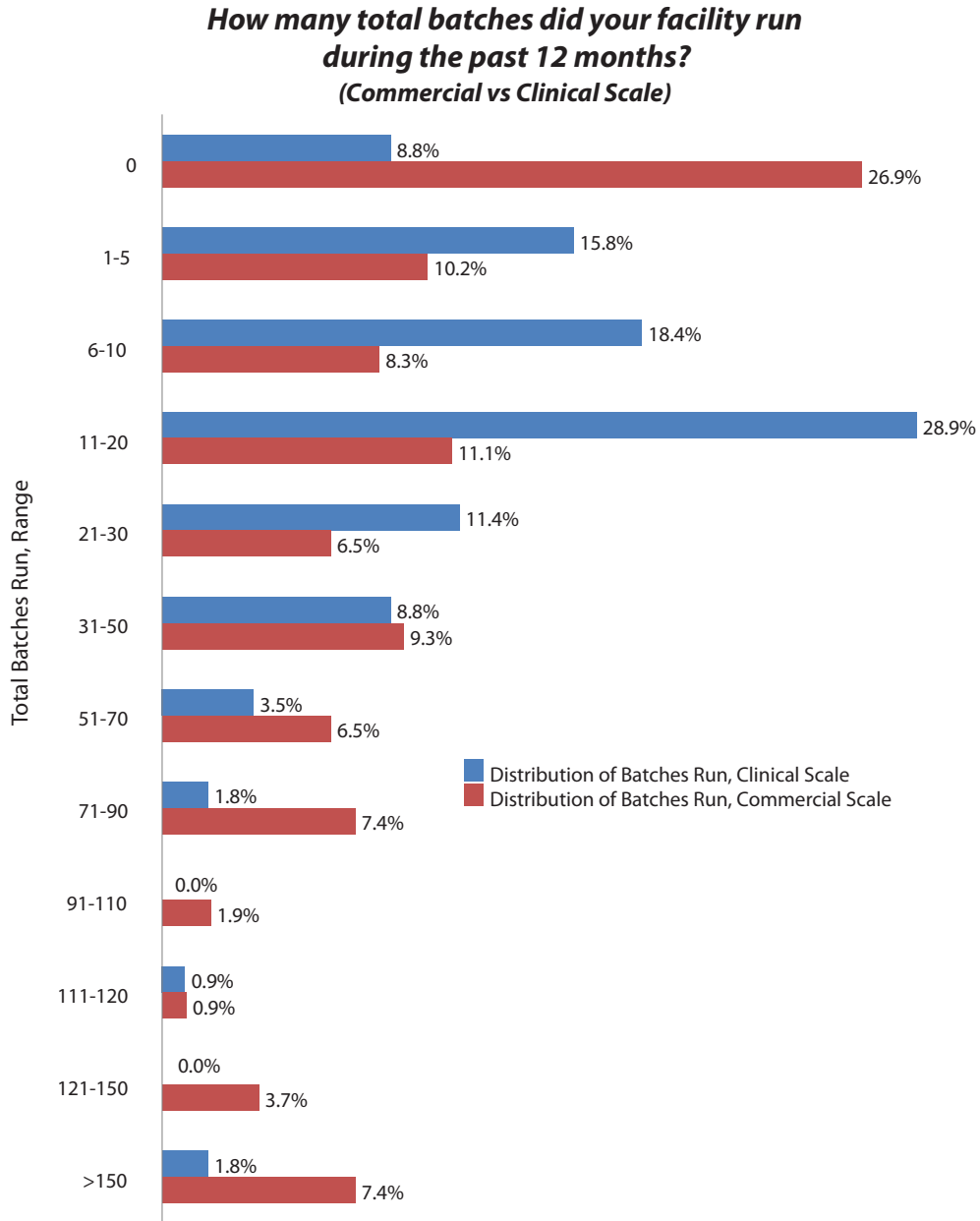


Batches Run at Facility per Year

To ensure we were capturing large organizations involved in significant manufacturing processes and to evaluate issues such as batch failure rates, we evaluated the number of batches or production runs the facility ran over the prior 12 months. For clinical scale manufacturing, the largest number of facilities reported producing between 1 and 20 batches per year (63%). At the commercial scale, 7% were producing over 150 batches per year, but most reported running between 1-50 batches per year (83%), which is a significant increase from 2013 (46.3%), and an even larger increase from 2012 (36%).

To compare consistency of respondents' operations, year-by-year, we evaluated the number of batches run. This year (asking about 2014) we found between "0-10" batches were run by 43% at clinical scale, and 45% at commercial scale. Last year, in 2013 the data were 49% at clinical scale and 46% at commercial scale. This is consistent with prior years: In 2012, "0-10" batches were run by 45% (clinical scale) and 46% (commercial scale.) In the 2011 study, the numbers were 44% clinical, and 47% commercial scale. In 2010, 40% and 43% ran "0-10" batches at clinical vs commercial scale, respectively.

Fig 0.9: Distribution of Total Batches Run at Facility Last Year, by Scale of Production



CHAPTER 1: INTRODUCTION AND DISCUSSION

1-1 INTRODUCTION: THE BIOPHARMACEUTICAL INDUSTRY

The pharmaceutical and biopharmaceutical industries remain active, profitable and growing segments, despite having recently recovering from worldwide economic problems. There are estimated to be over well over 10,000 therapeutics in R&D, both drugs (chemical substance pharmaceuticals) and biopharmaceuticals (biotechnology-derived pharmaceuticals), with nearly 40,000 ongoing (or recently reported) clinical trials. Among these, an estimated 40% or likely over 4,000-5,000 candidate products in R&D are biopharmaceuticals. A significant portion, about 900 products in the development pipeline, is follow-on biopharmaceuticals, mostly biosimilars but also a large number of biobetters. This industry activity represents a considerable increase from as short as five years ago and reflects a basic shift in the pharmaceutical industry from small molecule drugs to biopharmaceuticals for new, innovative and profitable products. And the large number of biosimilars and biobetters in development indicate the maturation of the biopharmaceutical industry, as its major products start to go off-patent.

However, as companies of all sizes continue to cut back on expenses as much as possible and consolidate R&D, they may be concentrating more on fewer products, so the overall pipeline may well be shrinking somewhat. This may be showing up more in clinical trials rather than preclinical phases. But in terms of biopharmaceuticals, any such decrease in R&D may well currently be counter-balanced by established, including Big Pharma companies, companies increasingly moving into biopharmaceuticals. But even if the pipeline is shrinking (which will only be evident in hindsight), this is not necessarily an indicator of problems. Any pipeline shrinkage may simply reflect the industry doing a good or better job in eliminating less promising candidates before they enter and in early-stage clinical trials. This 'failing faster,' i.e., earlier in development, is much less costly and disruptive than products failing later in development. If industry is doing a better job of weeding out poor candidate products earlier, industry may actually be on track for increased future success, with fewer costly late-stage failures and a higher percentage of pipeline products making it to the market.

The pharmaceutical R&D pipeline and industry are becoming increasingly dependent on biopharmaceuticals. These products are being developed by an ever-increasing cross-section of the pharmaceutical industry, including Big Pharma and even generic drug companies, with many of these also active in developing biosimilars. These sources, along with smaller biopharmaceutical developers, which have been the traditional source for most innovative biopharmaceuticals, are continuing to expand the global biologics pipeline. And new entrants based in China, India and other developing countries are increasingly entering biopharmaceutical R&D. Thus, an increasing number and percentage of new pharmaceuticals

entering the market will be biopharmaceuticals vs. small molecule drugs. Combine this with biopharmaceuticals generally costing much more and providing higher profit margins, and the pharmaceutical industry will increasingly be dependent on biopharmaceuticals for profits, innovation and its basic survival.

As biopharmaceuticals become an even more important part of the pharmaceutical industry, many new players are entering the field and most current manufacturers are expanding their bioprocessing capacity. Not only must bioprocessing output (if not liter capacity) expand to handle manufacture of an increasing number of approved products and higher volumes as markets for many products further expand, e.g., with approvals for new indications, the industry must also be capable of handling a large number of pipeline products. Most recent capacity expansion generally has involved building large fixed stainless steel bioreactor-based bioprocessing systems for commercial product manufacture, while production of supplies for R&D and clinical testing are now essentially dominated by use of single-use/disposable bioreactor-based systems, with this requiring much less facilities and infrastructure investment and construction. The strategic importance of biopharmaceutical manufacturing and manufacturing capacity are increasing, and understanding the markets for bioprocessing equipment, technologies and services is becoming ever more important to those in the biopharmaceutical industry.

Planning and decision-making concerning the manufacture of biopharmaceuticals are becoming more complex as companies continue to implement cost-saving efforts, including cutting back on the number of products in their development pipelines, and outsourcing even more support and even critical tasks. In addition, manufacturers must choose from an ever-increasing number and diversity of bioprocessing options. This includes new and improved cell lines and genetic engineering/expression systems technologies; bioprocessing equipment, including new and improved single-use equipment; and outsourcing manufacturing to CMOs which are expanding their capacity, technologies, and service offerings. Increasingly, companies must make difficult and costly strategic decisions about commercial manufacture earlier in product development.

A number of questions need to be answered by biopharmaceutical developer even before a product is shown effective in clinical trials. These include aspects such as:

- ◆ Should we use an older, off-patent expression system or a new, much higher yield, but royalty-bearing system?
- ◆ Should we use single-use/disposable or fixed stainless steel bioprocessing equipment for clinical supplies manufacture?
- ◆ If we use single-use bioprocessing systems to support development, do we want to be among the first pioneers to use single-use equipment for commercial manufacture or should we stick with familiar, trusted, but more expensive and labor-intensive, fixed stainless steel equipment for manufacture?

Effective planning within the biopharmaceutical and bioprocessing markets is required to avoid problems later on. This demands a high level of partnership, information sharing and communication between manufacturers, CMOs and bioprocessing technology and equipment suppliers to develop new manufacturing technologies, devices and capacity to keep pace with industry needs. Strategic production decisions must be based on solid bioprocess data, combined with a broad understanding of trends tracking and effective benchmarking of capacity and production issues.

This study provides an on-going evaluation of the vital manufacturing trends shaping this industry, and is designed to help keep those in the industry aware of all the external trends and issues affecting biopharmaceutical manufacture decision-making.

1-2 CURRENT BIOPHARMACEUTICAL MARKET TRENDS

The biopharmaceutical industry survived recent years' worldwide economic downturn. In fact, the industry has done rather well for itself during this period – not contracting or losing much at all in recent years – and is now showing clear signs of full recovery and renewed growth. As much of the world economy still slowly improves, the biopharmaceutical industry continues to remain dynamic and growing. This year, as in 2013 and prior years, survey results show that companies are spending and investing more in their R&D, new technologies, bioprocessing capacity, staff and other infrastructure. In fact, survey data now show companies increasing investments in all 12 categories surveyed! Companies, particularly larger and more established ones, are continuing to aggressively look for opportunities to cut costs and increase efficiency, with this continuing to benefit contract manufacturing and research organizations (CMOs and CROs.) Prior rather common severe cuts in staff and divestment of facilities have largely ended, but this may simply reflect reaching the limits of eliminating in-house expertise and facilities. Some specific trends are discussed below.

The industry is healthy and its status is improving: The world market for biopharmaceuticals is now about ≥\$190 billion; growing at ~15% annually, definitely a very healthy rate. New products and new markets, particularly internationally, continue to support market growth. The world market for recombinant protein therapeutics is now ~\$115 billion. The continued high growth rate in biopharmaceutical markets (revenue) will continue to drive investment in the industry, including at the expense of traditional small molecule drug development. Biopharmaceuticals vs. drugs have simply proven themselves to be profitable investments, e.g., with much higher profits per sale and likelihood of attaining success, including capturing market share, with this often simpler or more straightforward with innovative biopharmaceuticals. A large portion of biopharmaceuticals coming to market still involve treatment of ignored or currently untreatable indications, making them particularly welcome or needed. Many new entrant companies of all sizes and types, including generic drug and foreign companies, are developing biosimilars and plan to use these to establish them in the industry. This is resulting in a significant increase in the number of players in the biopharmaceutical industry.

Overall, 2014, like 2013, is fully expected to be a good year for the biotechnology and biopharmaceutical industries, with these remaining viable, relatively insulated from the worst of the world's economic problems, growing and well-positioned for solid future growth.

Cost-containment and Controls: The past year was another rather quiet year in the U.S. and most other major markets in terms of new calls for and implementation of cost-containment measures or cost controls for pharmaceuticals, including biopharmaceuticals. But in some other countries, cost containment and government-directed cost controls continue to adversely affect biopharmaceuticals. This includes the U.K. National Institute for Health and Clinical Excellence (NICE) issuing more product reviews rejecting some biopharmaceuticals as too expensive and not cost-effective for use by the country's National Health Service (NHS), effectively making these products non-marketable in the U.K. In the U.S., insurance providers continue to take control of prescription writing and use away from physicians and consumers, forcing use of products for which they have secured preferential prices and often simply just refusing to pay for expensive biopharmaceuticals that they (not the prescribing physician and his patient) do not consider the most appropriate. As biosimilars become available, much as with generic drugs, U.S. insurers will surely force physicians, pharmacists and consumers to use these rather than more expensive innovator products.

• **Manufacture in Developing Countries is Increasing:** Biopharmaceutical manufacture outside of the usual major market countries is increasing, as indicated by BioPlan's Top 1000 Global Biopharmaceutical Facilities Index (www.top1000bio.com), which ranks facilities worldwide in terms of known or estimated capacity, employment, and production. Much new and increased capacity is being added internationally, with biopharmaceutical markets in many developing countries rapidly growing and domestic/regional companies increasingly serving these markets, often with biogeneric or outright copies of innovator products that are simply marketed as substitutable for the innovator product (without much real testing.) Innovator companies seeking to expand international markets will increasingly have to deal with such local/regional competition. Another factor that will result in increasing manufacture in lesser-developed countries is that these countries' governments are increasingly seeking to assure domestic manufacture of biopharmaceuticals being sold in their markets. Already, many countries are starting to tell vaccine manufacturers that they want products for their markets manufactured in-country, preferably or requiring this be done by locally-owned or joint venture companies. And as single-use equipment and manufacturing technologies continue to improve and, particularly, as modular bioprocessing facilities enter the market, foreign countries (or their proxy/subsidized companies) will increasingly undertake manufacture of needed products, such as commonly-used vaccines, with or without the assistance and participation of original product developers and current manufacturers.

• **Worldwide Standardization of Manufacturing:** Particularly with larger companies, as more biopharmaceutical manufacturing is performed worldwide, companies are working to standardize their products and manufacturing processes on a worldwide basis. For many, this includes having 2nd- or even 3rd-source facilities either actively manufacturing or serving as backups, having received approvals for manufacture for the U.S. and other major markets. Adoption of single-use and modular bioprocessing systems for commercial manufacturing will accelerate this trend.

1-3 MARKET POTENTIAL

The biopharmaceutical market will continue to expand. There are currently 1,000s of therapeutics in R&D, including 40% or more now being biopharmaceuticals. This shift towards biopharmaceuticals reflects a fundamental shift within the pharmaceutical industry, with the largest traditionally small molecule drug-oriented Big Pharma companies moving heavily and rapidly into biopharmaceuticals. These companies are increasingly developing their own, licensing in or otherwise acquiring more biopharmaceutical products. For these companies and others, biopharmaceuticals provide higher revenue (cost more) and profits per sale, and with biopharmaceuticals often requiring more complex detailing and other sales support, increasingly fit well with the resources and marketing-intensive business models of large international pharmaceutical companies. Overall, there is a major shift towards biopharmaceutical R&D, manufacturing and marketing, often at the expense of traditional small molecule drug candidates.

However, due to economic concerns, all pharmaceuticals, particularly biopharmaceuticals which tend to be the most expensive, face increasing cost containment and control efforts worldwide. The U.S. remains the world's main pharmaceutical market, including in terms of sales and profits. Government-based cost-containment and control efforts remain limited in the U.S. Despite political demands for lowering pharmaceutical expenses by government programs, such as Medicare for older patients, the major U.S. health care overhaul legislation enacted in late 2010 is expected to have minimal impact on biopharmaceutical usage. If anything, this health care overhaul will actually provide continued long-term support for use of innovative (bio) pharmaceuticals, particularly if the alternative treatments or no treatment (none being available) are overall less cost-effective options. Cost-containment and control efforts can be expected to increase in most other countries, particularly, those already having implemented cost controls, with expensive biopharmaceuticals being an easy target for elimination or reduction. India has substantially boosted its price controls and generics-favoring policies, including not allowing pharmaceuticals to be marketed by trade name (only by generic name.)

However, since most biopharmaceuticals are used for indications for which there are few, if any, alternatives; the overall market is rather protected from widespread cost-containment and controls. Those countries that have imposed cost controls, so far, generally represent small markets. Improved manufacturing methods and cost management for biopharmaceutical production will continue to slowly advance, which will tend to reduce the cost of goods. With continued reductions in manufacturing costs, including better process monitoring, higher-yield expression systems and increased use of more cost-effective single-use/ disposable bioprocessing systems, biopharmaceuticals appear to be positioned to further increase their role in world pharmaceutical markets.

The world biopharmaceutical market is currently about \$190 billion/year. This continues to grow worldwide at about 15%/year, making biopharmaceuticals a fairly recession-proof, growing and profitable industry. The market for recombinant proteins now is about \$115 billion. Much of this growth in biopharmaceutical revenue is due to an increasing number and sales of recombinant monoclonal antibodies, now a >\$45 billion market, approaching 50% of the recombinant protein and 33% of the overall biopharmaceutical market. These products have been shown to be rather reliable in terms of development and reaching the market, with antibodies generally being very specific, targeted, not causing severe adverse effects and well-received in the marketplace. Recombinant monoclonal antibody sales will further rapidly increase in coming years as new products enter the market and approved indications are expanded for existing products.

But despite the industry being healthy and growing, broader economic issues will continue to force biopharmaceutical companies of all size to cut costs wherever possible. This is shown in this year's survey data showing that the industry continues to recognize the need for continual improvements in performance and optimization of R&D, manufacturing and marketing.

Financing, particularly for smaller companies, has gotten tighter and will remain restricted in 2014. Many companies of all sizes are having to seek alternative funding methods, increase their collaborations and licensing (vs. conducting in-house R&D), decrease the number of candidates in development, and are otherwise taking steps to make themselves more efficient and productive.

The use of contract manufacturing organizations and the use of single-use bioprocessing equipment are making product manufacture, particularly for R&D and clinical trials, more efficient and in some cases less costly. Especially for smaller and under-funded companies, going with CMOs for production or using single-use equipment for in-house candidate product manufacture is the only financially viable options. These approaches reduce capital and financing needs, because companies can avoid \$50-\$150 million facilities costs for construction of fixed, dedicated stainless steel bioreactor-based bioprocessing systems, while a typical fully single-use facility for commercial manufacture can still easily cost \$25-\$40 million.

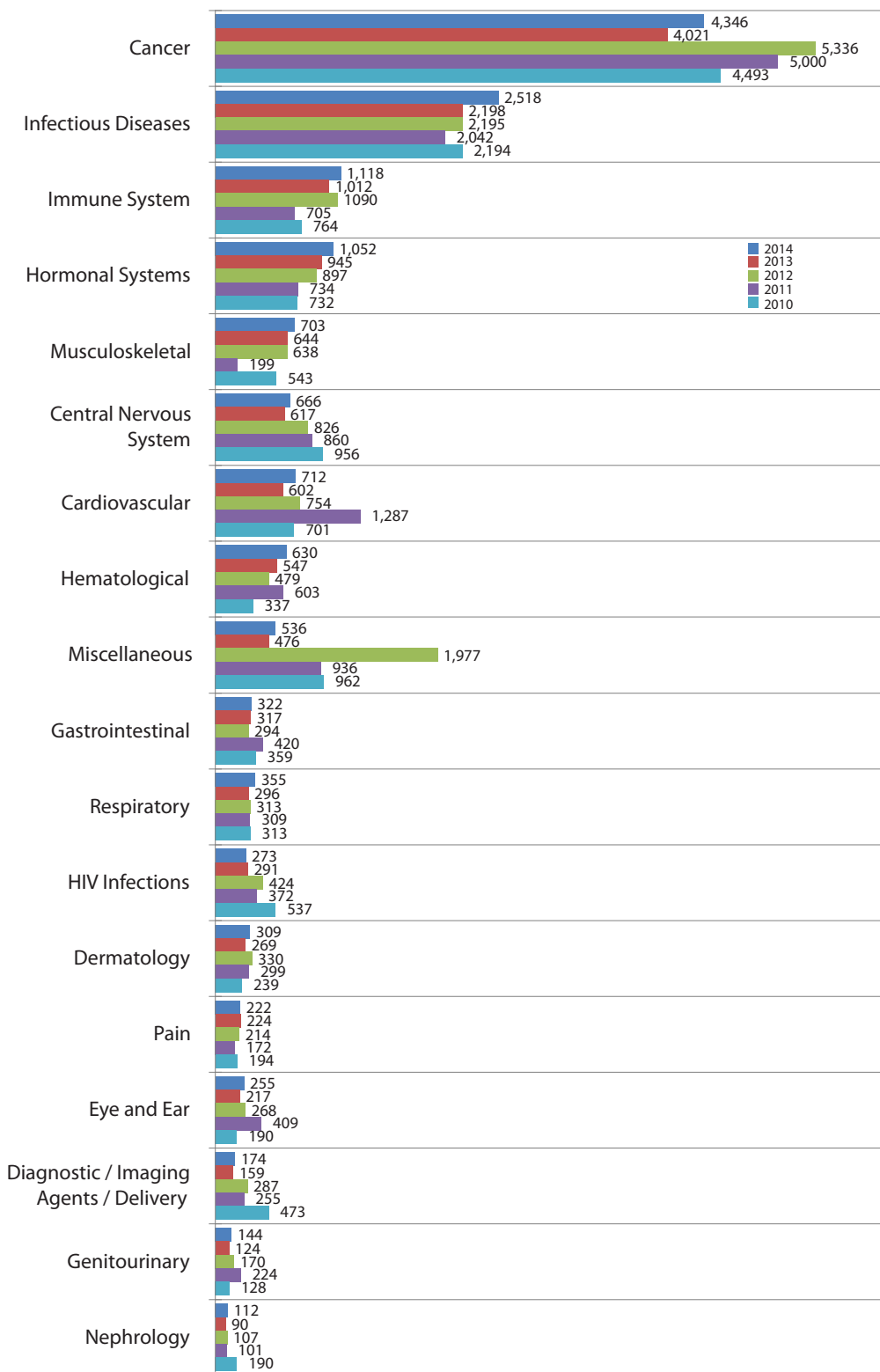
Despite the biopharma industry's bright future, successful companies in this complex worldwide industry will continue to require complete and accurate knowledge of the market and competing technologies, along with adequate lead-times, large capital expenditures, and careful planning. Biopharmaceutical development and manufacture is very costly, and no company can afford to make tactical or strategic mistakes. This makes accurate market and manufacturing planning all the more essential. The industry needs to keep on top of the current situation and future trends.

This report summarizes survey data and information obtained from biopharmaceutical manufacturers worldwide in late 2013 and early 2014. Its intent is to provide a quantitative-based overview and assessment of industry capacity, production trends, and benchmarks, along with presenting industry views on these and other subjects. As an on-going benchmarking effort, this study offers a view into current and future potential global industry problems and opportunities.

1-4 BIOPHARMACEUTICAL R&D PIPELINES

Table 1.1 provides an overview of worldwide biopharmaceutical product R&D and marketing situation by indication. As can be readily seen, cancer and infectious diseases clearly dominate the biopharmaceutical development pipeline. Cancer treatment is by far the most active, with over 4,000 products now in development. Note this and other data provided by Biopharma Insight do not count products in development, the usual pipeline evaluation parameter; rather they cumulate significant milestones, such as approvals, trials, etc., for multiple indications, countries, etc. These data are still rather useful for spotting trends.

Fig 1.1: Investigational Drugs: Large Molecule (Protein Therapeutics), Worldwide, 2010 - 2014



Source: BioPharm Insight, www.biopharminsight.com, January 2014

Note: "BioPharm Insight includes multiple counts for the same drug, when in multiple phases and locations of clinical trials. Therefore the total counts will be higher than the actual number of drugs"

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